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: 談旭中
Gender: Male
ID No.: B121226079
History No.: 46442459
Age: 46

Ordering Doctor: DOC3064F 陳育民
Ordering REQ.: D5E9856
Signing in Date: 2020/10/07

Path No.: S109-89710
MP No.: F20082
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-78063A+B
Percentage of tumor cells: 40%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page

Report Highlights

1 Relevant Biomarkers
0 Therapies Available
55 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 p.(A763_Y764insFQEA) c.2284-5_2290dup***	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EGFR p.(A763_Y764insFQEA) c.2284-5_2290dup* epidermal growth factor receptor Allele Frequency: 25.60%	None	None	55

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
EGFR	p.(A763_Y764insFQEA)	c.2284-5_2290dup	COSM26720	chr7:55248980	25.60%	NM_005228.4	nonframeshift Insertion	3485
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	47.57%	NM_002227.3	synonymous	1997
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	100.00%	NM_004304.4	missense	1997
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.95%	NM_004304.4	missense	2000
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.90%	NM_004304.4	synonymous	1993
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.88%	NM_000142.4	synonymous	863
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.90%	NM_006206.5	synonymous	1998
KIT	p.(M541L)	c.1621A>C	.	chr4:55593464	43.31%	NM_000222.2	missense	1997
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.22%	NM_213647.2	missense	1800
MET	p.(=)	c.1131C>T	.	chr7:116340269	41.42%	NM_001127500.2	synonymous	1999
MET	p.(T1114S)	c.3341C>G	.	chr7:116417470	56.48%	NM_001127500.2	missense	1983

Biomarker Descriptions

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[1]. 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[2,3].

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[4,5,6,7]. 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[8]. 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

Biomarker Descriptions (continued)

mutations that are less common include E709K, G719X, S768I, L861Q, and short in-frame insertions in exon 20[9,10,11,12]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[13]. 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[8,14]. 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[5,6,7,14,15]. 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[16,17,18].

Potential relevance: Erlotinib[19] (2004), afatinib[20] (2013), gefitinib[21] (2015), osimertinib[22] (2015), and dacomitinib[23] (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[8]. 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[24] (2004), panitumumab[25] (2006), and necitumumab[26] (2016) are also under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, JNJ-61186372[27], targeting EGFR and MET, and the tyrosine kinase inhibitor[28] each received a breakthrough designation from the FDA (2020) for NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy CNVN-202[29] in combination with the EGFR inhibitor, osimertinib, received a fast track designation from the FDA (2020) for NSCLC tumors harboring 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[30].

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 p.(A763_Y764insFQEA) c.2284-5_2290dup

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
apatinib + EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (IV)
apatinib, gefitinib	✖	✖	✖	✖	● (IV)
EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (IV)
gefitinib, radiation therapy	✖	✖	✖	✖	● (IV)
icotinib hydrochloride, radiation therapy	✖	✖	✖	✖	● (IV)
bevacizumab, atezolizumab, chemotherapy	✖	✖	✖	✖	● (III)
durvalumab, chemotherapy	✖	✖	✖	✖	● (III)
gefitinib	✖	✖	✖	✖	● (III)
icotinib hydrochloride, chemotherapy	✖	✖	✖	✖	● (III)
nivolumab, chemotherapy	✖	✖	✖	✖	● (III)
afatinib	✖	✖	✖	✖	● (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 p.(A763_Y764insFQEA) c.2284-5_2290dup (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
afatinib, bevacizumab	✖	✖	✖	✖	● (II)
afatinib, chemotherapy, radiation therapy	✖	✖	✖	✖	● (II)
anlotinib hydrochloride	✖	✖	✖	✖	● (II)
anlotinib hydrochloride, gefitinib	✖	✖	✖	✖	● (II)
bevacizumab, osimertinib	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor + chemotherapy	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor + chemotherapy, EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor, apatinib	✖	✖	✖	✖	● (II)
EGFR tyrosine kinase inhibitor, radiation therapy	✖	✖	✖	✖	● (II)
erlotinib	✖	✖	✖	✖	● (II)
erlotinib + chemotherapy	✖	✖	✖	✖	● (II)
erlotinib, chemotherapy, sintilimab, anlotinib hydrochloride	✖	✖	✖	✖	● (II)
erlotinib, radiation therapy	✖	✖	✖	✖	● (II)
famitinib, HS-10296	✖	✖	✖	✖	● (II)
icotinib hydrochloride	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
osimertinib	✖	✖	✖	✖	● (II)
pirotinib	✖	✖	✖	✖	● (II)
ramucirumab, chemotherapy, cytokine	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
tyrosine kinase inhibitors, radiation therapy	✖	✖	✖	✖	● (II)
anlotinib hydrochloride, chemotherapy	✖	✖	✖	✖	● (I/II)
bevacizumab + erlotinib + chemotherapy	✖	✖	✖	✖	● (I/II)
DZD-9008	✖	✖	✖	✖	● (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 p.(A763_Y764insFQEA) c.2284-5_2290dup (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
EMB01	✖	✖	✖	✖	● (I/II)
icotinib hydrochloride + chemotherapy	✖	✖	✖	✖	● (I/II)
ningetinib, gefitinib	✖	✖	✖	✖	● (I/II)
lazertinib, JNJ-61186372	✖	✖	✖	✖	● (I)
neratinib, palbociclib, everolimus, trametinib	✖	✖	✖	✖	● (I)
TP-0903	✖	✖	✖	✖	● (I)
TQB 3804	✖	✖	✖	✖	● (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 2020-05-01. 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 p.(A763_Y764insFQEA) c.2284-5_2290dup

⛔ atezolizumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- " Therefore, subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK fusions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

EGFR p.(A763_Y764insFQEA) c.2284-5_2290dup (continued)

nivolumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- " Therefore, subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK fusions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

pembrolizumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- " Therefore, subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK fusions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

pembrolizumab

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

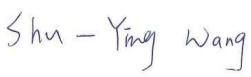
Other criteria: CD274 overexpression

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 4.2020]

Signatures

Testing Personnel:



2020.10.13
15:12:07 +08'00'

Laboratory Supervisor:

2020.10.13
15:12:23 +08'00'

Pathologist:

2020.10.13
15:12:38 +08'00'

References

1. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6. PMID: 2992089
2. ErbB Receptors and Cancer. Methods Mol. Biol. 2017;1652:3-35. PMID: 28791631
3. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711
4. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. FEBS Lett. 2010 Jun 18;584(12):2699-706. PMID: 20388509
5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
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. da et al. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
9. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol. Cancer Ther. 2013 Feb;12(2):220-9. PMID: 23371856
10. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. Clin Cancer Res. 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867
11. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med. 2013 Dec 18;5(216):216ra177. PMID: 24353160
12. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. J Thorac Oncol. 2015 May;10(5):793-9. PMID: 25668120
13. Karachaliou et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013 May;14(3):205-14. PMID: 23122493
14. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
15. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
16. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. FEBS J. 2010 Jan;277(2):301-8. PMID: 19922469
17. Ji et al. Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. Proc. Natl. Acad. Sci. U.S.A. 2006 May 16;103(20):7817-22. PMID: 16672372
18. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201292s015lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208065s013lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211288s000lbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf
25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125547s000lbl.pdf
27. https://www.jnj.com/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-jnj-6372-for-the-treatment-of-non-small-cell-lung-cancer
28. https://www.takeda.com/newsroom/newsreleases/2020/takeda-announces-u.s.-fda-breakthrough-therapy-designation-for-mobocertinib-tak-788-for-the-treatment-of-nsclc-patients-with-egfr-exon-20-insertion-mutations/

References (continued)

29. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/
30. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]