



Sample Information

Patient Name: 陳淑蜜**Gender:** Female**ID No.:** A210404406**History No.:** 26623950**Age:** 63**Ordering Doctor:** DOC6284J 張祐寧**Ordering REQ.:** 0ATRCMN**Signing in Date:** 2020/07/15**Path No.:** S109-99688**MP No.:** F20042**Assay:** Oncomine Focus Assay**Sample Type:** FFPE**Block No.:** S109-02111A**Percentage of tumor cells:** 70%**Note:**

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents

Page

Variants (Exclude variant in Taiwan
BioBank with >1% allele frequency)

2

Biomarker Descriptions

2

Relevant Therapy Summary

3

Relevant Therapy Details

4

Report Highlights

1 Relevant Biomarkers

1 Therapies Available

22 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	Not detected	NTRK3	Not detected
ERBB2	ERBB2 exon 20 insertion	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
ERBB2 exon 20 insertion erb-b2 receptor tyrosine kinase 2 Tier: IA Allele Frequency: 55.88%	■ ado-trastuzumab emtansine	None	22

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.

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
ERBB2	p.(E770_A771insAYV M)	c.2324_2325insATAC GTGATGGC	COSM20959	chr17:37880981	55.88%	NM_004448.3	nonframeshift Insertion	1972

Biomarker Descriptions

ERBB2 (erb-b2 receptor tyrosine kinase 2)

Background: The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family¹. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases. However, ERBB2/HER2 is an orphan receptor with no known ligand. ERBB2 preferentially binds other ligand bound ERBB/HER family members to form hetero-dimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival². Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding^{3,4,5}.

Alterations and prevalence: ERBB2 gene amplification occurs in 10-20% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers^{6,7,8,9,10,11,12,13}. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types^{13,14,15}. In breast, bladder, and colorectal cancers, the most common recurrent ERBB2 activating mutations include kinase domain mutations L755S and V777L and the extracellular domain mutation S310F. In lung cancer, the most common recurrent ERBB2 activating mutations include in-frame exon 20 insertions, particularly Y772_A775dup.

Potential relevance: The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987 led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2^{16,17}. Trastuzumab¹⁸ was FDA approved for the treatment of HER2 positive breast cancer in 1998, and subsequently in HER2 positive metastatic gastric and gastroesophageal junction adenocarcinoma in 2010. Additional monoclonal antibody therapies have been approved by the FDA for HER2-positive breast cancer including pertuzumab¹⁹ (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine²⁰ (2013), a conjugate of trastuzumab and a potent antimicrotubule agent. The combination of pertuzumab, trastuzumab, and a taxane is the preferred front-line regimen for HER2-positive metastatic breast cancer²¹. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib²², with specificity for both EGFR and ERBB2, was FDA approved (2007) for the treatment of patients with advanced HER2-positive breast cancer who have received prior therapy including trastuzumab. In 2017, the FDA approved the use of neratinib²³, an irreversible kinase inhibitor of EGFR, ERBB2/HER2, and ERBB4, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer. In 2020, the FDA approved neratinib²³ in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. The FDA has



Biomarker Descriptions (continued)

granted fast-track designation to two therapies including the novel bispecific antibody ZW25²⁴ in patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA), and the vaccine nelipepimut-S²⁵ in patients with low to intermediate HER2 expressing (IHC score 1+ or 2+) breast cancer. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies^{26,27,28,29,30}. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy³¹. However, this was shown to be overcome by neratinib in combination with therapies targeting ER³¹.

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

ERBB2 exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ado-trastuzumab emtansine	✕	●	✕	✕	● (II)
afatinib	✕	✕	✕	✕	● (II)
anti-PD-L1 antibody, pyrotinib	✕	✕	✕	✕	● (II)
pertuzumab + trastuzumab	✕	✕	✕	✕	● (II)
pertuzumab, trastuzumab	✕	✕	✕	✕	● (II)
poziotinib	✕	✕	✕	✕	● (II)
pyrotinib	✕	✕	✕	✕	● (II)
RC-48	✕	✕	✕	✕	● (II)
sintilimab	✕	✕	✕	✕	● (II)
targeted therapy, chemotherapy	✕	✕	✕	✕	● (II)
tarloxotinib	✕	✕	✕	✕	● (II)
trastuzumab	✕	✕	✕	✕	● (II)
trastuzumab deruxtecan	✕	✕	✕	✕	● (II)
trastuzumab, pertuzumab	✕	✕	✕	✕	● (II)
trastuzumab, pertuzumab, chemotherapy	✕	✕	✕	✕	● (II)
CBT-502, anlotinib hydrochloride	✕	✕	✕	✕	● (I/II)
DZD-9008	✕	✕	✕	✕	● (I/II)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✕	✕	✕	✕	● (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

ERBB2 exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pirotinib	✕	✕	✕	✕	● (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.

ERBB2 exon 20 insertion

● ado-trastuzumab emtansine

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Non-Small Cell Lung Cancer; Emerging targeted agents

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

🗨 afatinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 mutation

Summary:

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

- "The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib (both for HER2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with HER2 mutations."

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



ERBB2 exon 20 insertion (continued)

trastuzumab

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 mutation

Summary:

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

- "The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib (both for HER2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with HER2 mutations."

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

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:



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. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
3. Di et al. erbB-2 is a potent oncogene when overexpressed in NIH/3T3 cells. *Science*. 1987 Jul 10;237(4811):178-82. PMID: 2885917
4. Hudziak et al. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. *Proc. Natl. Acad. Sci. U.S.A.* 1987 Oct;84(20):7159-63. PMID: 2890160
5. Lonardo et al. The normal erbB-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. *New Biol.* 1990 Nov;2(11):992-1003. PMID: 1983208
6. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell*. 2015 Oct 8;163(2):506-19. PMID: 26451490
7. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
8. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
9. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012 Jul 18;487(7407):330-7. PMID: 22810696
10. 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
11. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011 Jun 29;474(7353):609-15. PMID: 21720365
12. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
13. 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
14. Petrelli et al. Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. *Breast Cancer Res. Treat.* 2017 Nov;166(2):339-349. PMID: 28762010
15. Bose et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov.* 2013 Feb;3(2):224-37. doi: 10.1158/2159-8290.CD-12-0349. Epub 2012 Dec 7. PMID: 23220880
16. Hudis. Trastuzumab--mechanism of action and use in clinical practice. *N. Engl. J. Med.* 2007 Jul 5;357(1):39-51. PMID: 17611206
17. Slamon et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987 Jan 9;235(4785):177-82. PMID: 3798106
18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5345lbl.pdf
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf
21. NCCN Guidelines® - NCCN-Breast Cancer [Version 1.2020]
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022059s024lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208051s004lbl.pdf
24. <https://ir.zymeworks.com/file/Index?KeyFile=398123202>
25. <https://www.globenewswire.com/news-release/2016/06/01/845166/0/en/Galena-Biopharma-Receives-Fast-Track-Designation-for-NeuVax-nelipepimut-S-PRESENT-Clinical-Trial.html>
26. Ma et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. *Clin. Cancer Res.* 2017 Oct 1;23(19):5687-5695. PMID: 28679771
27. De et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer*. 2012 Apr;76(1):123-7. PMID: 22325357



References (continued)

28. Kris et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann. Oncol.* 2015 Jul;26(7):1421-7. PMID: 25899785
29. Falchook et al. Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. *J Thorac Oncol.* 2013 Feb;8(2):e19-20. PMID: 23328556
30. David et al. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study. *AACR 2017. Abstract CT001*
31. Nayar et al. Acquired HER2 mutations in ER+ metastatic breast cancer confer resistance to estrogen receptor-directed therapies. *Nat. Genet.* 2019 Feb;51(2):207-216. PMID: 30531871