



Sample Information

Patient Name: 邱珀花**Gender:** Female**ID No.:** F223062962**History No.:** 17392233**Age:** 54**Ordering Doctor:** DOC3067J 許哲敏**Ordering REQ.:** 0AUZXXF**Signing in Date:** 2020/08/20**Path No.:** S109-99891**MP No.:** F20062**Assay:** Oncomine Focus Assay**Sample Type:** FFPE**Block No.:** S109-25527A**Percentage of tumor cells:** 60%**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	Not detected	NTRK3	Not detected
ERBB2	ERBB2 exon 20 insertion	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	ERBB2 exon 20 insertion erb-b2 receptor tyrosine kinase 2 Allele Frequency: 47.04%	ado-trastuzumab emtansine	None	26

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.(G776delinsVC)	c.2326_2327insTGT	COSM12553	chr17:37880997	47.04%	NM_004448.3	nonframeshift Insertion	1958
RET	p.(=)	c.2305C>T	.	chr10:43613841	48.25%	NM_020975.4	synonymous	2000

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 vaccine,



Biomarker Descriptions (continued)

nelipepimut-S²⁴, was granted fast-track designation by the FDA (2016) in patients with low to intermediate HER2 expressing (IHC score 1+ or 2+) breast cancer. Additionally, fast-track designation was granted (2018) to the monoclonal antibody margetuximab²⁵ in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy as well as the novel bispecific antibody ZW25²⁶ (2019) in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies^{27,28,29,30,31}. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy³². However, this was shown to be overcome by neratinib in combination with therapies targeting ER³².

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)
neratinib	✕	✕	✕	✕	● (II)
pertuzumab + trastuzumab	✕	✕	✕	✕	● (II)
pertuzumab, trastuzumab	✕	✕	✕	✕	● (II)
poziotinib	✕	✕	✕	✕	● (II)
pyrotinib	✕	✕	✕	✕	● (II)
sintilimab	✕	✕	✕	✕	● (II)
targeted therapy, chemotherapy	✕	✕	✕	✕	● (II)
tarloxotinib	✕	✕	✕	✕	● (II)
trastuzumab deruxtecan	✕	✕	✕	✕	● (II)
trastuzumab, pertuzumab, chemotherapy	✕	✕	✕	✕	● (II)
BDTX-189	✕	✕	✕	✕	● (I/II)
CBT-502, anlotinib hydrochloride	✕	✕	✕	✕	● (I/II)
DZD-9008	✕	✕	✕	✕	● (I/II)
zotatifin	✕	✕	✕	✕	● (I/II)
disitamab vedotin	✕	✕	✕	✕	● (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*
neratinib, palbociclib, everolimus, trametinib	✕	✕	✕	✕	● (I)
pirotinib	✕	✕	✕	✕	● (I)
trastuzumab deruxtecan, pembrolizumab	✕	✕	✕	✕	● (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.

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 biomarker in metastatic disease (Not specified)

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

⚠ 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 ERBB2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with ERBB2 mutations."

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



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 ERBB2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with ERBB2 mutations."

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

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:



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