Taipei Veterans General Hospital

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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

Table of Contents	Page

Report Highlights

1 Relevant Biomarkers
1 Therapies Available
26 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

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, **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
ERBB2	p.(G776delinsVC)	c.2326_2327insTGT	COSM12553	chr17:37880997	47.04%	NM_004448.3	nonframeshift Insertion	1958
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	59.67%	NM_002227.3	synonymous	1986
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.70%	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	99.75%	NM_004304.4	synonymous	1985
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.70%	NM_000142.4	synonymous	1990
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	51.53%	NM_006206.5	synonymous	1995
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.70%	NM_006206.5	synonymous	1997
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.05%	NM_213647.2	missense	2000
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 family[1]. 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 survival[2]. 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

Biomarker Descriptions (continued)

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]. Trastuzumab[18] 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 pertuzumab[19] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[20] (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 cancer[21]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[22], 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 neratinib[23], 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 neratinib[23] in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. The vaccine, nelipepimut-S[24], 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 margetuximab[25] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy as well as the novel bispecific antibody ZW25[26] (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 therapy[32]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[32].

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)

* 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*
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)
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]

⛔ 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: Shin-Ying Lin 2020.08.25 09:08:50 +08'00'

Laboratory Supervisor:

2020.08.25
09:09:05 +08'00'

Pathologist:

2020.08.25
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