Taipei Veterans General Hospital

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Sample Information

Patient Name: 呂春嬌
Gender: Female
ID No.: H201407549
History No.: 48851225
Age: 66

Ordering Doctor: DOC3064F 陳育民
Ordering REQ.: D7499HK
Signing in Date: 2023/02/15

Path No.: M112-00027
MP No.: F23007
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-79002 (From Linkou Chang Gung Memorial Hospital)
Percentage of tumor cells: 30%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	***ERBB2 exon 20 insertion***	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None 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: 35.38%	**trastuzumab deruxtecan** [1]	trastuzumab	8

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.

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.(Y772_A775dup)	c.2324_2325insATACGTGATGGC	COSM20959	chr17:37880981	35.38%	NM_004448.3	nonframeshift Insertion	1956

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 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. Also in 2020, the TKI irbinitinib[24] was FDA approved for HER2 overexpressing or amplified breast cancer in combination with trastuzumab and capecitabine. In 2021, the PD-1 blocking antibody, pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy, was approved for HER2 amplified gastric or gastroesophageal (GEJ) adenocarcinoma in the first line[25]. The vaccine, nelipepimut-S[26], was granted fast-track designation by the FDA (2016) in patients with low to intermediate HER2 expressing (IHC score 1+ or 2+) breast cancer. In 2018 fast-track designation was granted to the monoclonal antibody margetuximab[27] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, fast track designation was granted to the HER2-targeting antibody drug conjugate, amcenestrant[28], for HER2-positive advanced or metastatic breast cancer after one or more

Biomarker Descriptions (continued)

prior anti-HER2 based regimens. Additionally, in 2019, the novel bispecific antibody, zanidatamab[29], received fast-track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA) and breakthrough therapy designation (2020) as a monotherapy for patients with HER2-amplified biliary tract cancer[30]. In 2020, BDTX-189[31] received fast-track designation for adult patients with solid tumors harboring an allosteric human ERBB2 mutation or exon 20 insertion, and the humanized anti-HER2 antibody drug conjugate disitamab vedotin received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment[32]. In 2021, the antibody-drug conjugate ARX788[33] received fast-track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Additionally, in 2021, fast track designation was granted to HER2 targeted chimeric antigen receptor macrophage (CAR-M), CT-0508[34], for HER2-overexpressing solid tumors. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[35,36,37,38,39]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[40,41]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[42]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[42].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

ERBB2 exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	●	●	✖	✖	✖
trastuzumab	✖	✖	✖	○	✖
pyrotinib	✖	✖	✖	✖	● (III)
trastuzumab deruxtecan, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
ABT-101	✖	✖	✖	✖	● (I/II)
sunvozertinib	✖	✖	✖	✖	● (I/II)
BAY-2927088	✖	✖	✖	✖	● (I)
SAR-443216	✖	✖	✖	✖	● (I)
SHR-A1811	✖	✖	✖	✖	● (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

FDA information is current as of 2022-12-14. For the most up-to-date information, search www.fda.gov.

ERBB2 exon 20 insertion

● trastuzumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-11-04 **Variant class:** ERBB2 Y772_A775dup mutation

Indications and usage:

ENHERTU® is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  - in the metastatic setting, or
  - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
  - This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2022-12-01. 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

● trastuzumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer **Variant class:** ERBB2 Y772_A775dup mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Not otherwise specified (NOS), Squamous Cell; Advanced, Metastatic, Progression (Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2022-12-01. For the most up-to-date information, search www.esmo.org.

ERBB2 exon 20 insertion

○ trastuzumab

Cancer type: Cholangiocarcinoma, Gallbladder Carcinoma

Variant class: ERBB2 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- Progression (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Biliary Cancer [Annals of Oncology (2022), doi: https://doi.org/10.1016/j.annonc.2022.10.506]

Clinical Trials in Taiwan region:

Clinical Trials Summary

ERBB2 exon 20 insertion

NCT ID	Title	Phase
NCT05532696	A Phase Ib/II, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ABT-101 in Patients With Advanced Solid Tumors and HER2 Exon 20 Insertions Mutated Non- Small Cell Lung Cancer	I/II
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation	I/II
NCT05099172	An Open Label, First-in-human Study of BAY 2927088 in Participants With Advanced Non-small Cell Lung Cancer (NSCLC) Harboring an EGFR and/or HER2 Mutation	I
NCT04447118	A Phase III, Randomized, Open-label, Multicenter Study of the Efficacy and Safety of Pyrotinib Versus Docetaxel in Patients With Advanced Non-squamous Non-small Cell Lung Cancer (NSCLC) Harboring a HER2 Exon 20 Mutation Who Progressed on or After Treatment With Platinum Based Chemotherapy	III
NCT05048797	An Open-label, Randomized, Multicenter, Phase III Study to Assess the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment of Unresectable, Locally Advanced, or Metastatic NSCLC Harboring HER2 Exon 19 or 20 Mutations (DESTINY-Lung04)	III
NCT05013554	A Phase I/Ib Open-label, First-in-human, Single Agent, Dose Escalation and Expansion Study for the Evaluation of Safety, Pharmacokinetics, Pharmacodynamics, and Anti-tumor Activity of SAR443216 in Participants with Relapsed/Refractory HER2 Expressing Solid Tumors.	I
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT04446260	A Phase I Multi-Country, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of SHR-A1811 in HER2 Expressing or Mutated Advanced Malignant Solid Tumor Subjects	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2022-12-14. For the most up-to-date information, search www.fda.gov.

ERBB2 exon 20 insertion

BDTX-189

Cancer type: Solid Tumor **Variant class:** ERBB2 exon 20 insertion

Supporting Statement:
The FDA has granted Fast Track Designation to BDTX-189 for solid tumors harboring a HER2 mutation or an EGFR or HER2 exon 20 insertion after progression on prior therapy.

Reference:

https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2022-12-01. 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

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2022]

Signatures

Testing Personnel:

2023.02.16
09:41:42 +08'00'

Laboratory Supervisor:

2023.02.16
09:41:51 +08'00'

Pathologist:

2023.02.16
09:42:02 +08'00'

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