Taipei Veterans General Hospital

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## Sample Information

**Patient Name:** 洪秀鸞
**Gender:** Female
**ID No.:** K201544825
**History No.:** 20712565
**Age:** 89

**Ordering Doctor:** DOC3016D 江起陸
**Ordering REQ.:** C32DJ58
**Signing in Date:** 2023/12/21

**Path No.:** M112-00333
**MP No.:** F23095
**Assay:** Oncomine Focus Assay
**Sample Type:** FFPE
**Block No.:** S112-62172A
**Percentage of tumor cells:** 80%

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

**Note:**

## Sample Cancer Type: Non-Small Cell Lung Cancer

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### Report Highlights

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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*<br>erb-b2 receptor tyrosine kinase 2<br>Allele Frequency: 45.55% | **trastuzumab deruxtecan** [1] | trastuzumab | 8 |

**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.

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*CTNNB1 p.(I35S) c.104T>G*

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect | Coverage |
|---|---|---|---|---|---|---|---|---|
| CTNNB1 | p.(I35S) | c.104T>G | COSM5674 | chr3:41266107 | 32.80% | NM_001904.4 | missense | 1701 |
| ERBB2 | p.(Y772_A775dup) | c.2324_2325insATACGTGATGGC | COSM20959 | chr17:37880981 | 45.55% | NM_004448.3 | nonframeshift Insertion | 1978 |
| PDGFRA | p.(G313=) | c.939T>G | . | chr4:55133726 | 50.08% | NM_006206.6 | synonymous | 1997 |
| PDGFRA | p.(V824=) | c.2472C>T | . | chr4:55152040 | 49.92% | NM_006206.6 | synonymous | 1997 |
| FGFR4 | p.(P136L) | c.407C>T | . | chr5:176517797 | 99.60% | NM_213647.3 | missense | 1984 |
| FGFR4 | p.(I197T) | c.590T>C | . | chr5:176518092 | 16.06% | NM_213647.3 | missense | 1407 |
| MET | p.(N375S) | c.1124A>G | . | chr7:116340262 | 39.10% | NM_001127500.3 | missense | 2000 |

## Biomarker Descriptions

**CTNNB1 (catenin beta 1)**

Background: The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions involved in maintaining adhesion and regulating the growth of epithelial cell layers[1]. CTNNB1 binds to the APC protein in the cytoplasm and also interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling[2]. Steady state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis[3,4,5].

Alterations and prevalence: Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-β and inhibit CTNNB1 degradation[6,7,8,9]. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% of uterine carcinoma, and 15% of adrenocortical carcinoma[10,11,12,13,14,15,16].

Potential relevance: Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors in EGFR positive lung cancer[17]. Mutation of CTNNB1 is considered useful as an ancillary diagnostic biomarker for desmoid fibromatosis[18].

**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[19]. 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[20]. Recurrent focal amplification of the ERBB2 gene leads to increased expression

## Biomarker Descriptions (continued)

in several cancer types. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[21,22,23].

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[15,16,24,25,26,27,28,29]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[16,30,31]. 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[32,33]. Trastuzumab[34] 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[35] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[36] (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[37]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[38], 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[39], 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[39] 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[40] 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[41]. The vaccine, nelipepimut-S[42], 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[43] 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[44], for HER2-positive advanced or metastatic breast cancer after one or more prior anti-HER2 based regimens. Additionally, in 2019, the novel bispecific antibody, zanidatamab[45], 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[46]. In 2020, BDTX-189[47] 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[48]. In 2021, the antibody-drug conjugate ARX788[49] 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[50], 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[51,52,53,54,55]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[56,57]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[58]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[58].

## 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 | ✖ | ✖ | ✖ | ○ | ✖ |
| trastuzumab deruxtecan, pembrolizumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (III) |

* 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 ✖ No evidence

### ERBB2 exon 20 insertion (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ado-trastuzumab emtansine | ✖ | ✖ | ✖ | ✖ | ● (II) |
| ABT-101 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| sunvozertinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| BAY-2927088 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| ELVN-002, trastuzumab deruxtecan | ✖ | ✖ | ✖ | ✖ | ● (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 2023-09-13. 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 2023-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

## 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 3.2023]

## 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 2023-09-01. For the most up-to-date information, search www.esmo.org.

## ERBB2 exon 20 insertion

### ● trastuzumab deruxtecan

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

**ESMO Level of Evidence/Grade of Recommendation:** III / B

**Population segment (Line of therapy):**
- Advanced, Metastatic, Unresectable (Second-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

### ○ 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 [Ann Oncol (2023), 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 |
| 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 |
| NCT05650879 | A Phase Ia/Ib Study of ELVN-002 for the Treatment of Patients With HER2 Mutant Non-Small Cell Lung Cancer | I |
| 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 2023-09-13. 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

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