Taipei Veterans General Hospital

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## Sample Information

**Patient Name:** 林玉珠
**Gender:** Female
**ID No.:** U200171068
**History No.:** 46748601
**Age:** 76

**Ordering Doctor:** DOC3109L 邱昭華
**Ordering REQ.:** C235LM2
**Signing in Date:** 2021/03/24

**Path No.:** S110-98468
**MP No.:** F21031
**Assay:** Oncomine Focus Assay
**Sample Type:** FFPE
**Block No.:** S110-75745B
**Percentage of tumor cells:** 80%
**Note:**

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

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### Report Highlights

1 Relevant Biomarkers
2 Therapies Available
33 Clinical Trials

## Relevant Non-Small Cell Lung Cancer Variants

| 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*<br>erb-b2 receptor tyrosine kinase 2<br>Allele Frequency: 38.81% | ado-trastuzumab emtansine<br>trastuzumab deruxtecan | None | 33 |

**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.

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect | Coverage |
|---|---|---|---|---|---|---|---|---|
| ERBB2 | p.(E770_A771insAYVM) | c.2324_2325insATACGTGATGGC | COSM20959 | chr17:37880981 | 38.81% | NM_004448.3 | nonframeshift Insertion | 1984 |
| ALK | p.(D1529E) | c.4587C>G | . | chr2:29416366 | 60.71% | NM_004304.4 | missense | 1998 |
| ALK | p.(=) | c.3375C>A | . | chr2:29445458 | 61.23% | NM_004304.4 | synonymous | 1994 |
| IDH1 | p.(=) | c.309G>A | . | chr2:209113198 | 39.27% | NM_005896.3 | synonymous | 1999 |
| PDGFRA | p.(=) | c.939T>G | . | chr4:55133726 | 69.42% | NM_006206.5 | synonymous | 1988 |
| PDGFRA | p.(=) | c.2472C>T | . | chr4:55152040 | 31.17% | NM_006206.5 | synonymous | 1999 |
| FGFR4 | p.(P136L) | c.407C>T | . | chr5:176517797 | 99.35% | NM_213647.2 | missense | 2000 |
| EGFR | p.(=) | c.2361G>A | . | chr7:55249063 | 49.07% | NM_005228.4 | synonymous | 1997 |

## 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

## Biomarker Descriptions (continued)

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. The vaccine, nelipepimut-S[25], 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[26] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, the novel bispecific antibody ZW25[27] received fast-track designation for patients with HER2-amplified biliary tract cancer or in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). In 2020, BDTX-189[28] 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[29]. In 2021, the antibody-drug conjugate ARX788[30] received fast-track designation as a monothreapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[31,32,33,34,35]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[36,37]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER +) breast cancer have been shown to confer resistance to hormone therapy[38]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[38].

## 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* |
|---|---|---|---|---|---|
| ado-trastuzumab emtansine | ✖ | ● | ✖ | ✖ | ● (II) |
| trastuzumab deruxtecan | ✖ | ● | ✖ | ✖ | ✖ |
| pyrotinib | ✖ | ✖ | ✖ | ✖ | ● (III) |
| ado-trastuzumab emtansine + atezolizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| afatinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| anti-PD-L1 antibody, pyrotinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| irbinitinib, trastuzumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| neratinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pertuzumab + trastuzumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| poziotinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pyrotinib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pyrotinib, thalidomide | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sintilimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| targeted therapy, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| tarloxotinib | ✖ | ✖ | ✖ | ✖ | ● (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 ✖ No evidence

### ERBB2 exon 20 insertion (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| BDTX-189 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| CBT-502, anlotinib hydrochloride | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| DZD-9008 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| mobocertinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| zotatifin | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| disitamab vedotin | ✖ | ✖ | ✖ | ✖ | ● (I) |
| neratinib, palbociclib, everolimus, trametinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| pirotinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| SHR-A1811 | ✖ | ✖ | ✖ | ✖ | ● (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

NCCN information is current as of 2021-02-01. 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):**
- Metastatic (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2021]

## ERBB2 exon 20 insertion (continued)

### trastuzumab deruxtecan

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Metastatic (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2021]

# Clinical Trials Summary

## ERBB2 exon 20 insertion

| NCT ID | Title | Phase |
|---|---|---|
| NCT03066206 | A Phase II Study of Poziotinib in EGFR in Exon 20 Mutant Advanced Non Small Cell Lung Cancer (NSCLC) | II |
| NCT03318939 | A Phase II Study of Poziotinib in Patients With Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, With EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20). | II |
| NCT04382300 | Safety and Efficacy of Pyrotinib Combined With Thalidomide in Advanced Non-Small-Cell Lung Cancer With HER2 Exon 20 Insertions: A Prospective, Single-arm, Open-label Phase II Study | II |
| No NCT ID | A Prospective, Single-center, Single-arm Phase II Clinical Study for Advanced Non-small Cell Lung Cancer with EGFR/HER2 gene exon 20 insertion Mutations Treated with Sintilimab | 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 |
| NCT02716116 | A Phase I/II Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer | I/II |
| NCT04402008 | A Phase I/II Dose Finding Study of Poziotinib in Japanese Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) | I/II |
| 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 |
| NCT04144569 | The Effectiveness and Safety Study on PD-1 Combined With Pyrotinib for First-line Chemotherapy Failed HER2 Insertion Mutation Advanced Non-small Cell Lung Cancer | II |
| NCT04579380 | A Phase II Basket Study of Tucatinib in Combination With Trastuzumab in Subjects With Previously Treated, Locally Advanced Unresectable or Metastatic Solid Tumors Driven by HER2 Alterations | II |
| No NCT ID | A Single-center, Open-label , Non-randomized Control Clinical Trial On Clinical Features and Medical Treatment of Advanced NSCLC With Rare Gene Mutations | II |
| NCT03805841 | Phase II Study - Evaluate the Clinical Activity of Tarloxotinib in Patients With Non-Small Cell Lung Cancer That Harbors an EGFR Exon 20 Insertion or HER2-Activating Mutation and Other Advanced Solid Tumors With NRG1/ERBB Family Gene Fusions. | II |
| NCT04311034 | A Phase Ib Study to Evaluate the Efficacy and Safety of RC48-ADC for Injection in Subjects With Advanced Non-small Cell Lung Cancer With HER2 Overexpression or HER2 Mutation | I |
| NCT02183883 | Deciphering Afatinib Response and Resistance With INtratumour Heterogeneity | II |

# Clinical Trials Summary (continued)

## ERBB2 exon 20 insertion (continued)

| NCT ID | Title | Phase |
|---|---|---|
| NCT02535507 | Single Arm Phase II Clinical Trial to Investigate the Efficacy and Safety of Pyrotinib as a Single Agent in HER2 Mutation Advanced Non-small Cell Lung Cancer Patients Who Failed to Previous at Least 2nd Line Treatments | II |
| NCT03574402 | An Open-label, Multi-center, Phase II Umbrella Study to Assess Efficacy of Targeted Therapy or Immunotherapy Directed by Next Generation Sequencing (NGS) in Chinese Patients With Advanced NSCLC (TRUMP) | II |
| NCT04706949 | A Prospective, Single Center, Single Arm, Phase II Clinical Trial of Pyrotinib Combined With Pemetrexed Plus Carboplatin in the First-line Treatment of Patients With HER2 Mutant or Amplified Recurrent / Metastatic Non-small Cell Lung Cancer | II |
| NCT04591431 | The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy | II |
| NCT03983928 | A Phase Ib, Open-label, Single Center, Non-randomized Study for Safety and Efficacy of TQB2450 Combined With Anlotinib in Subjects With Advanced Mutation Positive Non-Small Cell Lung Cancer | I/II |
| No NCT ID | Phase I Study of DZD9008 in EGFR or HER2 Mutant NSCLC Chinese Patients | I |
| NCT04042701 | A Phase Ib, Multicenter, Two-Part, Open-Label Study of Trastuzumab Deruxtecan (DS-8201a), An Anti-Human Epidermal Growth Factor Receptor-2 (HER2)-Antibody Drug Conjugate (ADC), In Combination With Pembrolizumab, An Anti-PD-1 Antibody, In Subjects With Locally Advanced/Metastatic Breast Or Non-Small Cell Lung Cancer (NSCLC). | I |
| NCT04209465 | MasterKey-01: A Phase I/II, Open-label, Two-part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics & Antitumor Activity of BDTX-189, an Inhibitor of Allosteric ErbB Mutations, in Patients w/ Advanced Solid Malignancies | I/II |
| NCT02675829 | A Phase II Trial of Ado-Trastuzumab Emtansine for Patients With HER2 Amplified or Mutant Cancers | II |
| NCT01953926 | An Open-Label, Phase II Basket Study of Neratinib in Patients With Solid Tumors With Somatic Activating HER Mutations | II |
| NCT04092673 | A Phase 1-2 Dose-Escalation and Cohort-Expansion Study of Intravenous Zotatifin (eFT226) in Subjects With Selected Advanced Solid Tumor Malignancies | I/II |
| NCT04589845 | Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial | II |
| NCT04632992 | MyTACTIC: An Open-Label Phase II Study Evaluating Targeted Therapies in Patients Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response | II |
| NCT03810872 | An Open Explorative Phase II, Open Label Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation | II |
| NCT02693535 | Targeted Agent and Profiling Utilization Registry (TAPUR) Study | II |
| NCT03065387 | Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib, or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/ Amplification, or HER3/4 Mutation or KRAS Mutation | I |
| No NCT ID | Phase I Clinical Study With Advanced Solid Tumors KBP-5209 Treatment | I |
| 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 |
| NCT03297606 | Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial | II |

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-02-17. 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 2021-02-01. 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 (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 2.2021]

#### 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."

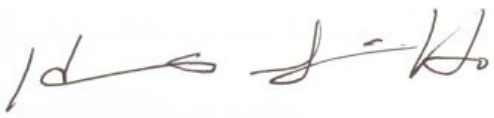
**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2021]

## Signatures

**Testing Personnel:**

2021.03.26
09:20:37 +08'00'

**Laboratory Supervisor:**



2021.03.26
09:22:11 +08'00'

**Pathologist:**

2021.03.26
09:22:26 +08'00'

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