



Sample Information

Patient Name: 黃水猛
Gender: Male
ID No.: Q101716369
History No.: 49328883
Age: 74

Ordering Doctor: DOC8147L 邱士育
Ordering REQ.: OCKFHTD
Signing in Date: 2023/05/04

Path No.: M112-00090
MP No.: F23028
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-13273F
Percentage of tumor cells: 50%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page	Report Highlights
Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)	2	1 Relevant Biomarkers
Biomarker Descriptions	2	3 Therapies Available
Relevant Therapy Summary	3	7 Clinical Trials
Relevant Therapy Details	5	
Clinical Trials Summary	8	
Alert Details	8	

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: 40.88%	trastuzumab deruxtecan ¹ ado-trastuzumab emtansine	trastuzumab	7

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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

MYC amplification

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.(G778_P780dup)	c.2339_2340insGGG CTCCCC	COSM12555	chr17:37881001	40.88%	NM_004448.3	nonframeshift Insertion	1969

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	5.06

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)

Biomarker Descriptions (continued)

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. Also in 2020, the TKI irbinetinib²⁴ 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 line²⁵. The vaccine, nelipecimut-S²⁶, 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 margetuximab²⁷ 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, amcenestrant²⁸, for HER2-positive advanced or metastatic breast cancer after one or more prior anti-HER2 based regimens. Additionally, in 2019, the novel bispecific antibody, zanidatamab²⁹, 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 cancer³⁰. In 2020, BDTX-189³¹ 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 treatment³². In 2021, the antibody-drug conjugate ARX788³³ 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-0508³⁴, 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 therapy⁴². However, this was shown to be overcome by neratinib in combination with therapies targeting ER⁴².

MYC (MYC proto-oncogene, bHLH transcription factor)

Background: The MYC gene encodes the MYC proto-oncogene (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation^{43,44,45,46}. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions⁴⁷. MYC functions as a heterodimer in complex with the transcription factor MAX^{44,48}.

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including codon T58, are infrequent and hypothesized to increase the stability of the MYC protein^{49,50}. MYC gene amplification is particularly common in diverse solid tumors. MYC amplification is observed in 30% of serous ovarian cancer, 20% of uterine serous carcinoma, 15% of esophageal and breast cancers, and is common (1-10%) in numerous other cancer types^{13,51,52}. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt's lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, which results in increased MYC expression^{53,54}.

Potential relevance: B-cell lymphoma with MYC translocations that co-occur with BCL2 or BCL6 are referred to as double hit lymphoma, while co-occurrence with BCL2 and BCL6 rearrangements is referred to as triple-hit lymphoma^{55,56}. MYC translocations are also indicative of high risk for multiple myeloma⁵⁷. Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression^{43,58,59,60}.

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	●	●	×	●	×
ado-trastuzumab emtansine	×	●	×	×	● (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	✕	✕	✕	○	✕
trastuzumab deruxtecan, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
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 2023-03-15. 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 G778_P780dup 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 2023-03-01. 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 G778_P780dup mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Not otherwise specified (NOS), Squamous Cell; Advanced, Metastatic, Progression (Subsequent therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2023]

☒ trastuzumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 G778_P780dup 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 2.2023]

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 2023-03-01. 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 G778_P780dup 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> (pre-proof)]

☐ 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
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 2023-03-15. 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>

References

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