Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳育鈴
Gender: Female
ID No.: A222942377
History No.: 25004095
Age: 50

Ordering Doctor: DOC3064F 陳育民
Ordering REQ.: C22BNMA
Signing in Date: 2020/12/16

Path No.: S109-96836
MP No.: F20112
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: C109-44249
Percentage of tumor cells: 30%
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 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 Fraction: 0.666	ado-trastuzumab emtansine	None	25
IIC	*MYC amplification* MYC proto-oncogene, bHLH transcription factor	None	None	3

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.
Although no fusion transcript can be detected, there is high imbalance of the number of 3' reads and 5' reads in the RET gene (3'/5' imbalance value: 25.86). A high 3'/5' imbalance value is suggestive of the presence of gene fusion. The possibility of RET fusion involving partners other than those targeted by the panel cannot be excluded. Further confirmation with other methodologies is suggested.

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
ERBB2	p.(V777_G778insGSP)	c.2340_2341insGGCTCCCCA	COSM12556	chr17:37881002	0.666	NM_004448.3	nonframeshift Insertion	1979
FGFR3	p.(G90del)	c.268_270delGGG	.	chr4:1801137	0.536	NM_000142.4	nonframeshift Deletion	1896
FGFR3	p.(Q92fs)	c.274delC	.	chr4:1801141	0.417	NM_000142.4	frameshift Deletion	1896

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	8.4

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,

Biomarker Descriptions (continued)

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. 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. Additionally, fast-track designation was granted (2018) to the monoclonal antibody margetuximab[26] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy, the novel bispecific antibody ZW25[27] (2019) in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA), and BDTX-189[28] (2020) for adult patients with solid tumors harboring an allosteric human ERBB2 mutation or exon 20 insertion. The humanized anti-HER2 antibody drug conjugate disitamab vedotin received a breakthrough designation (2020) for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment[29]. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[30,31,32,33,34]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[35,36]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[37]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[37].

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[38,39,40,41]. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions[42]. MYC functions as a heterodimer in complex with the transcription factor MAX[39,43].

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[44,45]. 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[13,46,47]. 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[48,49].

Potential relevance: 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[38,50,51,52].

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	✖	●	✖	✖	✖
afatinib	✖	✖	✖	✖	● (II)
anti-PD-L1 antibody, pyrotinib	✖	✖	✖	✖	● (II)
neratinib	✖	✖	✖	✖	● (II)
pertuzumab + trastuzumab	✖	✖	✖	✖	● (II)
poziotinib	✖	✖	✖	✖	● (II)
pyrotinib	✖	✖	✖	✖	● (II)
sintilimab	✖	✖	✖	✖	● (II)
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)

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
berzosertib	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BMS-986158	✖	✖	✖	✖	● (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 2020-10-01. 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 8.2020]

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
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
NCT03845270	Phase II Trial of Trastuzumab in Combination With Pertuzumab in Pretreated Patients With Non-small Cell Lung Cancer (NSCLC) Harboring a Her2 Mutation and Receiving Docetaxel	II
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
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
NCT03505710	A Phase II, Multicenter, Open-Label, 2-Cohort Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2 Antibody Drug Conjugate (ADC), for HER2-Over-Expressing or -Mutated, Unresectable and/or Metastatic Non Small Cell Lung Cancer (NSCLC) (DESTINY-Lung01)	II

Clinical Trials Summary (continued)

ERBB2 exon 20 insertion (continued)

NCT ID	Title	Phase
NCT02183883	Deciphering Afatinib Response and Resistance With INtratumour Heterogeneity	II
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
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
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
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
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
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
NCT01953926	An Open-Label, Phase II Basket Study of Neratinib in Patients With Solid Tumors With Somatic Activating HER Mutations	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
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
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
NCT04092673	A Phase I-II Dose-Escalation and Cohort-Expansion Study of Intravenous eFT226 in Subjects With Selected Advanced Solid Tumor Malignancies	I/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

Clinical Trials Summary (continued)

MYC amplification

NCT ID	Title	Phase
NCT03718091	A Phase II Study of M6620 (VX-970) in Selected Solid Tumors	II
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT03936465	Phase I Study of the Bromodomain (BRD) and Extra-Terminal Domain (BET) Inhibitor BMS-986158 in Pediatric Cancer	I

Alerts Informed By Public Data Sources

Current NCCN Information

Contraindicated Not recommended Resistance

NCCN information is current as of 2020-10-01. 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 8.2020]

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 8.2020]

Signatures

Testing Personnel:

2020.12.16
16:17:37 +08'00'

Laboratory Supervisor:

2020.12.16
16:17:50 +08'00'

Pathologist:

2020.12.16
16:18:01 +08'00'

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