Taipei Veterans General Hospital

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Sample Information

Patient Name: 譚許秋華
Gender: Female
ID No.: H200374238
History No.: 14030069
Age: 77

Ordering Doctor: DOC1878G 沈佳儀
Ordering REQ.: 0BYDLCS
Signing in Date: 2022/08/03

Path No.: S111-97822
MP No.: F22077
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S111-92042A
Percentage of tumor cells: 10%

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 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC***	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 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCT C* erb-b2 receptor tyrosine kinase 2 Allele Frequency: 6.92%	trastuzumab deruxtecan	None	4
IIC	*AR amplification* androgen receptor	None	hormone therapy	0

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
MYCN 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.(L755_E757delinsPQ)	c.2263_2269delTTGAGGGinsCCTC	.	chr17:37880219	6.92%	NM_004448.3	nonframeshift Block Substitution	1980

Copy Number Variations

Gene	Locus	Copy Number
MYCN	chr2:16080663	11.4
AR	chrX:66776186	12

Biomarker Descriptions

AR (androgen receptor)

Background: The AR gene encodes the androgen receptor protein (AR), a ligand-activated transcription factor regulated by the binding of the hormones testosterone and dihydrotestosterone[1,2]. Hormone binding to AR results in receptor dimerization, nuclear translocation, and target gene transcription, thus activating the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR signaling pathways, which promote cell proliferation and survival[2,3,4].

Alterations and prevalence: Alterations in AR function can result from overexpression, gene amplification, or mutations. AR mutations, including L702H, W742C/L, H875Y, and T878A, are commonly observed in 10-30% of castration-resistant prostate cancer and result in decreased ligand specificity, allowing other nuclear hormones to activate AR[5]. Androgen receptor splice variants have been reported in castration resistant prostate cancer[6,7]. The androgen receptor splice variant 7 (AR-V7) is a result of aberrant mRNA splicing of AR exons 1-3 and a cryptic exon 3, resulting in the expression of a constitutively active protein[7].

Potential relevance: The FDA has granted fast track designation (2022) to the selective androgen receptor targeting agonist, enobosarm, for or the treatment of patients with androgen AR-positive, estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer[8]. The FDA also granted fast track designation (2016) to the small-molecule CYP17 lyase-selective inhibitor, seviteronel, for AR-positive triple-negative breast cancer (TNBC) patients[9]. Androgen deprivation therapy (ADT) such as abiraterone[10] (2011) and enzalutamide[11] (2011) are FDA approved for use in locally advanced and metastatic prostate cancers. Although many men initially respond to ADT, most will develop hormone resistance. Resistance to ADT is also associated with other aberrations of the AR gene including mutations within the ligand binding domain and gene amplification[5,12,13]. The androgen receptor splice variant, AR-V7, lacks

Biomarker Descriptions (continued)

the ligand binding domain, resulting in constitutive activation and is associated with resistance to androgen deprivation therapy (ADT) in advanced prostate cancer[6].

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[14]. 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[15]. 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[16,17,18].

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[19,20,21,22,23,24,25,26]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[26,27,28]. 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[29,30]. Trastuzumab[31] 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[32] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[33] (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[34]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[35], 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[36], 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[36] 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[37] 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[38]. The vaccine, nelipepimut-S[39], 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[40] 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[41], 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[42], 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[43]. In 2020, BDTX-189[44] 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[45]. In 2021, the antibody-drug conjugate ARX788[46] 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[47], 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[48,49,50,51,52]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[53,54]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[55]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[55].

MYCN (MYCN proto-oncogene, bHLH transcription factor)

Background: The MYCN gene encodes the MYCN proto-oncogene (n-MYC), a basic helix-loop-helix transcription factor. MYCN is a member of the MYC oncogene family that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[56,57,58,59,60]. MYCN amplification is correlated with failure of cells to arrest in G1 phase

Biomarker Descriptions (continued)

of the cell cycle, leading to uncontrolled proliferation[61]. Like MYC, MYCN functions as a heterodimer in complex with the transcription factor MAX[58,62].

Alterations and prevalence: Recurrent somatic mutations in MYCN, including codon P44, are observed in approximately 2% of neuroblastoma with the same variants observed in Wilms' tumor[63,64]. MYCN amplification is found in 20 to 30% of neuroblastoma[65]. Amplification and overexpression of MYCN is also common in other central nervous system cancers as well as prostate cancer, hematologic malignancies, and pancreatic cancer[66].

Potential relevance: Currently, no therapies are approved for MYCN aberrations. Dysregulation of MYCN is associated with poor prognosis of several pediatric tumor types including neuroblastoma, Wilms' tumor, retinoblastoma, medulloblastoma, and rhabdomyosarcoma[61]. In neuroblastoma, increased MYCN signaling is directly related to tumor aggressiveness and increased metastatic potential[61,67]. Strategies targeting MYCN driven cancers currently focus on targeting MYCN expression, transcription, and synthetic lethality associated with MYCN overexpression[66].

Relevant Therapy Summary

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

ERBB2 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	✖	●	✖	✖	✖
trastuzumab deruxtecan, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
SAR-443216	✖	✖	✖	✖	● (I)
SHR-A1811	✖	✖	✖	✖	● (I)

AR amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bicalutamide	✖	○	✖	✖	✖
leuprorelin	✖	○	✖	✖	✖

* 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 2022-06-01. 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 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC

● 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 3.2022]

AR amplification

○ bicalutamide

Cancer type: Head and Neck Cancer **Variant class:** AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

○ leuprorelin

Cancer type: Head and Neck Cancer **Variant class:** AR positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

Clinical Trials in Taiwan region:

Clinical Trials Summary

ERBB2 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC

NCT ID	Title	Phase
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 2022-06-15. For the most up-to-date information, search www.fda.gov.

ERBB2 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC

trastuzumab deruxtecan

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

Supporting Statement:
The FDA has granted Breakthrough Designation for the HER2-directed antibody drug conjugate, Enhertu (trastuzumab deruxtecan), for the treatment of HER2 mutated metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based therapy.

Reference:

https://www.astrazeneca.com/media-centre/press-releases/2020/enhertu-granted-breakthrough-therapy-designation-in-the-us-for-her2-mutant-metastatic-non-small-cell-lung-cancer.html

ERBB2 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC (continued)

BDTX-189

Cancer type: Solid Tumor **Variant class:** ERBB2 mutation

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

AR amplification

enobosarm

Cancer type: Breast Cancer **Variant class:** AR positive

Other criteria: ERBB2 negative, ER positive

Supporting Statement:
The FDA has granted Fast Track Designation to enobosarm for AR+/ER+/HER2- in metastatic breast cancer.

Reference:

https://www.cancernetwork.com/view/fda-grants-fast-track-designation-to-enobosarm-in-ar-er-her2--metastatic-breast-cancer

seviteronel

Cancer type: Triple Negative Breast Cancer **Variant class:** AR positive

Supporting Statement:

The FDA has granted Fast Track Designation to the small-molecule CYP17 lyase-selective inhibitor, seviteronel, for:

- Androgen receptor (AR) positive advanced triple negative breast cancer (TNBC).
- Estrogen receptor (ER) positive advanced breast cancer.

Reference:

https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2022-06-01. 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 p.(L755_E757delinsPQ) c.2263_2269delTTGAGGGinsCCTC

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 3.2022]

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 3.2022]

Signatures

Testing Personnel:

2022.08.04
14:16:11 +08'00'

Laboratory Supervisor:

2022.08.04
14:16:22 +08'00'

Pathologist:

2022.08.04
14:16:34 +08'00'

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