Taipei Veterans General Hospital

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Sample Information

Patient Name: 尹正文
Gender: M
ID No.: S120840506
History No.: 44215761
Age: 51

Ordering Doctor: DOC6273E 葉雲凱
Ordering REQ.: 0APXGTT
Signing in Date: 2020/03/05

Path No.: S109-99206
MP No.: F2002
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-06420A
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

2 Clinically Significant Biomarkers
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Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	MET	Not detected
BRAF	Not detected	NTRK1	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	***ERBB2 exon 20 insertion***	RET	Not detected
KRAS	Not detected	ROS1	Not detected

Clinically Significant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
ERBB2 exon 20 insertion erb-b2 receptor tyrosine kinase 2 Tier: IA Allele Frequency: 28.34%	ado-trastuzumab emtansine	None	24

Sources included in relevant therapies: FDA[1], NCCN, EMA[2], ESMO

Clinically Significant Biomarkers (continued)

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
MYC amplification MYC proto-oncogene, bHLH transcription factor Tier: IIC	None	None	4

Sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Tier Criteria Met

Genomic Alteration	Tier Classification for Non-Small Cell Lung Cancer
ERBB2 exon 20 insertion Tier: IA	IA: Biomarker is included in NCCN or ESMO guidelines that predict response or resistance to therapies in this cancer type IIC: Biomarker is an inclusion criteria for clinical trials
MYC amplification Tier: IIC	IIC: Biomarker is an inclusion criteria for clinical trials

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	28.34%	NM_004448.3	nonframeshift Insertion	1976
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	47.34%	NM_002227.3	synonymous	1996
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	100.00%	NM_004304.4	missense	1999
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.85%	NM_004304.4	missense	1997
ALK	p.(=)	c.3375C>A	.	chr2:29445458	100.00%	NM_004304.4	synonymous	1994
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.80%	NM_000142.4	synonymous	1994
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	18.73%	NM_006206.5	synonymous	1997
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.85%	NM_006206.5	synonymous	1998
PDGFRA	p.(=)	c.2472C>T	.	chr4:55152040	20.15%	NM_006206.5	synonymous	2000
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.50%	NM_213647.2	missense	1999
FGFR4	p.(G544R)	c.1630G>A	.	chr5:176522441	28.86%	NM_213647.2	missense	1999
EGFR	p.(=)	c.2361G>A	.	chr7:55249063	51.80%	NM_005228.4	synonymous	2000
RET	p.(=)	c.2307G>T	.	chr10:43613843	49.12%	NM_020975.4	synonymous	1999

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
RET	p.(=)	c.2712C>G	.	chr10:43615633	49.55%	NM_020975.4	synonymous	1998

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	6.22

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 over-expression 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 clinical relevance: The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987[16] led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2[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. The novel bispecific antibody ZW25 has been granted fast-track designation (2019) by the FDA for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA)[24]. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[25,26,27,28,29]. Additionally, acquired HER2 mutations in ER+ breast cancer have been shown to confer resistance to hormone therapy[30]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[30].

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[31,32,33,34].

Biomarker Descriptions (continued)

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[35]. MYC functions as a heterodimer in complex with the transcription factor MAX[32,36].

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[37,38]. 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[13,39,40]. 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[41,42].

Potential clinical 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[31,43,44,45].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

ERBB2 exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ado-trastuzumab emtansine	✖	●	✖	✖	● (II)
afatinib	✖	✖	✖	✖	● (II)
chemotherapy, pertuzumab, trastuzumab	✖	✖	✖	✖	● (II)
chemotherapy, targeted therapy	✖	✖	✖	✖	● (II)
lapatinib	✖	✖	✖	✖	● (II)
neratinib, trastuzumab	✖	✖	✖	✖	● (II)
pertuzumab + trastuzumab	✖	✖	✖	✖	● (II)
pertuzumab, trastuzumab	✖	✖	✖	✖	● (II)
poziotinib	✖	✖	✖	✖	● (II)
pyrotinib	✖	✖	✖	✖	● (II)
RC-48	✖	✖	✖	✖	● (II)
sintilimab	✖	✖	✖	✖	● (II)
tarloxotinib	✖	✖	✖	✖	● (II)
trastuzumab deruxtecan	✖	✖	✖	✖	● (II)
anlotinib hydrochloride, CBT-502	✖	✖	✖	✖	● (I/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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

ERBB2 exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
DZD-9008	✖	✖	✖	✖	● (I/II)
TAK788	✖	✖	✖	✖	● (I/II)
everolimus + neratinib, neratinib + palbociclib, neratinib + trametinib	✖	✖	✖	✖	● (I)
pirotinib	✖	✖	✖	✖	● (I)

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
prexasertib	✖	✖	✖	✖	● (II)
VX-970	✖	✖	✖	✖	● (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 ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

NCCN information is current as of 2019-08-15. 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 targeted agents

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2019]

ERBB2 exon 20 insertion (continued)

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 HER2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with HER2 mutations."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2019]

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 HER2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with HER2 mutations."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2019]

Signatures

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Laboratory Supervisor: 2020.03.05 14:23:00 +08'00'

Pathologist: Yi-Chu Yeh 2020.03.05 14:23:19 +08'00'

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