Taipei Veterans General Hospital

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Sample Information

Patient Name: 王廷秀
Gender: Male
ID No.: H102057443
History No.: 22383397
Age: 84

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: D595AE2
Signing in Date: 2020/07/23

Path No.: S109-99749
MP No.: F20047
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-76768A
Percentage of tumor cells: 50%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page

Report Highlights

2 Relevant Biomarkers
1 Therapies Available
41 Clinical Trials

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	Not detected	RET	Not detected
KRAS	***KRAS p.(G12R) c.34G>C***	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
KRAS p.(G12R) c.34G>C KRAS proto-oncogene, GTPase Tier: IA Allele Frequency: 52.23%	None	cabozantinib **cetuximab** [1, 2] **panitumumab** [1] **cetuximab + chemotherapy** [2] **panitumumab + chemotherapy** [2]	37
CCND1 amplification cyclin D1 Tier: IIC	None	None	4

Public data sources included in relevant therapies: FDA1, 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
KRAS	p.(G12R)	c.34G>C	COSM518	chr12:25398285	52.23%	NM_033360.3	missense	1997
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	27.76%	NM_002227.3	synonymous	1747
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	100.00%	NM_004304.4	missense	1998
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.90%	NM_004304.4	missense	2000
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.90%	NM_004304.4	synonymous	1989
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	100.00%	NM_000142.4	synonymous	980
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	1998
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.34%	NM_213647.2	missense	1516
EGFR	p.(=)	c.2361G>A	.	chr7:55249063	60.55%	NM_005228.4	synonymous	1564
RET	p.(=)	c.2307G>T	.	chr10:43613843	100.00%	NM_020975.4	synonymous	1997

Copy Number Variations

Gene	Locus	Copy Number
CCND1	chr11:69456942	10.6

Biomarker Descriptions

CCND1 (cyclin D1)

Background: The CCND1 gene encodes the Cyclin D1 protein, which belongs to the highly conserved cyclin family that functions as regulators of cyclin-dependent kinases (CDKs)[1,2]. CCND1 binds and activates CDK4 and CDK6 to phosphorylate and inactivate the RB protein, which promotes progression through the G1/S phase transition of the cell cycle[3,4,5].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[6,7,8,9]. These mutations block phosphorylation-dependent nuclear export and proteolysis[10,11,12,13]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[6,8,14]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[15,16].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. Small molecule inhibitors targeting CDK4/6-- including palbociclib (2015), abemaciclib (2017), and ribociclib (2017)-- are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor positive, HER2-negative advanced or metastatic breast cancer. To date, CCND1 alterations are not indicated for CDK4/6 inhibitors.

KRAS (KRAS proto-oncogene, GTPase)

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[17,18,19].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[8]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[8,20,21]. Mutations at A59, K117, and A146 have also been observed but are less frequent[6,22].

Potential relevance: Currently, no therapies are approved for KRAS aberrations. However, the KRAS G12C inhibitor, AMG 510[23], was granted fast track designation (2019) for previously treated non-small cell lung cancer (NSCLC) patients with KRAS G12C mutations. The EGFR antagonists, cetuximab[24] and panitumumab[25], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[22]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[26].

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

KRAS p.(G12R) c.34G>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab	⊘	⊘	⊘	⊘	✖

* 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

KRAS p.(G12R) c.34G>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
panitumumab	⊘	⊘	✖	⊘	✖
cetuximab + oxaliplatin	✖	✖	⊘	✖	✖
panitumumab + oxaliplatin	✖	✖	⊘	✖	✖
cabozantinib	✖	✖	✖	○	✖
cetuximab + chemotherapy	✖	✖	✖	⊘	✖
panitumumab + chemotherapy	✖	✖	✖	⊘	✖
bevacizumab, chemotherapy	✖	✖	✖	✖	● (III)
lenvatinib, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
atezolizumab, cobimetinib	✖	✖	✖	✖	● (II)
regorafenib, chemotherapy	✖	✖	✖	✖	● (II)
spartalizumab	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
TVB-2640	✖	✖	✖	✖	● (II)
ulixertinib, selumetinib	✖	✖	✖	✖	● (II)
afatinib + selumetinib	✖	✖	✖	✖	● (I/II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)
binimetinib + palbociclib, binimetinib, palbociclib	✖	✖	✖	✖	● (I/II)
cobimetinib	✖	✖	✖	✖	● (I/II)
lapatinib, trametinib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
RMC-4630, cobimetinib	✖	✖	✖	✖	● (I/II)
selinexor + chemotherapy	✖	✖	✖	✖	● (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

KRAS p.(G12R) c.34G>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selumetinib, durvalumab, tremelimumab	✖	✖	✖	✖	● (I/II)
telaglenastat, palbociclib	✖	✖	✖	✖	● (I/II)
belvarafenib + cobimetinib	✖	✖	✖	✖	● (I)
BI-1701963, trametinib	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
KO-947	✖	✖	✖	✖	● (I)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	● (I)
LXH254 , spartalizumab	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
NBF-006	✖	✖	✖	✖	● (I)
neratinib + trametinib	✖	✖	✖	✖	● (I)
pembrolizumab + trametinib	✖	✖	✖	✖	● (I)
ponatinib, trametinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766	✖	✖	✖	✖	● (I)
RO-5126766, defactinib	✖	✖	✖	✖	● (I)
RO-5126766, everolimus + RO-5126766	✖	✖	✖	✖	● (I)
TAK 659, chemotherapy	✖	✖	✖	✖	● (I)

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)

* 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 ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

FDA information is current as of 2020-02-28. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12R) c.34G>C

⊘ cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2019-04-23 **Variant class:** KRAS G12 mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf

KRAS p.(G12R) c.34G>C (continued)

⊘ panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **Variant class:** KRAS G12 mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
- Limitation of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf

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 2019-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KRAS p.(G12R) c.34G>C

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]

panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]

KRAS p.(G12R) c.34G>C (continued)

EGFR tyrosine kinase inhibitor

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

Summary:
NCCN Guidelines® include the following supporting statement(s):

- "EGFR TKI therapy is not effective in patients with KRAS mutations, BRAF V600E mutations, ALK gene rearrangements, or ROS1 rearrangements."
- "KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

Current EMA Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

EMA information is current as of 2020-02-28. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12R) c.34G>C

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **Variant class:** KRAS exon 2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-24 **Variant class:** KRAS exon 2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated 👎 Not recommended 🛡 Resistance

ESMO information is current as of 2019-11-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12R) c.34G>C

○ cabozantinib

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** RAS mutation

ESMO Level of Evidence/Grade of Recommendation: II / C

Population segment (Line of therapy):
- Metastatic Thyroid Gland Medullary Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology (2019): mdz400, https://doi.org/10.1093/annonc/mdz400]

⊘ cetuximab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:
- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

KRAS p.(G12R) c.34G>C (continued)

⊘ cetuximab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

⊘ panitumumab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

KRAS p.(G12R) c.34G>C (continued)

⊘ panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

Signatures

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