Taipei Veterans General Hospital

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Sample Information

Patient Name: 林義賢
Gender: Male
ID No.: Q120542816
History No.: 46460462
Age: 58

Ordering Doctor: DOC3153J 黃煦晴
Ordering REQ.: 0AVUETR
Signing in Date: 2020/09/09

Path No.: S109-99982
MP No.: F20070
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-28573A
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Other Solid Tumor

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Report Highlights

1 Relevant Biomarkers
1 Therapies Available
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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*KRAS p.(Q61L) c.182_183delAAinsTT* KRAS proto-oncogene, GTPase Allele Frequency: 53.81%	None	cabozantinib	67

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.

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
KRAS	p.(Q61L)	c.182_183delAAinsTT	.	chr12:25380275	53.81%	NM_033360.3	missense	1994

Biomarker Descriptions

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[1,2,3].

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[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,5,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: Currently, no therapies are approved for KRAS aberrations. However, the KRAS G12C inhibitor, sotorasib (AMG 510)[9], was granted fast track designation (2019) for previously treated non-small cell lung cancer (NSCLC) patients with KRAS G12C mutations. The EGFR antagonists, cetuximab[10] and panitumumab[11], 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)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[12].

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.(Q61L) c.182_183delAAinsTT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab	⊘	⊘	⊘	⊘	✖
panitumumab	⊘	⊘	✖	⊘	✖
cetuximab + oxaliplatin	✖	✖	⊘	✖	✖
panitumumab + oxaliplatin	✖	✖	⊘	✖	✖
cabozantinib	✖	✖	✖	○	○ (IV)
cetuximab + chemotherapy	✖	✖	✖	⊘	✖
panitumumab + chemotherapy	✖	✖	✖	⊘	✖
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (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.(Q61L) c.182_183delAAinsTT (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
RMC-4630, cobimetinib	✖	✖	✖	✖	● (I/II)
zotatifin	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
LXH254 , spartalizumab	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
neratinib, trametinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
TAK 659, chemotherapy	✖	✖	✖	✖	● (I)
apatinib + chemotherapy	✖	✖	✖	✖	○ (IV)
bevacizumab, chemotherapy	✖	✖	✖	✖	○ (III)
lenvatinib, pembrolizumab, chemotherapy	✖	✖	✖	✖	○ (III)
aflibercept, chemotherapy	✖	✖	✖	✖	○ (II)
alpelisib	✖	✖	✖	✖	○ (II)
atezolizumab, cobimetinib	✖	✖	✖	✖	○ (II)
avelumab	✖	✖	✖	✖	○ (II)
bevacizumab + chemotherapy	✖	✖	✖	✖	○ (II)
binimetinib, palbociclib	✖	✖	✖	✖	○ (II)
cetuximab, chemotherapy	✖	✖	✖	✖	○ (II)
panitumumab, trametinib	✖	✖	✖	✖	○ (II)
pembrolizumab	✖	✖	✖	✖	○ (II)
ramucirumab, chemotherapy	✖	✖	✖	✖	○ (II)
regorafenib	✖	✖	✖	✖	○ (II)
regorafenib, chemotherapy	✖	✖	✖	✖	○ (II)
sintilimab, anlotinib hydrochloride	✖	✖	✖	✖	○ (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.(Q61L) c.182_183delAAinsTT (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
spartalizumab	✖	✖	✖	✖	○ (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	○ (II)
trametinib	✖	✖	✖	✖	○ (II)
trametinib, radiation therapy	✖	✖	✖	✖	○ (II)
TVB-2640	✖	✖	✖	✖	○ (II)
afatinib + selumetinib	✖	✖	✖	✖	○ (I/II)
binimetinib + palbociclib, binimetinib, palbociclib	✖	✖	✖	✖	○ (I/II)
BMS-986179, nivolumab	✖	✖	✖	✖	○ (I/II)
durvalumab, tremelimumab, chemotherapy	✖	✖	✖	✖	○ (I/II)
lapatinib, trametinib	✖	✖	✖	✖	○ (I/II)
onvansertib, chemotherapy, bevacizumab	✖	✖	✖	✖	○ (I/II)
selinexor, chemotherapy	✖	✖	✖	✖	○ (I/II)
selumetinib, durvalumab, tremelimumab	✖	✖	✖	✖	○ (I/II)
ABBV-621, chemotherapy, bevacizumab	✖	✖	✖	✖	○ (I)
adavosertib, chemotherapy	✖	✖	✖	✖	○ (I)
chemotherapy, binimetinib	✖	✖	✖	✖	○ (I)
COM701, nivolumab	✖	✖	✖	✖	○ (I)
GGTI-2418	✖	✖	✖	✖	○ (I)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	○ (I)
NBF-006	✖	✖	✖	✖	○ (I)
pembrolizumab + trametinib	✖	✖	✖	✖	○ (I)
RO-5126766	✖	✖	✖	✖	○ (I)
selinexor, pembrolizumab	✖	✖	✖	✖	○ (I)
siremadlin, trametinib	✖	✖	✖	✖	○ (I)
TNO-155, ribociclib	✖	✖	✖	✖	○ (I)

* 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.(Q61L) c.182_183delAAinsTT (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP-0903	✖	✖	✖	✖	○ (I)
trametinib, chemotherapy	✖	✖	✖	✖	○ (I)
trametinib, ruxolitinib	✖	✖	✖	✖	○ (I)
ulixertinib, antimalarial	✖	✖	✖	✖	○ (I)
utomilumab, cetuximab, chemotherapy	✖	✖	✖	✖	○ (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 ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

FDA information is current as of 2020-05-26. For the most up-to-date information, search www.fda.gov.

KRAS p.(Q61L) c.182_183delAAinsTT

⊘ cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2019-04-23 **Variant class:** KRAS Q61 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.(Q61L) c.182_183delAAinsTT (continued)

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **Variant class:** KRAS Q61 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 2020-05-01. 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.(Q61L) c.182_183delAAinsTT

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS exon 3 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 3.2020]

cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 3 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 4.2020]

panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS exon 3 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 3.2020]

panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 3 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 4.2020]

KRAS p.(Q61L) c.182_183delAAinsTT (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):

- "Non-responsiveness to EGFR TKI therapy is associated with KRAS and BRAF mutations and ALK or ROS1 gene fusions."
- "KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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 2020-05-26. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(Q61L) c.182_183delAAinsTT

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **Variant class:** KRAS exon 3 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 3 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 2020-05-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(Q61L) c.182_183delAAinsTT

○ 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 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

⊘ cetuximab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 3 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.(Q61L) c.182_183delAAinsTT (continued)

cetuximab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 3 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 3 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.(Q61L) c.182_183delAAinsTT (continued)

⊘ panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 3 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

Testing Personnel:

2020.09.11
17:07:07 +08'00'

Laboratory Supervisor:

2020.09.11
17:07:27 +08'00'

Pathologist:

2020.09.11
17:07:42 +08'00'

References

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