Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 黃文霙
Gender: Female
ID No.: A221763943
History No.: 47703117
Age: 52

Ordering Doctor: DOC2247H 郭伯仲
Ordering REQ.: 0BMQKPD
Signing in Date: 2021/10/28

Path No.: S110-99865
MP No.: F21089
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-92459A
Percentage of tumor cells: 30%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Thyroid Cancer

Table of Contents	Page

Report Highlights

1 Relevant Biomarkers
4 Therapies Available
0 Clinical Trials

Relevant Thyroid Cancer Variants

Gene	Finding
BRAF	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*NRAS p.(Q61K) c.181C>A* NRAS proto-oncogene, GTPase Allele Frequency: 18.78% **Prognostic significance:** None **Diagnostic significance:** None	cabozantinib	anti-CTLA-4 + anti-PD-1 anti-PD-1 binimetinib	0

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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
NRAS	p.(Q61K)	c.181C>A	COSM580	chr1:115256530	18.78%	NM_002524.5	missense	1986

Biomarker Descriptions

NRAS (NRAS proto-oncogene, GTPase)

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS 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. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[4,5]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[4,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[9] and panitumumab[10], are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[8]. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[11] as well as melanoma[12]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[13].

Relevant Therapy Summary

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

NRAS p.(Q61K) c.181C>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
binimetinib	✖	○	✖	✖	✖
cabozantinib	✖	✖	✖	●	✖
anti-CTLA-4 + anti-PD-1	✖	✖	✖	○	✖

Relevant Therapy Summary (continued)

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

NRAS p.(Q61K) c.181C>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
anti-PD-1	✖	✖	✖	○	✖

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 2021-08-02. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NRAS p.(Q61K) c.181C>A

○ **binimetinib**

Cancer type: Cutaneous Melanoma **Variant class:** NRAS mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2021-08-02. For the most up-to-date information, search www.esmo.org.

NRAS p.(Q61K) c.181C>A

● 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 (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

○ anti-CTLA-4 + anti-PD-1

Cancer type: Cutaneous Melanoma **Variant class:** NRAS mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

○ anti-PD-1

Cancer type: Cutaneous Melanoma **Variant class:** NRAS mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

Clinical Trials in Taiwan region:

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-08-18. For the most up-to-date information, search www.fda.gov.

NRAS p.(Q61K) c.181C>A

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-04-06 **Variant class:** NRAS 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/2021/125084s277s280lbl.pdf

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **Variant class:** NRAS 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

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-08-02. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NRAS p.(Q61K) c.181C>A

cetuximab

Cancer type: Colon Cancer **Variant class:** NRAS 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 2.2021]

---

cetuximab

Cancer type: Rectal Cancer **Variant class:** NRAS 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 1.2021]

---

panitumumab

Cancer type: Colon Cancer **Variant class:** NRAS 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 2.2021]

---

panitumumab

Cancer type: Rectal Cancer **Variant class:** NRAS 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 1.2021]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2021-08-18. For the most up-to-date information, search www.ema.europa.eu/ema.

NRAS p.(Q61K) c.181C>A

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **Variant class:** NRAS 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:** 2021-07-29 **Variant class:** NRAS exon 3 mutation

Reference:

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

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-08-02. For the most up-to-date information, search www.esmo.org.

NRAS p.(Q61K) c.181C>A

cetuximab

Cancer type: Colorectal Cancer **Variant class:** NRAS 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)]

NRAS p.(Q61K) c.181C>A (continued)

cetuximab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** NRAS 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:** NRAS 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)]

---

panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** NRAS 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:

Laboratory Supervisor:

Pathologist:

References

1. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
2. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
3. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
4. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
5. Janku et al. PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS ONE. 2011;6(7):e22769. PMID: 21829508
6. Ohashi et al. Characteristics of lung cancers harboring NRAS mutations. Clin. Cancer Res. 2013 May 1;19(9):2584-91. PMID: 23515407
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
9. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf
11. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2021]
12. Johnson et al. Treatment of NRAS-Mutant Melanoma. Curr Treat Options Oncol. 2015 Apr;16(4):15. doi: 10.1007/s11864-015-0330-z. PMID: 25796376
13. Dummer et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017 Apr;18(4):435-445. PMID: 28284557