Taipei Veterans General Hospital

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Sample Information

Patient Name: 胡淑娟
Gender: Female
ID No.: A201592153
History No.: 8553295
Age: 66

Ordering Doctor: DOC1885G楊慕華
Ordering REQ.: 0AXYUQC
Signing in Date: 2020/11/04

Path No.: S109-89815
MP No.: F20094
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-42700A
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Melanoma

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Report Highlights

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Relevant Melanoma Findings

Gene	Finding
BRAF	Not detected
KIT	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*NRAS p.(Q61R) c.182A>G* NRAS proto-oncogene, GTPase Allele Fraction: 0.521	anti-CTLA-4 + anti-PD-1 anti-PD-1 binimetinib	cabozantinib	20

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.

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
NRAS	p.(Q61R)	c.182A>G	COSM584	chr1:115256529	0.521	NM_002524.4	missense	1990

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.(Q61R) c.182A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
binimetinib	✖	●	✖	✖	✖

* 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 ✖ No evidence

NRAS p.(Q61R) c.182A>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
anti-CTLA-4 + anti-PD-1	✖	✖	✖	●	✖
anti-PD-1	✖	✖	✖	●	✖
cabozantinib	✖	✖	✖	○	✖
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
trametinib, dabrafenib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
trametinib, antimalarial	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
FCN-159	✖	✖	✖	✖	● (I)
IN10018, cobimetinib	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	● (I)
LXH254 , spartalizumab	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
MLN-2480	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (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

NCCN information is current as of 2020-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NRAS p.(Q61R) c.182A>G

● binimetinib

Cancer type: Melanoma

Variant class: NRAS mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy; Progression after prior immune checkpoint inhibitor therapy (Second-line or subsequent therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 3.2020]

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 2020-09-01. For the most up-to-date information, search www.esmo.org.

NRAS p.(Q61R) c.182A>G

● anti-CTLA-4 + anti-PD-1

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

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz41]

● anti-PD-1

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

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz41]

○ 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]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance

FDA information is current as of 2020-09-16. For the most up-to-date information, search www.fda.gov.

NRAS p.(Q61R) c.182A>G

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2019-04-23 **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/2019/125084s273lbl.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

NCCN information is current as of 2020-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NRAS p.(Q61R) c.182A>G

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 4.2020]

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 6.2020]

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 4.2020]

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 6.2020]

Current EMA Information

Contraindicated Not recommended Resistance

EMA information is current as of 2020-09-16. For the most up-to-date information, search www.ema.europa.eu/ema.

NRAS p.(Q61R) c.182A>G

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:** 2020-01-24 **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

ESMO information is current as of 2020-09-01. For the most up-to-date information, search www.esmo.org.

NRAS p.(Q61R) c.182A>G

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.(Q61R) c.182A>G (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)]

NRAS p.(Q61R) c.182A>G (continued)

⊘ 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:

2020.11.05
09:34:28 +08'00'

Laboratory Supervisor:

2020.11.05
09:34:41 +08'00'

Pathologist:

2020.11.05
09:34:58 +08'00'

References

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2. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
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