Taipei Veterans General Hospital

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Sample Information

Patient Name: 林陳月霞
Gender: Female
ID No.: Y200506885
History No.: 29181893
Age: 78

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: D567J2P
Signing in Date: 2020/06/11

Path No.: S109-99578
MP No.: F20032
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S108-36515A
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Thyroid Cancer

Report Highlights

1 Relevant Biomarkers
4 Therapies Available
17 Clinical Trials

Relevant Thyroid Cancer Findings

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

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
NRAS p.(Q61R) c.182A>G NRAS proto-oncogene, GTPase Tier: IA Allele Frequency: 44.97%	cabozantinib	binimetinib anti-CTLA-4 + anti-PD-1 anti-PD-1 **cetuximab** [1, 2]	17

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.

Relevant Biomarkers (continued)

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		panitumumab [1]	
		cetuximab + chemotherapy [2]	
		panitumumab + chemotherapy [2]	

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
NRAS	p.(Q61R)	c.182A>G	COSM584	chr1:115256529	44.97%	NM_002524.4	missense	1997
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.75%	NM_004304.4	missense	1997
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.80%	NM_004304.4	missense	1996
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.85%	NM_004304.4	synonymous	1995
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.78%	NM_000142.4	synonymous	459
PDGFRA	p.(=)	c.939T>G	.	chr4:55133726	49.50%	NM_006206.5	synonymous	1994
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.70%	NM_006206.5	synonymous	1998
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.13%	NM_213647.2	missense	1385
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	13.69%	NM_213647.2	synonymous	716
EGFR	p.(V592I)	c.1774G>A	.	chr7:55233024	48.72%	NM_005228.4	missense	1999
MET	p.(N375S)	c.1124A>G	.	chr7:116340262	51.20%	NM_001127500.2	missense	2000
RET	p.(=)	c.2307G>T	.	chr10:43613843	51.81%	NM_020975.4	synonymous	1488

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].

Biomarker Descriptions (continued)

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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab	⊘	⊘	⊘	⊘	✖
panitumumab	⊘	⊘	✖	⊘	✖
binimetinib	✖	○	✖	✖	✖
cetuximab + oxaliplatin	✖	✖	⊘	✖	✖
panitumumab + oxaliplatin	✖	✖	⊘	✖	✖
cabozantinib	✖	✖	✖	●	● (IV)
anti-CTLA-4 + anti-PD-1	✖	✖	✖	○	✖
anti-PD-1	✖	✖	✖	○	✖
cetuximab + chemotherapy	✖	✖	✖	⊘	✖
panitumumab + chemotherapy	✖	✖	✖	⊘	✖
atezolizumab, cobimetinib	✖	✖	✖	✖	● (II)
trametinib	✖	✖	✖	✖	● (II)
trametinib, radiation therapy	✖	✖	✖	✖	● (II)
ulixertinib, selumetinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)
cobimetinib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
belvarafenib + cobimetinib	✖	✖	✖	✖	● (I)
KO-947	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus + RO-5126766	✖	✖	✖	✖	● (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 2020-02-28. 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

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

⊘ 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

● 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.

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 1.2020]

⊘ 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 1.2020]

⊘ 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 1.2020]

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

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 1.2020]

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 1.2020]

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.

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

● 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.

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

● 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]

○ 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 (2019), mdz411, https://doi.org/10.1093/annonc/mdz411]

○ 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 (2019), mdz411, https://doi.org/10.1093/annonc/mdz411]

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

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)]

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

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Pathologist:
Yi-Chu Yeh 2020.06.11 18:22:37 +08'00'

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/2019/125084s273lbl.pdf
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf
11. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2020]
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