



Sample Information

Patient Name: 徐榮忠
Gender: Male
ID No.: F102685436
History No.: 50092610
Age: 77

Ordering Doctor: DOC3160J 羅永鴻
Ordering REQ.: D7A3FE9
Signing in Date: 2024/1/22

Path No.: M113-00019
MP No.: F24010
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-64118A
Percentage of tumor cells: 80%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page	Report Highlights
Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)	2	1 Relevant Biomarkers
Biomarker Descriptions	2	1 Therapies Available
Relevant Therapy Summary	3	0 Clinical Trials
Relevant Therapy Details	3	
Alert Details	6	

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	KRAS p.(G12F) c.34_35delGGinsTT	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	KRAS p.(G12F) c.34_35delGGinsTT KRAS proto-oncogene, GTPase Allele Frequency: 50.68%	None	bevacizumab + chemotherapy	0

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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.(G12F)	c.34_35delGGinsTT	COSM512	chr12:25398284	50.68%	NM_033360.4	missense	1995
FGFR4	p.(A553=)	c.1659C>T	.	chr5:176522562	63.70%	NM_213647.3	synonymous	2000

Biomarker Descriptions

KRAS p.(G12F) c.34_35delGGinsTT

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 cancer⁴. 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: The FDA has approved the small molecule inhibitors, sotorasib⁹ (2021) and adagrasib¹⁰ (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036¹¹, for KRAS G12C mutation in non-small cell lung cancer. The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer¹². The PLK1 inhibitor, onvansertib¹³, was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). Additionally, the SHP2 inhibitor, BBP-398¹⁴ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The EGFR antagonists, cetuximab¹⁵ and panitumumab¹⁶, 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 NSCLC¹⁷.

Relevant Therapy Summary

☒ In this cancer type

☐ In other cancer type

☒ In this cancer type and other cancer types

☒ No evidence

KRAS p.(G12F) c.34_35delGGinsTT					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	×	×	×	○	×
bevacizumab + FOLFIRI	×	×	×	○	×
bevacizumab + FOLFOX	×	×	×	○	×
bevacizumab + FOLFOXIRI	×	×	×	○	×

Relevant Therapy Details

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 2023-12-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12F) c.34_35delGGinsTT

☐ bevacizumab + CAPOX

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

☐ bevacizumab + FOLFOX

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

KRAS p.(G12F) c.34_35delGGinsTT (continued)

○ bevacizumab + FOLFOXIRI

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 2

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

○ bevacizumab + CAPOX

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Resectable (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

○ bevacizumab + FOLFIRI

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Resectable (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

○ bevacizumab + FOLFOX

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Resectable (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

KRAS p.(G12F) c.34_35delGGinsTT (continued)

○ bevacizumab + FOLFOXIRI

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

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

Population segment (Line of therapy):

- Resectable (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

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 2023-12-13. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12F) c.34_35delGGinsTT

cetuximab

Cancer type: Colorectal Cancer

Label as of: 2021-09-24

Variant class: KRAS G12 mutation

Indications and usage:

Erbix® 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.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

- in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

KRAS p.(G12F) c.34_35delGGinsTT (continued)**🚫 panitumumab****Cancer type:** Colorectal Cancer**Label as of:** 2021-08-25**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/2021/125147s210lbl.pdf

A bevacizumab + onvansertib + FOLFIRI**Cancer type:** Colorectal Cancer**Variant class:** KRAS mutation**Supporting Statement:**

The FDA has granted Fast Track Designation to the Polo-like Kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab, for KRAS mutations in metastatic colorectal cancer in the second line.

Reference:

<https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer>

Current NCCN Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

NCCN information is current as of 2023-12-01. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org).

For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

All guidelines cited below are referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) National Comprehensive Cancer Network, Inc. 2023. All rights reserved. NCCN makes no warranties regarding their content.

KRAS p.(G12F) c.34_35delGGinsTT

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, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2023]

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 (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 6.2023]

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, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2023]

KRAS p.(G12F) c.34_35delGGinsTT (continued)**🚫 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 (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 6.2023]

Current EMA Information**🚫** Contraindicated**⊖** Not recommended**🛡** Resistance**🚀** Breakthrough**A** Fast TrackEMA information is current as of 2023-12-13. For the most up-to-date information, search www.ema.europa.eu/ema.**KRAS p.(G12F) c.34_35delGGinsTT****🚫 cetuximab, cetuximab + oxaliplatin**

Cancer type: Colorectal Cancer

Label as of: 2022-05-25

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: 2022-07-06

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

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

ESMO information is current as of 2023-12-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12F) c.34_35delGGinsTT

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

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