



## Sample Information

**Patient Name:** 潘明賜

**Gender:** Male

**ID No.:** T121538908

**History No.:** 46168369

**Age:** 60

**Ordering Doctor:** DOC3109L 邱昭華

**Ordering REQ.:** D57B8F5

**Signing in Date:** 2020/07/01

**Path No.:** S109-99652

**MP No.:** F20040

**Assay:** Oncomine Focus Assay

**Sample Type:** FFPE

**Block No.:** S109-15771A+B

**Percentage of tumor cells:** 50%

**Note:**

## Sample Cancer Type: Non-Small Cell Lung Cancer

### Table of Contents

	Page
Variant Details	2
Biomarker Descriptions	2
Relevant Therapy Summary	3
Relevant Therapy Details	6

### Report Highlights

1 Relevant Biomarkers  
1 Therapies Available  
39 Clinical Trials

## Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	<b>KRAS p.(G12V) c.35G&gt;T</b>	ROS1	Not detected
MET	Not detected		



## Relevant Biomarkers

■ Indicated ■ Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
<b>KRAS p.(G12V) c.35G&gt;T</b> KRAS proto-oncogene, GTPase Tier: IA Allele Frequency: 24.19%	None	<span style="color: green;">■</span> cabozantinib <span style="color: red;">■</span> cetuximab <sup>1, 2</sup> <span style="color: red;">■</span> panitumumab <sup>1</sup> <span style="color: red;">■</span> cetuximab + chemotherapy <sup>2</sup> <span style="color: red;">■</span> panitumumab + chemotherapy <sup>2</sup>	39

Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	24.19%	NM_033360.3	missense	1997
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	48.29%	NM_002227.3	synonymous	1988
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	49.15%	NM_004304.4	missense	1996
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.90%	NM_004304.4	missense	1997
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.95%	NM_004304.4	synonymous	1992
IDH1	p.(=)	c.315C>T	.	chr2:209113192	52.38%	NM_005896.3	synonymous	1997
FGFR3	p.(G90del)	c.268_270delGGG	.	chr4:1801137	48.26%	NM_000142.4	nonframeshift Deletion	1927
FGFR3	p.(Q92fs)	c.274delC	.	chr4:1801141	46.81%	NM_000142.4	frameshift Deletion	1927
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.95%	NM_000142.4	synonymous	1992
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.80%	NM_006206.5	synonymous	1997
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.30%	NM_213647.2	missense	2000
RET	p.(=)	c.2307G>T	.	chr10:43613843	52.53%	NM_020975.4	synonymous	1997
RET	p.(=)	c.2712C>G	.	chr10:43615633	47.97%	NM_020975.4	synonymous	1999

## 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<sup>1,2,3</sup>.



## Biomarker Descriptions (continued)

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

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

## 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.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab	⛔	⛔	⛔	⛔	✕
panitumumab	⛔	⛔	✕	⛔	✕
cetuximab + oxaliplatin	✕	✕	⛔	✕	✕
panitumumab + oxaliplatin	✕	✕	⛔	✕	✕
cabozantinib	✕	✕	✕	○	✕
cetuximab + chemotherapy	✕	✕	✕	⛔	✕
panitumumab + chemotherapy	✕	✕	✕	⛔	✕
bevacizumab, chemotherapy	✕	✕	✕	✕	● (III)
lenvatinib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
atezolizumab, cobimetinib	✕	✕	✕	✕	● (II)
regorafenib, chemotherapy	✕	✕	✕	✕	● (II)
spartalizumab	✕	✕	✕	✕	● (II)
targeted therapy, chemotherapy	✕	✕	✕	✕	● (II)
TVB-2640	✕	✕	✕	✕	● (II)
ulixertinib, selumetinib	✕	✕	✕	✕	● (II)
afatinib + selumetinib	✕	✕	✕	✕	● (I/II)
anti-KRAS G12V mTCR	✕	✕	✕	✕	● (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.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ASTX029	✕	✕	✕	✕	● (I/II)
avelumab, binimetinib, talazoparib	✕	✕	✕	✕	● (I/II)
binimetinib + palbociclib, binimetinib, palbociclib	✕	✕	✕	✕	● (I/II)
cobimetinib	✕	✕	✕	✕	● (I/II)
lapatinib, trametinib	✕	✕	✕	✕	● (I/II)
mirdametinib, lifirafenib	✕	✕	✕	✕	● (I/II)
navitoclax, trametinib	✕	✕	✕	✕	● (I/II)
neratinib, valproic acid	✕	✕	✕	✕	● (I/II)
RMC-4630, cobimetinib	✕	✕	✕	✕	● (I/II)
selinexor + chemotherapy	✕	✕	✕	✕	● (I/II)
selumetinib, durvalumab, tremelimumab	✕	✕	✕	✕	● (I/II)
telaglenastat, palbociclib	✕	✕	✕	✕	● (I/II)
belvarafenib + cobimetinib	✕	✕	✕	✕	● (I)
BI-1701963, trametinib	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
KO-947	✕	✕	✕	✕	● (I)
LXH254, LTT-462, trametinib, ribociclib	✕	✕	✕	✕	● (I)
LXH254, spartalizumab	✕	✕	✕	✕	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✕	✕	✕	✕	● (I)
mRNA-5671, pembrolizumab	✕	✕	✕	✕	● (I)
NBF-006	✕	✕	✕	✕	● (I)
neratinib + trametinib	✕	✕	✕	✕	● (I)
pembrolizumab + trametinib	✕	✕	✕	✕	● (I)
ponatinib, trametinib	✕	✕	✕	✕	● (I)
RMC-4630	✕	✕	✕	✕	● (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.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
RO-5126766	✕	✕	✕	✕	● (I)
RO-5126766, defactinib	✕	✕	✕	✕	● (I)
RO-5126766, everolimus + RO-5126766	✕	✕	✕	✕	● (I)
TAK 659, 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 2020-02-28. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

### KRAS p.(G12V) c.35G>T

#### ☒ cetuximab

Cancer type: Colorectal Cancer

Label as of: 2019-04-23

Variant class: KRAS G12 mutation

#### Indications and usage:

Erbixux® 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf)

**KRAS p.(G12V) c.35G>T (continued)****🚫 panitumumab****Cancer type:** Colorectal Cancer**Label as of:** 2017-06-29**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/2017/125147s207lbl.pdf](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](http://www.nccn.org).  
For NCCN International Adaptations & Translations, search [www.nccn.org/global/international\\_adaptations.aspx](http://www.nccn.org/global/international_adaptations.aspx).

### KRAS p.(G12V) c.35G>T

#### ☒ 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."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

#### ☒ 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 (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]

#### ☒ 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."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

#### ☒ 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 (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]





## KRAS p.(G12V) c.35G>T (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):

- "EGFR TKI therapy is not effective in patients with KRAS mutations, BRAF V600E mutations, ALK gene rearrangements, or ROS1 rearrangements."
- "KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



## 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](http://www.ema.europa.eu/ema).

### KRAS p.(G12V) c.35G>T

#### ☒ cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2020-01-30

Variant class: KRAS exon 2 mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information\\_en.pdf](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 2 mutation

Reference:

[https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information\\_en.pdf](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](http://www.esmo.org).

### KRAS p.(G12V) c.35G>T

#### ☐ 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>]

#### ☒ cetuximab

**Cancer type:** Colorectal Cancer

**Variant class:** KRAS exon 2 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.(G12V) c.35G>T (continued)

### ⊘ cetuximab + chemotherapy

**Cancer type:** Colorectal Cancer

**Variant class:** KRAS exon 2 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 2 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.(G12V) c.35G>T (continued)

### 🚫 panitumumab + chemotherapy

Cancer type: Colorectal Cancer

Variant class: KRAS exon 2 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:



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