



## Sample Information

**Patient Name:** 張鐵軍  
**Gender:** Male  
**ID No.:** C101221506  
**History No.:** 17484296  
**Age:** 72

**Ordering Doctor:** DOC3016D 江起陸  
**Ordering REQ.:** OBLVKNU  
**Signing in Date:** 2021/10/06

**Path No.:** S110-99713  
**MP No.:** F21081  
**Assay:** Oncomine Focus Assay  
**Sample Type:** FFPE  
**Block No.:** C110-31606  
**Percentage of tumor cells:** 60%

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

**Note:**

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

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### Report Highlights

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- 3 Clinical Trials

## 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	<b>KRAS p.(G12C) c.34G&gt;T</b>	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
IA	<b>KRAS p.(G12C) c.34G&gt;T</b> KRAS proto-oncogene, GTPase Allele Frequency: 8.26% <b>Prognostic significance:</b> None <b>Diagnostic significance:</b> None	sotorasib <sup>1</sup>	cabozantinib	3

Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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.

## Variant Details

### DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	8.26%	NM_033360.4	missense	1997
JAK1	p.(P733=)	c.2199A>G	.	chr1:65310489	50.20%	NM_002227.4	synonymous	1994
PIK3CA	p.(L429F)	c.1287G>C	.	chr3:178928009	8.08%	NM_006218.4	missense	458
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.75%	NM_213647.3	missense	2000
FGFR1	p.(T726=)	c.2178T>G	.	chr8:38271771	6.03%	NM_001174067.1	synonymous	1858
RET	p.(L769=)	c.2307G>T	.	chr10:43613843	100.00%	NM_020975.6	synonymous	1997
JAK3	p.(L485=)	c.1453C>T	.	chr19:17949188	49.15%	NM_000215.4	synonymous	2000

## 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>.

**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:** The KRAS inhibitor, sotorasib<sup>9</sup>, is approved (2021) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has granted breakthrough therapy designation (2021) to the small molecule inhibitor, adagrasib, for KRAS G12C positive in non-small cell lung cancer following prior systemic therapy<sup>10</sup>. The small molecular inhibitor, RO-5126766, was also 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 cancer<sup>11</sup>. Additionally, onvansertib<sup>12</sup> was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab<sup>13</sup> and panitumumab<sup>14</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>15</sup>.

## Relevant Therapy Summary

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

### KRAS p.(G12C) c.34G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sotorasib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
cabozantinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
D-1553	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (I/II)
RMC-4630, pembrolizumab	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (I/II)
mRNA-5671, pembrolizumab	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (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

FDA information is current as of 2021-08-18. For the most up-to-date information, search [www.fda.gov](https://www.fda.gov).

### KRAS p.(G12C) c.34G>T

#### ☒ sotorasib

Cancer type: Non-Small Cell Lung Cancer

Label as of: 2021-05-28

Variant class: KRAS G12C mutation

#### Indications and usage:

LUMAKRAS™ is an inhibitor of the RAS GTPase family indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

#### Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/214665s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf)

## 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](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.(G12C) c.34G>T

#### ● sotorasib

Cancer type: Non-Small Cell Lung Cancer

Variant class: KRAS G12C mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Large Cell, Non-squamous Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 5.2021]

## 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](http://www.esmo.org).

### KRAS p.(G12C) c.34G>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 (First-line therapy)

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

## Clinical Trials in Taiwan region:

### Clinical Trials Summary

#### KRAS p.(G12C) c.34G>T

NCT ID	Title	Phase
NCT03948763	A Phase I, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma	I
NCT04418661	A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I/II
NCT04585035	A Phase I/II, Open Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of D-1553 in Subjects With Advanced or Metastatic Solid Tumors With KRasG12C Mutation	I/II

### 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](http://www.fda.gov).

#### KRAS p.(G12C) c.34G>T

#### cetuximab

**Cancer type:** Colorectal Cancer

**Label as of:** 2021-04-06

**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:** Erbixux® 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf)

## KRAS p.(G12C) c.34G>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)

### adagrasib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Breakthrough Designation to the small molecule inhibitor, adagrasib, for KRAS G12C positive in non-small cell lung cancer following prior systemic therapy.

**Reference:**

<https://ir.mirati.com/press-releases/press-release-details/2021/Mirati-Therapeutics-Adagrasib-Receives-Breakthrough-Therapy-Designation-from-U.S.-Food-and-Drug-Administration-for-Patients-with-Advanced-Non-Small-Cell-Lung-Cancer-Harboring-the-KRAS-G12C-Mutation/default.aspx>

### defactinib + RO-5126766

**Cancer type:** Endometrial Carcinoma

**Variant class:** KRAS mutation

**Supporting Statement:**

The FDA has granted Breakthrough Designation to the small molecule inhibitor, RO-5126766 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 cancer.

**Reference:**

<https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs>

### 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 2021-08-02. 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.(G12C) c.34G>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 2.2021]

#### 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 1.2021]

#### 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 2.2021]

#### 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 1.2021]



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

### KRAS p.(G12C) c.34G>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: 2021-07-29

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

 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](http://www.esmo.org).

### KRAS p.(G12C) c.34G>T

#### 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.(G12C) c.34G>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)]

### ⊘ 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)]

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## Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

## References

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11. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs>
12. <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>
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