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Tel: 02-2875-7449

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Sample Information

Patient Name: 黃勇 Gender: Male ID No.: A102180851 History No.: 19725281

Age: 79

Ordering Doctor: DOC6486C 許庭瑞

Ordering REQ.: 0CVJXME Signing in Date: 2024/1/4

Path No.: M113-00002 **MP No.:** F24001

Assay: Oncomine Focus Assay

Sample Type: FFPE Block No.: C112-46703A Percentage of tumor cells: 40%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

- 1 Relevant Biomarkers
- 1 Therapies Available
- 0 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	KRAS p.(G12A) c.35G>C	ROS1	None detected	
MET	None detected			

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	KRAS p.(G12A) c.35G>C	None	bevacizumab + chemotherapy	0
	KRAS proto-oncogene, GTPase Allele Frequency: 52.81%			

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 vari	ants						
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KRAS	p.(G12A)	c.35G>C	COSM522	chr12:25398284	52.81%	NM_033360.4	missense	1990

Biomarker Descriptions

KRAS p.(G12A) c.35G>C

KRAS proto-oncogene, GTPase

<u>Background:</u> 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	O In other cancer type	In this cancer	type and other car	ncer types	✗ No eviden	ce
KRAS p.(G12A)	c.35G>C					
Relevant Therapy		FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPO	Х	×	×	×	0	×

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Relevant Therapy Summary (continued)

In this cancer type

O In other cancer type

In this cancer type and other cancer types

× No evidence

KRAS p.(G12A) c.35G>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + FOLFIRI	×	×	×	0	×
bevacizumab + FOLFOX	×	×	×	0	×
bevacizumab + FOLFOXIRI	×	×	×	0	×

Relevant Therapy Details

Current ESMO Information

In this cancer type

O In other cancer type

In this cancer type and other cancer types

ESMO information is current as of 2023-11-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12A) c.35G>C

O 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)]

O 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

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KRAS p.(G12A) c.35G>C (continued)

O 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)]

O 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)]

O 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)]

O 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)

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KRAS p.(G12A) c.35G>C (continued)

O 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)

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Clinical Trials in Taiwan region:

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended

Resistance

Breakthrough

A Fast Track

FDA information is current as of 2023-11-15. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12A) c.35G>C

cetuximab

Cancer type: Colorectal Cancer Label as of: 2021-09-24 Variant class: KRAS G12 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 platinumbased 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

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KRAS p.(G12A) c.35G>C (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 irinotecancontaining 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

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

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Current NCCN Information

Contraindicated

Not recommended



Breakthrough

Fast Track

NCCN information is current as of 2023-11-01. To view the most recent and complete version of the guideline, go online to 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.(G12A) c.35G>C

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 3.2023]

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 5.2023]

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 3.2023]

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KRAS p.(G12A) c.35G>C (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 5.2023]

Current EMA Information

EMA information is current as of 2023-11-15. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12A) c.35G>C

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

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Current ESMO Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

ESMO information is current as of 2023-11-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12A) c.35G>C

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]".

References

- 1. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
- Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
- Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/ PPO.0000000000187. 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. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. Mol Cancer. 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
- Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer-preliminary study. J Med Life. 2014 Oct-Dec;7(4):581-7. PMID: 25713627
- 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
- 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
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214665s004lbl.pdf
- 10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/2163400rig1s000Corrected_lbl.pdf
- 11. https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf
- https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-reports-third-quarter-2022-financialresults
- 13. 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
- 14. https://bridgebio.com/news/bridgebio-pharma-announces-first-lung-cancer-patient-dosed-in-phase-1-2-trial-and-us-fda-fast-track-designation-for-shp2-inhibitor-bbp-398-in-combination-with-amgens-lumakras-sotorasib/
- 15. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
- 16. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf
- 17. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N. Engl. J. Med. 1990 Aug 30;323(9):561-5. PMID: 2199829