



Sample Information

Patient Name: 曾光星
Gender: Male
ID No.: E100322971
History No.: 41674059
Age: 69

Ordering Doctor: DOC6238J 李君陽
Ordering REQ.: 0CBVJQN
Signing in Date: 2022/11/03

Path No.: S111-97972
MP No.: F22120
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-07523B
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Pancreatic Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	1 Relevant Biomarkers
Biomarker Descriptions	2	0 Therapies Available
Alert Details	3	0 Clinical Trials

Relevant Pancreatic Cancer Variants

Gene	Finding
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected

Relevant Biomarkers

No relevant biomarkers found in this sample.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KRAS	p.(G13D)	c.38G>A	COSM532	chr12:25398281	5.17%	NM_033360.4	missense	1991
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	48.72%	NM_004304.5	missense	1993
ALK	p.(G1125=)	c.3375C>A	.	chr2:29445458	48.34%	NM_004304.5	synonymous	1990
FGFR3	p.(G90del)	c.268_270delGGG	.	chr4:1801137	44.32%	NM_000142.4	nonframeshift Deletion	1909
FGFR3	p.(Q92Sfs*6)	c.274delC	.	chr4:1801141	23.78%	NM_000142.4	frameshift Deletion	1909
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.05%	NM_213647.3	missense	2000
EGFR	p.(Q787=)	c.2361G>A	.	chr7:55249063	52.20%	NM_005228.5	synonymous	2000
RET	p.(L769=)	c.2307G>T	.	chr10:43613843	99.90%	NM_020975.6	synonymous	1991

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^{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 KRAS inhibitor, sotorasib⁹, 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 therapy¹⁰. 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 cancer¹¹. Additionally, onvansertib¹² was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab¹³ and panitumumab¹⁴, 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 NSCLC¹⁵.

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 2022-08-17. For the most up-to-date information, search www.fda.gov.

KRAS p.(G13D) c.38G>A

cetuximab

Cancer type: Colorectal Cancer

Label as of: 2021-09-24

Variant class: KRAS G13 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: Erbix® 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.(G13D) c.38G>A (continued)

panitumumab

Cancer type: Colorectal Cancer

Label as of: 2021-08-25

Variant class: KRAS G13 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

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 2022-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KRAS p.(G13D) c.38G>A

cetuximab

Cancer type: Colon Cancer

Variant class: KRAS G13D mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

cetuximab

Cancer type: Rectal Cancer

Variant class: KRAS G13D mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

panitumumab

Cancer type: Colon Cancer

Variant class: KRAS G13D mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

panitumumab

Cancer type: Rectal Cancer

Variant class: KRAS G13D mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

KRAS p.(G13D) c.38G>A (continued)**⊘ 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 1.2022]**⊘ 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 1.2022]**⊘ 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 1.2022]**⊘ 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 1.2022]

Current EMA Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

EMA information is current as of 2022-08-17. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G13D) c.38G>A

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 2022-08-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G13D) c.38G>A

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.(G13D) c.38G>A (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)]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

References

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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
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