Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
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## Sample Information

**Patient Name:** 薛仲義
**Gender:** Male
**ID No.:** W100070325
**History No.:** 23449889
**Age:** 58

**Ordering Doctor:** DOC3153J 黃煦晴
**Ordering REQ.:** 0CSPQMZ
**Signing in Date:** 2023/11/02

**Path No.:** M112-00279
**MP No.:** F23079
**Assay:** Oncomine Focus Assay
**Sample Type:** FFPE
**Block No.:** S112-53183A
**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
3 Therapies Available
8 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.(G12C) c.34G>T*** | 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 | *KRAS p.(G12C) c.34G>T*<br>KRAS proto-oncogene, GTPase<br>Allele Frequency: 31.56% | **adagrasib** [1]<br>**sotorasib** [1, 2] | adagrasib<br>bevacizumab + chemotherapy<br>sotorasib | 8 |

**Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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.

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*SMO p.(Q477K) c.1429C>A*

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect | Coverage |
|---|---|---|---|---|---|---|---|---|
| SMO | p.(Q477K) | c.1429C>A | . | chr7:128849201 | 19.77% | NM_005631.5 | missense | 1998 |
| KRAS | p.(G12C) | c.34G>T | COSM516 | chr12:25398285 | 31.56% | NM_033360.4 | missense | 1996 |
| ALK | p.(D1529E) | c.4587C>G | . | chr2:29416366 | 51.50% | NM_004304.5 | missense | 2000 |
| FGFR4 | p.(P136L) | c.407C>T | . | chr5:176517797 | 99.70% | NM_213647.3 | missense | 2000 |
| MET | p.(N375S) | c.1124A>G | . | chr7:116340262 | 49.30% | NM_001127500.3 | missense | 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[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 cancer[4]. 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, sotorasib[9] (2021) and adagrasib[10] (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-6036[11], 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 cancer[12]. The PLK1 inhibitor, onvansertib[13], 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-398[14] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC.The EGFR antagonists, cetuximab[15] and panitumumab[16], 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 NSCLC[17].

**SMO (smoothened, frizzled class receptor)**

Background: The SMO gene encodes the smoothened, frizzled class receptor, a transmembrane G protein-coupled receptor that is part of the Hedgehog (Hh) signaling pathway[18]. SMO is negatively regulated by the tumor suppressor gene patched transmembrane receptor (PTCH). However, binding of the ligand sonic hedgehog (Shh) stops this inhibition thereby activating downstream genes

## Biomarker Descriptions (continued)

such as glioma-associated (GLI) transcription factors[19]. Consequently, aberrations in SMO leading to constitutive activation have been identified to promote oncogenesis in certain cancer types including basal cell carcinoma (BCC)[20,21,22].

Alterations and prevalence: Somatic mutations in SMO are observed in 10% of BCC and medulloblastoma, and in 5% of uterine cancer, 4% of stomach cancer, and 3% of lung adenocarcinoma[4,7]. SMO is amplified in up to 7% of ovarian cancer, 5% of glioma, and 4% of melanoma[4,7].

Potential relevance: Currently, no therapies are approved for SMO aberrations. However, FDA approved Hh pathway inhibitors that include SMO as a target include vismodegib (2012) and sonidegib (2015) for BCC and glasdegib (2018) for acute myeloid leukemia. Several missense mutations in SMO, including G497W and D473Y/H, have been associated with resistance to vismodegib in clinical cohorts of BCC patients[23,24,25]. Similarly, in a clinical trial of BCC patients treated with sonidegib, SMO W535L, Q477E, D473H, S533N, and D473G mutations demonstrated progressive disease[26].

## 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 | ● | ◑ | ● | ● | ✖ |
| adagrasib | ● | ◑ | ✖ | ● | ✖ |
| bevacizumab + CAPOX | ✖ | ✖ | ✖ | ○ | ✖ |
| bevacizumab + FOLFIRI | ✖ | ✖ | ✖ | ○ | ✖ |
| bevacizumab + FOLFOX | ✖ | ✖ | ✖ | ○ | ✖ |
| bevacizumab + FOLFOXIRI | ✖ | ✖ | ✖ | ○ | ✖ |
| JDQ-443 | ✖ | ✖ | ✖ | ✖ | ● (III) |
| adagrasib, pembrolizumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II/III) |
| GDC-6036 | ✖ | ✖ | ✖ | ✖ | ● (II/III) |
| D-1553 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| GDC-6036, pembrolizumab | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| JDQ-443, TNO-155, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| sotorasib, afatinib, pembrolizumab, atezolizumab, chemotherapy, BI-1701963 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| RMC-6291 | ✖ | ✖ | ✖ | ✖ | ● (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 2023-08-16. For the most up-to-date information, search www.fda.gov.

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

### ● adagrasib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-12-12 **Variant class:** KRAS G12C mutation

**Indications and usage:**

KRAZATI™ 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 objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216340Orig1s000Corrected_lbl.pdf

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### ● sotorasib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2023-04-24 **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/2023/214665s004lbl.pdf

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## 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 2023-08-01. For the most up-to-date information, search 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.

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

### ● adagrasib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

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### ● adagrasib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy, Second-line therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

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### ● 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, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy, Second-line therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

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### ○ adagrasib

**Cancer type:** Pancreatic Cancer **Variant class:** KRAS G12C mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2023]

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

### sotorasib

**Cancer type:** Pancreatic Cancer **Variant class:** KRAS G12C mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2023]

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### adagrasib

**Cancer type:** Pancreatic Cancer **Variant class:** KRAS G12C mutation

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2023]

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### sotorasib

**Cancer type:** Pancreatic Cancer **Variant class:** KRAS G12C mutation

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2023]

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## Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

EMA information is current as of 2023-08-16. For the most up-to-date information, search www.ema.europa.eu/ema.

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

● **sotorasib**

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-11-29 **Variant class:** KRAS G12C mutation

**Reference:**

https://www.ema.europa.eu/en/documents/product-information/lumykras-epar-product-information_en.pdf

## 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 2023-08-01. For the most up-to-date information, search www.esmo.org.

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

### ● sotorasib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

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

**Population segment (Line of therapy):**
- Stage IV; Metastatic, Advanced (Subsequent therapy); ESMO-MCBS v1.1 score: 3

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### ● adagrasib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

**ESMO Level of Evidence/Grade of Recommendation:** III / B

**Population segment (Line of therapy):**
- Stage IV; Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 2

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: https://doi.org/10.1016/j.annonc.2022.12.009 (Published)]

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### ○ 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)]

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### ○ 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)]

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

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### 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)]

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### 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)]

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### 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)]

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

## Clinical Trials Summary

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

| NCT ID | Title | Phase |
|---|---|---|
| NCT05132075 | A Randomized, Controlled, Open Label, Phase III Study Evaluating the Efficacy and Safety of JDQ443 Versus Docetaxel in Previously Treated Subjects With Locally Advanced or Metastatic KRAS G12C Mutant Non-small Cell Lung Cancer | III |
| NCT04613596 | A Phase II Trial of MRTX849 Monotherapy and in Combination With Pembrolizumab and a Phase III Trial of Adagrasib in Combination With Pembrolizumab Versus Pembrolizumab Plus Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer With KRAS G12C Mutation | II/III |
| NCT03178552 | A Phase II/III Multicenter Study Evaluating the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Patients With Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring Actionable Somatic Mutations Detected in Blood (B-FAST: Blood-First Assay Screening Trial) | II/III |
| NCT05789082 | A PHASE IB/II, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY, ACTIVITY, AND PHARMACOKINETICS OF GDC-6036 IN COMBINATION WITH OTHER ANTI-CANCER THERAPIES IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED OR METASTATIC NON SMALL CELL LUNG CANCER WITH A KRAS G12C MUTATION | I/II |
| NCT04699188 | A Phase Ib/II Open-label, Multi-center Dose Escalation Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation | I/II |
| NCT04185883 | A Phase Ib/II, Protocol Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Sotorasib Monotherapy and in Combination With Other Anti-cancer Therapies in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101) | 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 |
| NCT05462717 | Phase I/Ib, Multicenter, Open-Label, Dose Escalation and Dose Expansion Study of RMC-6291 Monotherapy in Subjects With Advanced KRASG12C Mutant Solid Tumors | I |

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

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

### 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 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

### 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

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

### GDC-6036

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

**Variant class:** KRAS G12C mutation

**Supporting Statement:**
The FDA has granted breakthrough designation to KRAS G12C inhibitor, GDC-6036, for KRAS G12C mutation in non-small cell lung cancer.

**Reference:**

https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf

### BBP-398 + sotorasib

**Cancer type:** Non-Small Cell Lung Cancer, Solid Tumor

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Fast Track Designation to a SHP2 inhibitor, BBP-398, in combination with LUMAKRAS for adult patients with previously treated KRAS G12C-mutated metastatic NSCLC.

**Reference:**

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/

### 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 2023-08-01. For the most up-to-date information, search 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.

## 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 2.2023]

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### 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 4.2023]

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### 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 2.2023]

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### 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 4.2023]

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## Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2023-08-16. For the most up-to-date information, search www.ema.europa.eu/ema.

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

#### 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 2023-08-01. For the most up-to-date information, search 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:

- "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)]

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

### ⊘ 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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