

Patient Name: 김철구  
Gender: M  
Sample ID: N25-47

Primary Tumor Site: Lung  
Collection Date: 2025.05.28

## Sample Cancer Type: Lung Cancer

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## Relevant Lung Cancer Findings

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		

  

Genomic Alteration	Finding
Tumor Mutational Burden	<b>11.39 Mut/Mb measured</b>

## 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: 6.45% Locus: chr12:25398285 Transcript: NM_033360.4	<b>adagrasib</b> <sup>1, 2 / II+</sup> <b>sotorasib</b> <sup>1, 2 / II+</sup>	<b>adagrasib + cetuximab</b> <sup>1 / I, II+</sup> <b>panitumumab + sotorasib</b> <sup>1 / I, II+</sup> adagrasib <sup>I, II+</sup> adagrasib + panitumumab <sup>I, II+</sup> cetuximab + sotorasib <sup>I, II+</sup> sotorasib <sup>I, II+</sup> bevacizumab + chemotherapy <sup>I</sup>	70
IIC	<b>CTNNB1 p.(T41A) c.121A&gt;G</b> catenin beta 1 Allele Frequency: 6.75% Locus: chr3:41266124 Transcript: NM_001904.4	None*	None*	1

\* 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

Line of therapy: I: First-line therapy, II+: Other line of therapy

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.

Relevant Biomarkers (continued)

 Alerts informed by public data sources:  Contraindicated,  Resistance,  Breakthrough,  Fast Track

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

 divarasisb<sup>1</sup>  
 avutometinib + sotorasib<sup>1</sup>, BBO-8520<sup>1</sup>, BBP-398 + sotorasib<sup>1</sup>

Public data sources included in alerts: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources  
PPP2R2A p.(R375\*) c.1123C>T, SMAD4 p.(P91Lfs\*3) c.270delT, HLA-B deletion, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	6.45%	NM_033360.4	missense
CTNNB1	p.(T41A)	c.121A>G	COSM5664	chr3:41266124	6.75%	NM_001904.4	missense
PPP2R2A	p.(R375*)	c.1123C>T	.	chr8:26227708	6.59%	NM_002717.4	nonsense
SMAD4	p.(P91Lfs*3)	c.270delT	.	chr18:48575073	7.31%	NM_005359.6	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	49.15%	NM_000903.3	missense
CNTNAP5	p.(T1113A)	c.3337A>G	.	chr2:125623005	6.55%	NM_130773.4	missense
PBRM1	p.(K1104Q)	c.3310A>C	.	chr3:52620443	50.00%	NM_018313.5	missense
MBOAT4	p.(I390T)	c.1169T>C	.	chr8:29989598	53.75%	NM_001100916.2	missense
CSMD3	p.(Q2858K)	c.8572C>A	.	chr8:113308104	4.85%	NM_198123.2	missense
PCDH17	p.(R884K)	c.2651G>A	.	chr13:58240821	5.26%	NM_001040429.3	missense
DICER1	p.(L505V)	c.1513C>G	.	chr14:95583029	7.05%	NM_030621.4	missense
ZFHX3	p.(T1147S)	c.3439A>T	.	chr16:72923639	7.53%	NM_006885.4	missense
AXIN2	p.(P744R)	c.2231C>G	.	chr17:63531750	6.85%	NM_004655.4	missense
KEAP1	p.(N251I)	c.752A>T	.	chr19:10602826	8.75%	NM_203500.2	missense
AURKC	p.(Y109*)	c.327T>A	.	chr19:57743940	45.67%	NM_001015878.2	nonsense

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0.4	0.6

## Biomarker Descriptions

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

*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>10,11,12</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>8</sup>. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61<sup>8,13,14</sup>. Mutations at A59, K117, and A146 have also been observed but are less frequent<sup>9,15</sup>.

**Potential relevance:** The FDA has approved the small molecule inhibitors, sotorasib<sup>16</sup> (2021) and adagrasib<sup>17</sup> (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma<sup>18</sup>. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036<sup>19</sup>, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398<sup>20</sup> was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutemetinib<sup>21</sup> was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520<sup>22</sup>, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001<sup>23</sup>, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib<sup>24</sup>, 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). The EGFR antagonists, cetuximab<sup>25</sup> and panitumumab<sup>26</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>15</sup>. Additionally, KRAS mutations are associated with poor prognosis in NSCLC<sup>27</sup>.

### CTNNB1 p.(T41A) c.121A>G

*catenin beta 1*

**Background:** The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions, which are involved in maintaining adhesion and regulating the growth of epithelial cell layers<sup>28</sup>. CTNNB1 binds to the APC protein in the cytoplasm and interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling<sup>29</sup>. Steady-state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis<sup>30,31,32</sup>. CTNNB1 exon 3 mutations can lead to persistent activation of the WNT/β-catenin pathway and alter downstream nuclear transcription<sup>33</sup>.

**Alterations and prevalence:** Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-3β and inhibit CTNNB1 degradation<sup>33,34,35,36</sup>. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% in uterine carcinoma, and 15% in adrenocortical carcinoma<sup>8,9,37,38,39,40,41</sup>. Alterations in CTNNB1 are also observed in pediatric cancers<sup>8,9</sup>. Somatic mutations are observed in 36% of hepatobiliary cancer (4 in 11 cases), 6% of embryonal tumor (21 in 332 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of Wilms tumor (11 in 710 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and bone cancer (1 in 327 cases)<sup>8,9</sup>.

**Potential relevance:** Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer<sup>42</sup>. Mutation of CTNNB1 is considered an ancillary diagnostic biomarker for desmoid fibromatosis and WNT-activated medulloblastoma<sup>43,44,45</sup>.

### PPP2R2A p.(R375\*) c.1123C>T

*protein phosphatase 2 regulatory subunit Balpha*

**Background:** The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)<sup>58,59</sup>. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway<sup>60</sup>. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway<sup>58</sup>.

## Biomarker Descriptions (continued)

**Alterations and prevalence:** Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer<sup>58,59,61,62</sup>. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma<sup>8</sup>.

**Potential relevance:** Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>63</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib<sup>58</sup>. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit<sup>64</sup>.

### SMAD4 p.(P91Lfs\*3) c.270delT

*SMAD family member 4*

**Background:** The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7<sup>46,47</sup>. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF- $\beta$  and BMP signaling pathways that are implicated in cancer initiation and progression<sup>47,48,49</sup>. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC<sup>46,47</sup>.

**Alterations and prevalence:** Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)<sup>46</sup>. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF- $\beta$  signaling<sup>9,49,50</sup>. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers<sup>8,9,51</sup>.

**Potential relevance:** Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers<sup>47,49,52,53,54</sup>. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy<sup>55,56</sup>. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)<sup>56</sup>. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors<sup>57</sup>.

### HLA-B deletion

*major histocompatibility complex, class I, B*

**Background:** The HLA-B gene encodes the major histocompatibility complex, class I, B<sup>1</sup>. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells<sup>2</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>3</sup>. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the  $\alpha$  polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self<sup>4,5,6</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B<sup>7</sup>.

**Alterations and prevalence:** Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma<sup>8,9</sup>. Biallelic loss of HLA-B is observed in 5% of DLBCL<sup>8,9</sup>.

**Potential relevance:** Currently, no therapies are approved for HLA-B aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated    Not recommended    Resistance    Breakthrough    Fast Track

FDA information is current as of 2025-04-16. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

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

panitumumab, panitumumab + sotorasib

Cancer type: Colorectal Cancer                      Label as of: 2025-01-16                      Variant class: KRAS G12C mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of:

Adult patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test) 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.

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)\*

- In combination with sotorasib, for the treatment of adult patients with KRAS G12C-mutated mCRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

\*Limitations of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC unless used in combination with sotorasib in KRAS G12C-mutated mCRC. VECTIBIX® is not indicated for the treatment of patients with mCRC for whom RAS mutation status is unknown.

Reference:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125147s213lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf)

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

### cetuximab

**Cancer type:** Colorectal Cancer

**Label as of:** 2021-09-24

**Variant class:** KRAS G12 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf)

### divarasib

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

**Variant class:** KRAS G12C mutation

#### Supporting Statement:

The FDA has granted Breakthrough Therapy 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>

### avutometinib + sotorasib

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

**Variant class:** KRAS G12C mutation

#### Supporting Statement:

The FDA has granted Fast Track designation to Verastem Oncology's investigational RAF/MEK clamp, avutometinib, in combination with Amgen's KRAS G12C inhibitor, LUMAKRASTM (sotorasib), for the treatment of patients with KRAS G12C-mutant metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor.

#### Reference:

<https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>

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

### **A** BBO-8520

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

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Fast Track designation to the KRAS G12C inhibitor, BBO-8520, for the treatment of adult patients with previously treated, KRAS<sup>G12C</sup>-mutated metastatic non-small cell lung cancer (NSCLC).

**Reference:**

<https://www.businesswire.com/news/home/20250109170439/en/>

### **A** 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/>

### **A** D3S-001

**Cancer type:** Colorectal Cancer

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Fast Track designation to the KRAS G12C inhibitor, D3S-001, for the treatment of KRAS G12C mutated patients with advanced unresectable or metastatic colorectal cancers.

The FDA has also granted Fast Track designation to D3S-001, for the treatment of late-line non-small cell lung cancer (NSCLC) and colorectal cancer (CRC).

**Reference:**

<https://www.d3bio.com/press-releases/d3-bios-d3s-001-receives-u-s-fda-fast-track-designation-for-the-treatment-of-colorectal-cancer-with-kras-g12c-mutation>

## Current NCCN Information

 Contraindicated    Not recommended    Resistance    Breakthrough    Fast Track

NCCN information is current as of 2025-04-01. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org).

For NCCN International Adaptations & Translations, search [www.nccn.org/global/what-we-do/international-adaptations](https://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.(G12C) c.34G>T

#### cetuximab

Cancer type: Colon Cancer

Variant class: KRAS G12 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 2.2025]

#### cetuximab

Cancer type: Rectal Cancer

Variant class: KRAS G12 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 2.2025]

#### panitumumab

Cancer type: Colon Cancer

Variant class: KRAS G12 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 2.2025]



**KRAS p.(G12C) c.34G>T (continued)****🚫 panitumumab**

Cancer type: Rectal Cancer

Variant class: KRAS G12 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 2.2025]

**Current EMA Information****🚫** Contraindicated**⊖** Not recommended**🛡️** Resistance**🚀** Breakthrough**⚡** Fast TrackEMA information is current as of 2025-04-16. For the most up-to-date information, search [www.ema.europa.eu](http://www.ema.europa.eu).**KRAS p.(G12C) c.34G>T****🚫 cetuximab, cetuximab + oxaliplatin**

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G12 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: 2022-07-06

Variant class: KRAS G12 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 2025-04-01. 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 G12 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 G12 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)]

## Genes Assayed

### Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDN, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPM1, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

## Genes Assayed (continued)

### Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDN, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

### Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

### Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

## 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*
adagrasib	●	◐	●	●	● (II)
sotorasib	●	◐	●	●	● (II)
adagrasib + cetuximab	○	○	✕	✕	✕
panitumumab + sotorasib	⚠	○	✕	✕	✕
panitumumab	⚠	✕	✕	✕	✕
adagrasib + panitumumab	✕	○	✕	✕	✕
cetuximab + sotorasib	✕	○	✕	✕	✕
bevacizumab + CAPOX	✕	✕	✕	○	✕
bevacizumab + FOLFIRI	✕	✕	✕	○	✕
bevacizumab + FOLFOX	✕	✕	✕	○	✕
bevacizumab + FOLFOXIRI	✕	✕	✕	○	✕
D-1553	✕	✕	✕	✕	● (III)
divarasib, sotorasib, adagrasib	✕	✕	✕	✕	● (III)
glecirasib, JAB-3312, tislelizumab, chemotherapy	✕	✕	✕	✕	● (III)
MK-1084, pembrolizumab	✕	✕	✕	✕	● (III)
olomorasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
sotorasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
adagrasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (II/III)
adagrasib, radiation therapy	✕	✕	✕	✕	● (II)
daratumumab, TG-01 (Targovax), QS-21 Stimulon, nivolumab	✕	✕	✕	✕	● (II)
divarasib	✕	✕	✕	✕	● (II)
glecirasib	✕	✕	✕	✕	● (II)
regorafenib	✕	✕	✕	✕	● (II)
sintilimab, catequentinib	✕	✕	✕	✕	● (II)
sotorasib, chemotherapy	✕	✕	✕	✕	● (II)
sotorasib, chemotherapy, bevacizumab (Allergan)	✕	✕	✕	✕	● (II)
sotorasib, durvalumab	✕	✕	✕	✕	● (II)
afatinib, selumetinib	✕	✕	✕	✕	● (I/II)
avutometinib, sotorasib, defactinib	✕	✕	✕	✕	● (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    
 ✕ No evidence

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
D-1553, ifebemtinib	✕	✕	✕	✕	● (I/II)
DCC-3116, sotorasib	✕	✕	✕	✕	● (I/II)
divarasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (I/II)
FMC-376	✕	✕	✕	✕	● (I/II)
glecirasib, JAB-3312	✕	✕	✕	✕	● (I/II)
HBI 2376, D-1553	✕	✕	✕	✕	● (I/II)
HS-10370	✕	✕	✕	✕	● (I/II)
HYP-2090PTSA	✕	✕	✕	✕	● (I/II)
IMM-1-104	✕	✕	✕	✕	● (I/II)
IMM-6-415	✕	✕	✕	✕	● (I/II)
MRTX0902, adagrasib	✕	✕	✕	✕	● (I/II)
RMC-6291, pembrolizumab, chemotherapy, RMC-6236	✕	✕	✕	✕	● (I/II)
YL-15293	✕	✕	✕	✕	● (I/II)
ZG-19018	✕	✕	✕	✕	● (I/II)
zotatifin, sotorasib	✕	✕	✕	✕	● (I/II)
adagrasib, olaparib	✕	✕	✕	✕	● (I)
BAY-3498264, sotorasib	✕	✕	✕	✕	● (I)
BBO-8520, pembrolizumab	✕	✕	✕	✕	● (I)
BEBT-607	✕	✕	✕	✕	● (I)
BPI-421286	✕	✕	✕	✕	● (I)
carfilzomib, sotorasib	✕	✕	✕	✕	● (I)
divarasib, bevacizumab, RLY-1971, inavolisib	✕	✕	✕	✕	● (I)
GEC-255	✕	✕	✕	✕	● (I)
HBI-2438	✕	✕	✕	✕	● (I)
HMPL-415	✕	✕	✕	✕	● (I)
HRS-7058	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
JSKN-016	✕	✕	✕	✕	● (I)
KO-2806, adagrasib	✕	✕	✕	✕	● (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

No evidence

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
KQB-365	×	×	×	×	● (I)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	×	×	×	×	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	×	×	×	×	● (I)
ladarixin, sotorasib	×	×	×	×	● (I)
MK-0472, MK-1084	×	×	×	×	● (I)
MK-1084	×	×	×	×	● (I)
Nest-1	×	×	×	×	● (I)
patritumab deruxtecan	×	×	×	×	● (I)
RMC-6291, RMC-6236	×	×	×	×	● (I)
sotorasib, afatinib, pembrolizumab, atezolizumab, chemotherapy, BI-1701963	×	×	×	×	● (I)
sotorasib, radiation therapy	×	×	×	×	● (I)
SY-5933	×	×	×	×	● (I)

CTNNB1 p.(T41A) c.121A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tegatrabetan	×	×	×	×	● (I/II)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	0.0%
Not Detected	Not Applicable

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.05(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from [www.fda.gov](http://www.fda.gov) and is current as of 2025-04-16. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-04-01. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-04-16. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. For the most up-to-date information regarding a particular trial, search [www.clinicaltrials.gov](http://www.clinicaltrials.gov) by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

## References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
3. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol.* 2013;31:529-61. PMID: 23298204
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
7. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. *Cancers (Basel).* 2020 Jul 2;12(7). PMID: 32630675
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
9. 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
10. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer.* 2011 Oct 13;11(11):761-74. PMID: 21993244
11. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
12. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.000000000000187. PMID: 27341593
13. 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
14. 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
15. 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
16. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/214665Orig1s009correctedlbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214665Orig1s009correctedlbl.pdf)
17. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/216340s005lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf)
18. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
19. <https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>
20. <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/>
21. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>
22. <https://www.businesswire.com/news/home/20250109170439/en/>
23. <https://www.d3bio.com/press-releases/d3-bios-d3s-001-receives-u-s-fda-fast-track-designation-for-the-treatment-of-colorectal-cancer-with-kras-g12c-mutation>
24. [https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff\\_Oncology\\_Investor\\_Presentation\\_July\\_2021.pdf](https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation_July_2021.pdf)
25. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125084s279lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf)
26. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125147s213lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf)
27. 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
28. Valenta et al. The many faces and functions of  $\beta$ -catenin. *EMBO J.* 2012 Jun 13;31(12):2714-36. PMID: 22617422
29. Korinek et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma. *Science.* 1997 Mar 21;275(5307):1784-7. PMID: 9065401
30. Aberle et al. beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J.* 1997 Jul 1;16(13):3797-804. PMID: 9233789
31. Winston et al. The SCFbeta-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates IkappaBalpha ubiquitination in vitro. *Genes Dev.* 1999 Feb 1;13(3):270-83. PMID: 9990852



## References (continued)

32. Kitagawa et al. An F-box protein, FWD1, mediates ubiquitin-dependent proteolysis of beta-catenin. *EMBO J.* 1999 May 4;18(9):2401-10. PMID: 10228155
33. Gao et al. Exon 3 mutations of CTNNB1 drive tumorigenesis: a review. *Oncotarget.* 2018 Jan 12;9(4):5492-5508. PMID: 29435196
34. Liu et al. Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism. *Cell.* 2002 Mar 22;108(6):837-47. PMID: 11955436
35. Miyoshi et al. Activation of the beta-catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. *Cancer Res.* 1998 Jun 15;58(12):2524-7. PMID: 9635572
36. Morin et al. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. *Science.* 1997 Mar 21;275(5307):1787-90. PMID: 9065402
37. Schulze et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat. Genet.* 2015 May;47(5):505-511. PMID: 25822088
38. Ahn et al. Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification. *Hepatology.* 2014 Dec;60(6):1972-82. PMID: 24798001
39. Harding et al. Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies. *Clin. Cancer Res.* 2018 Oct 29. PMID: 30373752
40. Cancer et al. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013 May 2;497(7447):67-73. PMID: 23636398
41. Soumerai et al. Clinical Utility of Prospective Molecular Characterization in Advanced Endometrial Cancer. *Clin. Cancer Res.* 2018 Dec 1;24(23):5939-5947. PMID: 30068706
42. Blakely et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. *Nat. Genet.* 2017 Dec;49(12):1693-1704. PMID: 29106415
43. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 5.2024]
44. Moreno et al. High frequency of WNT-activated medulloblastomas with CTNNB1 wild type suggests a higher proportion of hereditary cases in a Latin-Iberian population. *Front Oncol.* 2023;13:1237170. PMID: 37746264
45. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021 Aug 2;23(8):1231-1251. PMID: 34185076
46. Ahmed et al. The TGF- $\beta$ /Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. *J Clin Med.* 2017 Jan 5;6(1). PMID: 28067794
47. Zhao et al. The role of TGF- $\beta$ /SMAD4 signaling in cancer. *Int. J. Biol. Sci.* 2018;14(2):111-123. PMID: 29483830
48. Cicas et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. *Cancers (Basel).* 2017 Apr 28;9(5). PMID: 28452926
49. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. *Biochem. Biophys. Res. Commun.* 2003 Jul 11;306(4):799-804. PMID: 12821112
50. Mehrvarz et al. Association of SMAD4 mutation with patient demographics, tumor characteristics, and clinical outcomes in colorectal cancer. *PLoS ONE.* 2017;12(3):e0173345. PMID: 28267766
51. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
52. Yan et al. Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer. *Clin. Cancer Res.* 2016 Jun 15;22(12):3037-47. PMID: 26861460
53. Voorneveld et al. A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer. *Transl Oncol.* 2015 Feb;8(1):18-24. PMID: 25749173
54. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. *Transl Oncol.* 2016 Feb;9(1):1-7. PMID: 26947875
55. Boulay et al. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. *Br. J. Cancer.* 2002 Sep 9;87(6):630-4. PMID: 12237773
56. Kozak et al. Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer. *J. Clin. Pathol.* 2015 May;68(5):341-5. PMID: 25681512
57. Ozawa et al. SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells. *Clin. Cancer Res.* 2017 Sep 1;23(17):5162-5175. PMID: 28522603
58. Kaley et al. Loss of PPP2R2A inhibits homologous recombination DNA repair and predicts tumor sensitivity to PARP inhibition. *Cancer Res.* 2012 Dec 15;72(24):6414-24. PMID: 23087057



## References (continued)

59. Álvarez-Fernández et al. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. *Cell Death Differ.* 2018 May;25(5):828-840. PMID: 29229993
60. Perrotti et al. Protein phosphatase 2A: a target for anticancer therapy. *Lancet Oncol.* 2013 May;14(6):e229-38. PMID: 23639323
61. Beca et al. Altered PPP2R2A and Cyclin D1 Expression Defines a Subgroup of Aggressive Luminal-Like Breast Cancer. *BMC Cancer.* 2015 Apr 15;15:285. doi: 10.1186/s12885-015-1266-1. PMID: 25879784
62. Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature.* 2012 Apr 18;486(7403):346-52. PMID: 22522925
63. <https://www.senhwabio.com/en/news/20220125>
64. NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2025]