

Patient Name: 조제웅
Gender: M
Sample ID: N25-25

Primary Tumor Site: Lung
Collection Date: 2025.04.25

Sample Cancer Type: Lung Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	4 Relevant Biomarkers
Biomarker Descriptions	2	1 Therapies Available
Alert Details	6	39 Clinical Trials
Relevant Therapy Summary	11	

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	KRAS p.(G12D) c.35G>A	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	6.69 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	KRAS p.(G12D) c.35G>A KRAS proto-oncogene, GTPase Allele Frequency: 16.02% Locus: chr12:25398284 Transcript: NM_033360.4	None*	bevacizumab + chemotherapy [†]	35
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	ARID1A p.(G1483Rfs*8) c.4446_4447insC AT-rich interaction domain 1A Allele Frequency: 12.51% Locus: chr1:27101163 Transcript: NM_006015.6	None*	None*	1

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	SMAD4 deletion SMAD family member 4 Locus: chr18:48573387	None*	None*	1

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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.

Prevalent cancer biomarkers without relevant evidence based on included data sources
Microsatellite stable, UGT1A1 p.(G71R) c.211G>A, CDH10 p.(R472C) c.1414C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ARID1A	p.(G1483Rfs*8)	c.4446_4447insC	.	chr1:27101163	12.51%	NM_006015.6	frameshift Insertion
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	47.95%	NM_000463.3	missense
CDH10	p.(R472C)	c.1414C>T	COSM337943	chr5:24498608	51.26%	NM_006727.5	missense
KRAS	p.(G12D)	c.35G>A	COSM521	chr12:25398284	16.02%	NM_033360.4	missense
AKT3	p.(E182Q)	c.544G>C	.	chr1:243800930	11.97%	NM_005465.7	missense
FAT1	p.(T2871A)	c.8611A>G	.	chr4:187539129	15.67%	NM_005245.4	missense
IL7R	p.(P222L)	c.665C>T	.	chr5:35873709	18.50%	NM_002185.5	missense
LMTK2	p.(L669S)	c.2006T>C	.	chr7:97821783	5.40%	NM_014916.4	missense
STK11	p.(D237V)	c.710A>T	.	chr19:1220692	26.07%	NM_000455.5	missense
PLCG1	p.(G11C)	c.31G>T	.	chr20:39766312	50.05%	NM_002660.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0	0.47
SMAD4	chr18:48573387	0.33	0.66

Biomarker Descriptions

CDH10 p.(R472C) c.1414C>T

cadherin 10

Background: The CDH10 gene encodes cadherin 10, a type II classical cadherin and member of the cadherin superfamily¹. Cadherins are important in calcium-dependent cell-cell adhesion, and are known to mediate cell recognition, cell movement, and maintain structural and functional cell and tissue polarity². CDH10 is classified as an atypical type II cadherin due to its lack of a histidine-

Biomarker Descriptions (continued)

alanine-valine (HAV) cell adhesion recognition motif, a hallmark characteristic to type I cadherins^{1,2}. Abnormal expression of cadherins results in increased tumor cell invasion, which precedes metastasis of tumors^{3,4}.

Alterations and prevalence: Somatic mutations of CDH10 are observed in 20% of lung squamous cell carcinoma, 16% of lung adenocarcinoma, 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 8% of stomach adenocarcinoma, and colorectal adenocarcinoma, 6% of head and neck squamous cell carcinoma, 4% of bladder urothelial carcinoma and esophageal adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of pancreatic adenocarcinoma, ovarian serous cystadenocarcinoma, uterine carcinosarcoma, and sarcoma^{5,6}. Amplification of CDH10 is observed in 10% of lung squamous cell carcinoma, 7% of lung adenocarcinoma and esophageal adenocarcinoma, 6% of bladder urothelial carcinoma, 5% of ovarian serous cystadenocarcinoma and cervical squamous cell carcinoma, 4% of sarcoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% uterine corpus endometrial carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for CDH10 aberrations.

KRAS p.(G12D) c.35G>A

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^{7,8,9}.

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 cancer⁵. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{5,10,11}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{6,12}.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib¹³ (2021) and adagrasib¹⁴ (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 adenocarcinoma¹⁵. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036¹⁶, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398¹⁷ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib¹⁸ 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-8520¹⁹, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001²⁰, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib²¹, 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, cetuximab²² and panitumumab²³, 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)¹². Additionally, KRAS mutations are associated with poor prognosis in NSCLC²⁴.

SMAD4 deletion

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^{25,26}. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF- β and BMP signaling pathways that are implicated in cancer initiation and progression^{26,27,28}. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC^{25,26}.

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)²⁵. 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- β signaling^{6,28,29}. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers^{5,6,30}.

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^{26,28,31,32,33}. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy^{34,35}. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when

Biomarker Descriptions (continued)

compared to SMAD4 positive patients (31 months vs 89 months)³⁵. 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 tumors³⁶.

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome³⁷. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{38,39}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁴⁰. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250⁴¹. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)⁴¹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{42,43,44,45,46}. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes³⁹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{38,39,43,47}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{38,39,48,49}. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers^{48,49}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁵⁰ (2014) and nivolumab⁵¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁵⁰ is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication⁵⁰. Dostarlimab⁵² (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer^{44,53}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁵⁴ (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location^{44,55,56}. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients⁵⁶. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors^{57,58}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{57,58}.

ARID1A p.(G1483Rfs*8) c.4446_4447insC

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein¹. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes ARID1B^{1,59}. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex^{59,60}. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B⁶⁰. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{60,61}. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription⁵⁹. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function⁵⁹.

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors⁶¹. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations⁵⁹. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma^{5,6,60}. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response⁶².

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800⁶³, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulimimostat⁶⁴, dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with

Biomarker Descriptions (continued)

advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes the cyclin-dependent kinase inhibitor 2A protein, a cell cycle regulator that controls G1/S progression¹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{65,66,67}. CDKN2A codes for two alternate transcript variants namely p16 and p14ARF, both of which exhibit differential tumor suppressor function⁶⁸. Specifically, the CDKN2A/p16 transcript functions as an inhibitor of cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript variant stabilizes the tumor suppressor protein p53 to prevent its degradation^{1,68,69}. CDKN2A aberrations commonly co-occur with CDKN2B. Loss of CDKN2A/p16 demonstrates downstream inactivation of Rb and p53 pathways leading to uncontrolled cell proliferation⁷⁰. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{71,72}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations. Copy number loss of CDKN2A is observed in 63% of esophageal cancer, 54% of glioblastoma, 45% of pleural mesothelioma, 31% of bladder urothelial carcinoma, and 29% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma^{5,6}. Additionally, CDKN2A mutations have been observed in 19% of pancreatic adenocarcinoma and 6% of bladder urothelial carcinoma cases^{5,6}.

Potential relevance: CDKN2A loss can be useful in the diagnosis of mesothelioma and mutations are used as an ancillary diagnostic marker of malignant peripheral nerve sheath tumors^{73,74,75}. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib^{76,77,78}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁷⁹. CDKN2A (p16) expression is also associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer^{80,81,82,83,84}.

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily^{1,85}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{85,86}. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance⁸⁷. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation^{87,88,89,90}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38⁹¹.

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-03-19. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12D) c.35G>A

cetuximab

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

Indications and usage:

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

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbixux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

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.(G12D) c.35G>A (continued)**🚫 panitumumab****Cancer type:** Colorectal Cancer**Label as of:** 2025-01-16**Variant class:** KRAS G12 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

Current NCCN Information**🚫** Contraindicated**⊖** Not recommended**🛡️** Resistance**🚀** Breakthrough**🏠** Fast Track

NCCN information is current as of 2025-03-03. To view the most recent and complete version of the guideline, go online to NCCN.org.

For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

All guidelines cited below are referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) National Comprehensive Cancer Network, Inc. 2023. All rights reserved. NCCN makes no warranties regarding their content.

KRAS p.(G12D) c.35G>A**🚫 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 1.2025]

KRAS p.(G12D) c.35G>A (continued)**❌ 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 1.2025]

❌ 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 1.2025]

❌ 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 1.2025]

Current EMA Information**❌** Contraindicated**⊖** Not recommended**🛡** Resistance**🚀** Breakthrough**A** Fast TrackEMA information is current as of 2025-03-19. For the most up-to-date information, search www.ema.europa.eu.**KRAS p.(G12D) c.35G>A****❌ 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**❌ 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

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2025-03-03. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12D) c.35G>A

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, MYOD1, 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, PXDNL, 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, TGFB1, 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
 ① In this cancer type and other cancer types
 ✕ No evidence

KRAS p.(G12D) c.35G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	✕	✕	✕	○	✕
bevacizumab + FOLFIRI	✕	✕	✕	○	✕
bevacizumab + FOLFOX	✕	✕	✕	○	✕
bevacizumab + FOLFOXIRI	✕	✕	✕	○	✕
daratumumab, TG-01 (Targovax), QS-21 Stimulon, nivolumab	✕	✕	✕	✕	● (II)
regorafenib	✕	✕	✕	✕	● (II)
afatinib, selumetinib	✕	✕	✕	✕	● (I/II)
anti-KRAS G12D mTCR	✕	✕	✕	✕	● (I/II)
AZD-0022	✕	✕	✕	✕	● (I/II)
DN-022150	✕	✕	✕	✕	● (I/II)
GDC-7035	✕	✕	✕	✕	● (I/II)
GFH-375	✕	✕	✕	✕	● (I/II)
HRS-4642, adebreliamab, SHR-9839, chemotherapy	✕	✕	✕	✕	● (I/II)
IMM-1-104	✕	✕	✕	✕	● (I/II)
IMM-6-415	✕	✕	✕	✕	● (I/II)
TSN-1611	✕	✕	✕	✕	● (I/II)
YL-15293	✕	✕	✕	✕	● (I/II)
zotatifin	✕	✕	✕	✕	● (I/II)
ASP 3082, cetuximab, chemotherapy	✕	✕	✕	✕	● (I)
ASP-4396	✕	✕	✕	✕	● (I)
AST-NS2101	✕	✕	✕	✕	● (I)
HMPL-415	✕	✕	✕	✕	● (I)
INCB-161734, cetuximab, retifanlimab	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	✕	✕	✕	✕	● (I)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✕	✕	✕	✕	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	✕	✕	✕	✕	● (I)
LY-3962673, cetuximab, chemotherapy	✕	✕	✕	✕	● (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.(G12D) c.35G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
LY-4066434, cetuximab, pembrolizumab, chemotherapy	×	×	×	×	● (I)
Nest-1	×	×	×	×	● (I)
NT-112	×	×	×	×	● (I)
NW-301D	×	×	×	×	● (I)
PT-0253	×	×	×	×	● (I)
QLC-1101	×	×	×	×	● (I)
QTX-3034, cetuximab	×	×	×	×	● (I)
QTX-3046, cetuximab	×	×	×	×	● (I)
RMC-6236	×	×	×	×	● (I)
RMC-9805, RMC-6236	×	×	×	×	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	● (II)
palbociclib, abemaciclib	×	×	×	×	● (II)
AMG 193	×	×	×	×	● (I/II)

ARID1A p.(G1483Rfs*8) c.4446_4447insC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	×	×	×	×	● (II)

SMAD4 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
regorafenib	×	×	×	×	● (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	20.76%
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 OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.0.2 data version 2025.04(004)). 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 and is current as of 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. For the most up-to-date information regarding a particular trial, search 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. Jinawath et al. Alterations of type II classical cadherin, cadherin-10 (CDH10), is associated with pancreatic ductal adenocarcinomas. *Genes Chromosomes Cancer.* 2017 May;56(5):427-435. PMID: 28124395
3. Paredes et al. Epithelial E- and P-cadherins: role and clinical significance in cancer. *Biochim Biophys Acta.* 2012 Dec;1826(2):297-311. PMID: 22613680
4. Cavallaro et al. Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. *Nat Rev Cancer.* 2004 Feb;4(2):118-32. PMID: 14964308
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
6. 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
7. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer.* 2011 Oct 13;11(11):761-74. PMID: 21993244
8. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
9. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.000000000000187. PMID: 27341593
10. 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
11. 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
12. 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
13. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214665Orig1s009correctedlbl.pdf
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf
15. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
16. <https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>
17. <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/>
18. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>
19. <https://www.businesswire.com/news/home/20250109170439/en/>
20. <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>
21. https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation-_July_2021.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf
24. 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
25. Ahmed et al. The TGF-β/Smad4 Signaling Pathway in Pancreatic Carcinogenesis and Its Clinical Significance. *J Clin Med.* 2017 Jan 5;6(1). PMID: 28067794
26. Zhao et al. The role of TGF-β/SMAD4 signaling in cancer. *Int. J. Biol. Sci.* 2018;14(2):111-123. PMID: 29483830
27. Cicens et al. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 Mutations in Pancreatic Cancer. *Cancers (Basel).* 2017 Apr 28;9(5). PMID: 28452926
28. Miyaki et al. Role of Smad4 (DPC4) inactivation in human cancer. *Biochem. Biophys. Res. Commun.* 2003 Jul 11;306(4):799-804. PMID: 12821112
29. 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
30. 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

References (continued)

31. 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
32. 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
33. Shugang et al. Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis. *Transl Oncol.* 2016 Feb;9(1):1-7. PMID: 26947875
34. 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
35. 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
36. 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
37. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
38. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol.* 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
39. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
40. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. *Front Microbiol.* 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
41. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998 Nov 15;58(22):5248-57. PMID: 9823339
42. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. *Cancer Res.* 2002 Jan 1;62(1):53-7. PMID: 11782358
43. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
44. NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2025]
45. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
46. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. *Medicine (Baltimore).* 2015 Dec;94(50):e2260. PMID: 26683947
47. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J. Clin. Oncol.* 2019 Feb 1;37(4):286-295. PMID: 30376427
48. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
49. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s172lbl.pdf
51. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125554s127lbl.pdf
52. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
53. NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2025]
54. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s132lbl.pdf
55. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003 Jul 17;349(3):247-57. PMID: 12867608
56. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann. Oncol.* 2015 Jan;26(1):126-32. PMID: 25361982
57. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
58. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
59. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. *Cancer Discov.* 2013 Jan;3(1):35-43. PMID: 23208470
60. Wilson et al. SWI/SNF nucleosome remodellers and cancer. *Nat. Rev. Cancer.* 2011 Jun 9;11(7):481-92. PMID: 21654818

References (continued)

61. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. *Nat Commun.* 8;14648. PMID: 28262751
62. Mehrvarz et al. ARID1A Mutation May Define an Immunologically Active Subgroup in Patients with Microsatellite Stable Colorectal Cancer. *Clin Cancer Res.* 2021 Mar 15;27(6):1663-1670. PMID: 33414133
63. <https://nuvectis.com/press-release-view/?i=114174>
64. <https://www.morphosys.com/en/news/morphosys-receives-us-fda-fast-track-designation-tulmimetostat-endometrial-cancer>
65. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. *Am. J. Respir. Cell Mol. Biol.* 2018 Aug;59(2):200-214. PMID: 29420051
66. Roussel. The INK4 family of cell cycle inhibitors in cancer. *Oncogene.* 1999 Sep 20;18(38):5311-7. PMID: 10498883
67. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). *Biochem. Biophys. Res. Commun.* 1999 Aug 27;262(2):534-8. PMID: 10462509
68. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet.* 2013;14:257-79. PMID: 23875803
69. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell.* 2006 Oct 20;127(2):265-75. PMID: 17055429
70. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
71. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
72. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
73. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2025]
74. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2025]
75. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 4.2024]
76. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med.* 2019 Jul 29;17(1):245. PMID: 31358010
77. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. *Anticancer Res.* 2013 Aug;33(8):2997-3004. PMID: 23898052
78. von et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway. *Cancer Res.* 2015 Sep 15;75(18):3823-31. PMID: 26183925
79. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. *Neuro-oncology.* 2012 Jul;14(7):870-81. PMID: 22711607
80. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. *Oncotarget.* 2018 Sep 7;9(70):33247-33248. PMID: 30279955
81. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J. Clin. Oncol.* 2014 Dec 10;32(35):3930-8. PMID: 25267748
82. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. *J. Natl. Cancer Inst.* 2018 Dec 1;110(12):1393-1399. PMID: 29878161
83. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. *Cancer Clin Oncol.* 2013;2(1):51-61. PMID: 23935769
84. NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2025]
85. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. *Front Cell Neurosci.* 2014;8:349. PMID: 25389387
86. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene.* 2006 Mar 13;25(11):1659-72. PMID: 16550166
87. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. *Br J Cancer.* 2020 Apr;122(9):1277-1287. PMID: 32047295
88. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. *Mol Carcinog.* 2014 Apr;53(4):314-24. PMID: 23143693
89. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. *Oncotarget.* 2017 Jan 10;8(2):3640-3648. PMID: 27690298
90. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. *PLoS One.* 2015;10(5):e0127524. PMID: 26010150

References (continued)

91. Karas et al. JCO Oncol Pract. 2021 Dec 3;OP2100624. PMID: 34860573