

Patient Name: 최중학
Gender: Male
Sample ID: N26-42

Primary Tumor Site: lung
Collection Date: 2024.07.02

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	KRAS p.(G12F) c.34_35delGGinsTT	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	6.63 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.(G12F) c.34_35delGGinsTT KRAS proto-oncogene, GTPase Allele Frequency: 25.63% Locus: chr12:25398284 Transcript: NM_033360.4	None*	bevacizumab + chemotherapy ¹	10
IIC	BARD1 deletion BRCA1 associated RING domain 1 Locus: chr2:215593375	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

Microsatellite stable, ACVR2A p.(I318Gfs*10) c.952_961delATATCTCACA, HDAC2 deletion, NQO1 p.(P187S) c.559C>T, DGCR8 p.(E518L) c.1552_1553delGAinsTT, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12F)	c.34_35delGGinsTT	COSM512	chr12:25398284	25.63%	NM_033360.4	missense
ACVR2A	p.(I318Gfs*10)	c.952_961delATATCTC . ACA	.	chr2:148676150	7.97%	NM_001616.5	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.30%	NM_000903.3	missense
DGCR8	p.(E518L)	c.1552_1553delGAinsT . T	.	chr22:20079439	21.11%	NM_022720.7	missense
REG1B	p.(A85D)	c.254C>A	.	chr2:79313560	22.81%	NM_006507.4	missense
MAP3K4	p.(S194C)	c.580A>T	.	chr6:161469884	29.37%	NM_005922.4	missense
PPP2R2A	p.(S194P)	c.580T>C	.	chr8:26218610	25.84%	NM_002717.4	missense
BRCA2	p.(R1845S)	c.5535G>C	.	chr13:32914027	24.56%	NM_000059.4	missense
MGA	p.(G698S)	c.2092G>A	.	chr15:41991139	26.03%	NM_001164273.1	missense
ZFHX3	p.(G699C)	c.2095G>T	.	chr16:72991950	28.51%	NM_006885.4	missense
AURKC	p.(K161E)	c.481A>G	.	chr19:57744873	48.37%	NM_001015878.2	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BARD1	chr2:215593375	1	0.77
HDAC2	chr6:114262171	0.6	0.67
FGFR1	chr8:38271452	0.67	0.68

Biomarker Descriptions

KRAS p.(G12F) c.34_35delGGinsTT

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 HRAS¹. 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^{2,3,4}. Germline mutations in *KRAS* lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in heart and congenital defects, growth inhibition, and facial dysmorphic features⁵. Somatic mutations in *KRAS* are commonly altered in several cancers including non-small cell lung cancer, pancreatic cancer, and multiple myeloma⁵.

Alterations and prevalence: The majority of *KRAS* mutations consist of point mutations occurring at G12, G13, and Q61^{6,7,8}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{9,10}. Somatic mutations in *KRAS* are observed in 66% of pancreatic adenocarcinoma, 41% of colorectal adenocarcinoma, 30% of lung adenocarcinoma, 19% of uterine corpus endometrial carcinoma, 12% of uterine carcinosarcoma, 9% of stomach adenocarcinoma, 8% of testicular germ cell tumors, 6% of cholangiocarcinoma, 5% of cervical squamous cell carcinoma, acute myeloid leukemia, and diffuse large B-cell lymphoma, 4% of bladder urothelial carcinoma, and 2% of skin cutaneous melanoma and kidney renal papillary cell carcinoma^{6,9}. *KRAS* is amplified in 9% of ovarian serous cystadenocarcinoma and testicular germ cell tumors, 8% of stomach adenocarcinoma, 7% of esophageal adenocarcinoma and uterine carcinosarcoma, 6% of lung adenocarcinoma, 4% of pancreatic adenocarcinoma and bladder urothelial carcinoma, 3% of lung squamous cell carcinoma, and 2% of sarcoma, mesothelioma, brain lower grade glioma, and uterine corpus endometrial carcinoma^{6,9}. Alterations in *KRAS* are also observed in pediatric cancers⁹. Somatic mutations in *KRAS* are observed in 10% of B-lymphoblastic leukemia/lymphoma (24 in 252 cases), 8% of leukemia (29 in 354 cases), and in less than 1% of embryonal

Biomarker Descriptions (continued)

tumors (2 in 332 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)⁹. KRAS is amplified in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)⁹. Structural alterations in KRAS are observed in less than 1% of acute lymphoblastic leukemia (1 in 85 cases)⁹.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib¹¹ (2021) and adagrasib¹² (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 adenocarcinoma¹³. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib¹⁴ (2025), for the treatment of adult patients with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) after prior systemic therapy. The FDA has granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036¹⁵, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib¹⁶, and the KRAS G12C inhibitor, D3S-001¹⁷, were both granted breakthrough therapy designation (2025) for KRAS G12C-mutated locally advanced or metastatic NSCLC in adults previously treated with chemotherapy and immunotherapy, excluding KRAS G12C inhibitors. The KRAS-G12C inhibitor, olomorasib¹⁸, was granted breakthrough designation (2025) in combination with pembrolizumab¹⁹ for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression \geq 50%. The RAF/MEK clamp, avutometinib²⁰ was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC in patients 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-8520²¹, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib²², was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375²³, was also granted fast track designation (2025) for first-line and previously treated KRAS G12D-mutated locally advanced or metastatic pancreatic adenocarcinoma. The KRAS G12C inhibitor, D3S-001²⁴, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib²⁵, 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, cetuximab²⁶ and panitumumab²⁷, 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)¹⁰. Additionally, KRAS mutations are associated with poor prognosis in NSCLC²⁸.

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene^{1,36}. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage^{1,36,37,38}. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction^{1,37,39,40}. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{40,41}. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility³⁹. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53⁴². Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer^{42,43}.

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma^{6,9}. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer^{6,9}.

Potential relevance: The PARP inhibitor, olaparib⁴⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁴⁵, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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 genome⁴⁹. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{50,51}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁵². 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 D17S250⁵³. 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)⁵³. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{54,55,56,57,58}. MSI-H is a hallmark of Lynch

Biomarker Descriptions (continued)

syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes⁵¹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{50,51,55,59}.

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^{50,51,60,61}. 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^{60,61}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹⁹ (2014) and nivolumab⁶² (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹⁹ 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 indication¹⁹. Dostarlimab⁶³ (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^{56,64}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁶⁵ (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^{56,66,67}. 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 patients⁶⁷. 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^{68,69}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{68,69}.

ACVR2A p.(I318Gfs*10) c.952_961delATATCTCACA

activin A receptor type 2A

Background: The ACVR2A gene encodes the activin A type 2A receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenetic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family^{1,46}. ACVR2A is a type II receptor that forms heterotetrameric complex with at least two type I receptors (ACVR1 and ACVR1B) and two type II receptors (including BMPR2 and ACVR2B)^{46,47}. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrameric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream signaling^{46,47}. Downregulation of ACVR2A has been associated with increased cell migration, tumor progression, and metastases in colon cancer⁴⁸.

Alterations and prevalence: Somatic mutations of ACVR2A are observed in 11% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 7% of colorectal adenocarcinoma, 3% of liver hepatocellular carcinoma, skin cutaneous melanoma, and cholangiocarcinoma, 2% of cervical squamous cell carcinoma, and 1% of kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, and glioblastoma multiforme, and esophageal adenocarcinoma^{6,9}. Biallelic deletion of ACVR2A is observed in 4% of prostate adenocarcinoma, 2% of liver hepatocellular carcinoma, and 1% of stomach adenocarcinoma, thymoma, testicular germ cell tumors, esophageal adenocarcinoma, and colorectal adenocarcinoma^{6,9}.

Potential relevance: Currently, no therapies are approved for ACVR2A aberrations.

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein¹. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)⁷⁰. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8⁷⁰. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation^{70,71}. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes⁷⁰. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells⁷⁰. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development^{70,72}.

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma^{6,9}. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma^{6,9}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies⁷³. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy⁷⁴. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL⁷⁵. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens⁷⁶.

DGCR8 p.(E518L) c.1552_1553delGinsTT

DGCR8, microprocessor complex subunit

Background: DGCR8 encodes DGCR8 microprocessor complex subunit¹. DGCR8 is part of the microprocessor complex along with DROSHA, which is an RNase III superfamily member²⁹. Both DROSHA and DGCR8 contribute to the biosynthesis of microRNAs (miRNA) by processing precursor miRNAs in the nucleus^{29,30,31}. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is further cleaved by DICER1 resulting in the production of mature miRNA³². Mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)^{32,33}. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing^{31,33,34,35}.

Alterations and prevalence: Somatic mutations in DGCR8 are observed in 7% of diffuse large B-cell lymphoma, 5% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, and 2% of colorectal adenocarcinoma, lung adenocarcinoma, uterine carcinosarcoma, bladder urothelial carcinoma, and esophageal adenocarcinoma^{6,9}.

Potential relevance: Currently, no therapies are approved for DGCR8 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12F) c.34_35delGGinsTT

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

KRAS p.(G12F) c.34_35delGGinsTT (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

daraxonrasib

Cancer type: Pancreatic Cancer

Variant class: KRAS G12 mutation

Supporting Statement:

The FDA has granted Breakthrough designation to the RAS inhibitor, daraxonrasib, for previously treated metastatic pancreatic adenocarcinoma (PDAC) in patients with KRAS G12 mutations.

Reference:

<https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy>

Current NCCN Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

NCCN information is current as of 2025-11-03. 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.

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.(G12F) c.34_35delGGinsTT

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 5.2025]

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 4.2025]

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 5.2025]

KRAS p.(G12F) c.34_35delGGinsTT (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 4.2025]

Current EMA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

EMA information is current as of 2025-11-25. For the most up-to-date information, search www.ema.europa.eu.

KRAS p.(G12F) c.34_35delGGinsTT

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: 2025-05-07

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 2025-11-03. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12F) c.34_35delGGinsTT

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, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, 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, CBF, 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, ERRF1, 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, PXDNL, 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, SLCO1B3, 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, CBF, 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, ERRF1, 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.(G12F) c.34_35delGGinsTT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	×	×	×	○	×
bevacizumab + FOLFIRI	×	×	×	○	×
bevacizumab + FOLFOX	×	×	×	○	×
bevacizumab + FOLFOXIRI	×	×	×	○	×
daraxonrasib	×	×	×	×	● (III)
afatinib, selumetinib	×	×	×	×	● (I/II)
ERAS-0015	×	×	×	×	● (I/II)
zotatifin	×	×	×	×	● (I/II)
BPI-442096	×	×	×	×	● (I)
imatinib, trametinib	×	×	×	×	● (I)
JAB-3312	×	×	×	×	● (I)
Nest-1	×	×	×	×	● (I)
ZEN-3694, binimetinib	×	×	×	×	● (I)

BARD1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (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	12.07%
BRCA2	SNV, R1845S, AF:0.25
BARD1	CNV, CN:1.0
BARD1	LOH, 2q35(215593375-215674205)x1

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 (6.2.4 data version 2025.12(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 and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. 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. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer.* 2011 Oct 13;11(11):761-74. PMID: 21993244
3. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
4. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.000000000000187. PMID: 27341593
5. Johnson et al. Classification of KRAS-Activating Mutations and the Implications for Therapeutic Intervention. *Cancer Discov.* 2022 Apr 1;12(4):913-923. PMID: 35373279
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
7. 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
8. 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
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. 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
11. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214665Orig1s009correctedlbl.pdf
12. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf
13. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219616s000lbl.pdf
15. <https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>
16. <https://ir.revmed.com/node/11881/pdf>
17. <https://www.prnewswire.com/news-releases/d3-bio-inc-announces-fda-breakthrough-therapy-designation-and-orphan-drug-designation-for-d3s-001-for-the-treatment-of-patients-with-kras-g12c-mutated-cancers-302540808.html>
18. <https://www.prnewswire.com/news-releases/lillys-olomorasib-receives-us-fdas-breakthrough-therapy-designation-for-the-treatment-of-certain-newly-diagnosed-metastatic-kras-g12c-mutant-lung-cancers-302545643.html>
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
20. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>
21. <https://www.businesswire.com/news/home/20250109170439/en/>
22. <https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy>
23. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375>
24. <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>
25. https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation_-_July_2021.pdf
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf
28. 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
29. Yeom et al. Characterization of DGCR8/Pasha, the essential cofactor for Drosha in primary miRNA processing. *Nucleic Acids Res.* 2006;34(16):4622-9. PMID: 16963499
30. Jiang et al. Evaluation of genetic variants in microRNA biosynthesis genes and risk of breast cancer in Chinese women. *Int J Cancer.* 2013 Nov;133(9):2216-24. PMID: 23629745
31. Wen et al. *Biosci Rep.* 2018 Jun 29;38(3). PMID: 29654164
32. Aharoni et al. Dynamical comparison between Drosha and Dicer reveals functional motion similarities and dissimilarities. *PLoS One.* 2019;14(12):e0226147. PMID: 31821368
33. Lee et al. MicroRNAs in cancer. *Annu Rev Pathol.* 2009;4:199-227. PMID: 18817506

References (continued)

34. Hammond. An overview of microRNAs. *Adv Drug Deliv Rev.* 2015 Jun 29;87:3-14. PMID: 25979468
35. Kumar et al. Impaired microRNA processing enhances cellular transformation and tumorigenesis. *Nat Genet.* 2007 May;39(5):673-7. PMID: 17401365
36. Morris et al. BRCA1 : BARD1 induces the formation of conjugated ubiquitin structures, dependent on K6 of ubiquitin, in cells during DNA replication and repair. *Hum. Mol. Genet.* 2004 Apr 15;13(8):807-17. PMID: 14976165
37. Baer et al. The BRCA1/BARD1 heterodimer, a tumor suppressor complex with ubiquitin E3 ligase activity. *Curr. Opin. Genet. Dev.* 2002 Feb;12(1):86-91. PMID: 11790560
38. Zhao et al. BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing. *Nature.* 2017 Oct 19;550(7676):360-365. PMID: 28976962
39. Cimmino et al. Dualistic Role of BARD1 in Cancer. *Genes (Basel).* 2017 Dec 8;8(12). PMID: 29292755
40. De Summa et al. BRCAness: a deeper insight into basal-like breast tumors. *Ann. Oncol.* 2013 Nov;24 Suppl 8:viii13-viii21. PMID: 24131964
41. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. *Cold Spring Harb Perspect Biol.* 2015 Apr 1;7(4):a016600. PMID: 25833843
42. Irminger-Finger et al. Identification of BARD1 as mediator between proapoptotic stress and p53-dependent apoptosis. *Mol. Cell.* 2001 Dec;8(6):1255-66. PMID: 11779501
43. Thai et al. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers. *Hum. Mol. Genet.* 1998 Feb;7(2):195-202. PMID: 9425226
44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
45. <https://www.senhwabio.com/en/news/20220125>
46. Valer et al. ACVR1 Function in Health and Disease. *Cells.* 2019 Oct 31;8(11). PMID: 31683698
47. Haupt et al. Variable signaling activity by FOP ACVR1 mutations. *Bone.* 2018 Apr;109:232-240. PMID: 29097342
48. Zhuo et al. Downregulation of Activin A Receptor Type 2A Is Associated with Metastatic Potential and Poor Prognosis of Colon Cancer. *J Cancer.* 2018;9(19):3626-3633. PMID: 30310521
49. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
50. 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
51. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
52. 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
53. 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
54. 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
55. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
56. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
57. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
58. 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
59. 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
60. 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
61. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
62. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
63. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
64. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
65. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf

References (continued)

66. 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
67. 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
68. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
69. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
70. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. *Nat Rev Drug Discov.* 2014 Sep;13(9):673-91. PMID: 25131830
71. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. *Biomed Pharmacother.* 2016 Dec;84:284-290. PMID: 27665474
72. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. *Cold Spring Harb Perspect Med.* 2016 Oct 3;6(10). PMID: 27599530
73. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf
74. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf
75. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
76. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf