

Patient Name: 최윤영
Gender: Male
Sample ID: N26-92

Primary Tumor Site: colon
Collection Date: 2024.06.26

Sample Cancer Type: Colon Cancer

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Relevant Colon Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK3	None detected
ERBB2	None detected	PIK3CA	None detected
KRAS	KRAS p.(G12V) c.35G>T	POLD1	None detected
NRAS	None detected	POLE	None detected
NTRK1	None detected	RET	None detected
NTRK2	None detected		

Genomic Alteration	Finding
Microsatellite Status	Microsatellite stable
Tumor Mutational Burden	1.9 Mut/Mb measured

HRD Status: **HR Proficient (HRD-)**

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	KRAS p.(G12V) c.35G>T KRAS proto-oncogene, GTPase Allele Frequency: 3.77% Locus: chr12:25398284 Transcript: NM_033360.4	bevacizumab + chemotherapy ¹	avutometinib + defactinib ^{1 / II+}	18

* 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.

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

KRAS p.(G12V) c.35G>T ⊘ cetuximab^{1,2}, cetuximab + chemotherapy², panitumumab¹, panitumumab + chemotherapy²

Public data sources included in alerts: FDA¹, NCCN, EMA², ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

Microsatellite stable, SF3B1 p.(R625C) c.1873C>T, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, HLA-B deletion, HLA-B p.(A15Gfs*5) c.44delC, NQO1 p.(P187S) c.559C>T, PPM1D p.(S468*) c.1403C>G, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	3.77%	NM_033360.4	missense
SF3B1	p.(R625C)	c.1873C>T	COSM110696	chr2:198267484	5.77%	NM_012433.4	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.95%	NM_000463.3	missense
HLA-B	p.(A15Gfs*5)	c.44delC	.	chr6:31324891	90.00%	NM_005514.8	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.75%	NM_000903.3	missense
PPM1D	p.(S468*)	c.1403C>G	COSM6907659	chr17:58740498	3.27%	NM_003620.4	nonsense
MAML3	p.(Q488_Q494delinsHD S)	c.1455_1506delACAGC . AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACACG ACAGCCAGCAGCAGC AGCAGCAGCAGCAA	.	chr4:140811084	66.14%	NM_018717.5	nonframeshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGC . AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACACG AACAGCCAGCAGCAGC CAGCAGCAGCAGCAA	.	chr4:140811084	33.86%	NM_018717.5	frameshift Block Substitution
FAT1	p.(A1285T)	c.3853G>A	.	chr4:187557858	50.68%	NM_005245.4	missense
CCND1	p.(A270T)	c.808G>A	.	chr11:69465970	7.57%	NM_053056.3	missense
NOTCH3	p.(G1347R)	c.4039G>C	.	chr19:15288700	43.36%	NM_000435.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-A	chr6:29910229	0.84	0.6
HLA-B	chr6:31322252	0.67	0.54

Biomarker Descriptions

KRAS p.(G12V) c.35G>T

KRAS proto-oncogene, GTPase

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and 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^{10,11,12}. Germline mutations in KRAS lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in

Biomarker Descriptions (continued)

heart and congenital defects, growth inhibition, and facial dysmorphic features¹³. Somatic mutations in KRAS are commonly altered in several cancers including non-small cell lung cancer, pancreatic cancer, and multiple myeloma¹³.

Alterations and prevalence: The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{8,14,15}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{9,16}. 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^{8,9}. 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^{8,9}. 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 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, sotorasib¹⁷ (2021) and adagrasib¹⁸ (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 adenocarcinoma¹⁹. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib²⁰ (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-6036²¹, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib²², and the KRAS G12C inhibitor, D3S-001²³, 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, olomorasib²⁴, was granted breakthrough designation (2025) in combination with pembrolizumab²⁵ for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression \geq 50%. The RAF/MEK clamp, avutometinib²⁶ 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-8520²⁷, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib²⁸, was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375²⁹, 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-001³⁰, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib³¹, 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, cetuximab³² and panitumumab³³, 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)¹⁶. Additionally, KRAS mutations are associated with poor prognosis in NSCLC³⁴.

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 genome³⁵. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{36,37}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2³⁸. 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 D17S250³⁹. 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)³⁹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{40,41,42,43,44}. 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 genes³⁷. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{36,37,41,45}.

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^{36,37,46,47}. 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^{46,47}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab²⁵ (2014) and nivolumab⁴⁸ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab²⁵ is also approved

Biomarker Descriptions (continued)

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 indication²⁵. Dostarlimab⁴⁹ (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^{42,50}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁵¹ (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^{42,52,53}. 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 patients⁵³. 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^{54,55}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{54,55}.

SF3B1 p.(R625C) c.1873C>T

splicing factor 3b subunit 1

Background: The SF3B1 gene encodes the splicing factor 3b subunit 1 protein, a core component of the U2 small nuclear ribonucleoprotein (snRNP) complex of the spliceosome responsible for RNA splicing¹. SF3B1 is involved in recognition of the branch point sequence during selection of the 3' splice site¹. Recurrent somatic mutations in SF3B1 and other components of the splicing machinery including SRSF2, U2AF1, and ZRSR2, are common in myelodysplasia⁵⁶. These components experience mutations in a mutually exclusive manner suggesting a common impact on RNA splicing and the pathogenesis of myelodysplasia⁵⁶. SF3B1 mutations are believed to contribute to aberrant post-translational inactivation of the regulatory complex PPP2R5A of protein phosphatase 2A (PP2A), leading to the activation and stabilization of MYC activation and impairing apoptosis⁵⁷.

Alterations and prevalence: SF3B1 mutations occur in the majority (70-80%) of myelodysplastic syndromes (MDS) with ring sideroblasts (RS) and at lower frequency in other myeloid neoplasms including MDS without RS (7%), chronic myelomonocytic leukemia (5-6%), therapy-related acute myeloid leukemia (AML) or AML with MDS features (5%), and de novo AML (3%)^{56,58,59}. Recurrent somatic SF3B1 mutations are also common in certain solid cancers including 23% of uveal melanoma, 9% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma and bladder urothelial carcinoma, 4% of colorectal adenocarcinoma, 3% of liver hepatocellular carcinoma, acute myeloid leukemia, lung squamous cell carcinoma, lung adenocarcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of adrenocortical carcinoma, stomach adenocarcinoma, breast invasive carcinoma, uterine carcinosarcoma, and thymoma^{8,9,60,61,62,63,64,65}. Cancer-associated recurrent missense mutations in SF3B1 occur within the HEAT repeat domains 5-9 at codon positions R625, K666, K700, G742, and D781⁶⁶. The functional significance of recurrent SF3B1 mutations is to alter branch point selection thus inducing cryptic 3' splice site selection^{66,67,68}. Amplification of SF3B1 is observed in 2% of ovarian serous cystadenocarcinoma, lung squamous cell carcinoma, and pancreatic adenocarcinoma^{8,9}. Alterations in SF3B1 are also observed in pediatric cancers⁹. Somatic mutations in SF3B1 are observed in less than 1% of embryonal tumors (3 in 332 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and glioma (1 in 297 cases)⁹. Amplification of SF3B1 is observed in less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)⁹.

Potential relevance: Currently, no therapies are approved for SF3B1 aberrations. SF3B1 mutations are associated with poor/adverse risk in AML, intermediate risk of distant metastasis in uveal melanoma, and aggressive disease and shorter survival in patients diagnosed with chronic lymphocytic leukemia (CLL)^{69,70,71}. Somatic mutations in SF3B1 at positions E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, and D781 are independently associated with favorable risk in myelodysplastic syndrome⁷². Investigational inhibitors of the spliceosome are in early clinical development^{73,74}.

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^{1,82}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{82,83}. 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 resistance⁸⁴. 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^{84,85,86,87}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28,

Biomarker Descriptions (continued)

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-38⁸⁸.

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^{8,9}.

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

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A¹. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells². MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M³. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{4,5,6}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁷.

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma^{8,9}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{8,9}.

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

HLA-B deletion, HLA-B p.(A15Gfs*5) c.44delC

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B¹. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells². MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M³. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{4,5,6}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B⁷.

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

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

PPM1D p.(S468*) c.1403C>G

protein phosphatase, Mg2+/Mn2+ dependent 1D

Background: The PPM1D gene encodes the protein phosphatase, Mg²⁺/Mn²⁺ dependent 1D, also known as wild-type p53-induced phosphatase 1 (WIP1) or protein phosphatase 2C delta (PP2C δ)⁷⁵. PPM1D is a member of the PP2C family of Ser/Thr protein phosphatases¹. PPM1D negatively regulates several key tumor suppressor pathways including ATM, CHK2, P38 MARK and P53, which are involved in cell stress, cell cycle regulation, DNA damage repair and tumor cell metabolism^{75,76}. PPM1D amplification/overexpression and/or mutations occur in various solid cancers, including breast cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, ovarian carcinoma and neuroblastoma⁷⁶. Truncating mutations in the last exon of PPM1D lead to the production of a stable, enzymatically active protein and are commonly associated with clonal hematopoiesis, a condition that has been shown to be present in patients with therapy-related myeloid neoplasm such as therapy-related acute myeloid leukemia (t-AML) or therapy-related myelodysplastic syndrome (t-MDS)^{77,78}.

Alterations and prevalence: Somatic mutations in PPM1D are predominantly truncating or missense and are observed in 6% of uterine corpus endometrial carcinoma, 2% of stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma^{8,9}. Amplification of PPM1D is observed in 8% of breast invasive carcinoma, 5% of mesothelioma, 4% of liver hepatocellular carcinoma, 3% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of adrenocortical carcinoma, skin cutaneous melanoma, ovarian serous cystadenocarcinoma, pheochromocytoma and paraganglioma, esophageal adenocarcinoma, pancreatic

Biomarker Descriptions (continued)

adenocarcinoma, thymoma, sarcoma, and lung adenocarcinoma^{9,9}. Alterations in PPM1D are also observed in pediatric cancers⁹. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma and glioma, and less than 1% of leukemia (1 in 311 cases), embryonal tumor (1 in 332 cases), and peripheral nervous system cancers (3 in 1158 cases)⁹. PPM1D amplification is observed in 2% of peripheral nervous system cancers, and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)⁹.

Potential relevance: Currently, no therapies are approved for PPM1D aberrations. Overexpression of PPM1D has been associated with tumor progression and poor prognosis in non-small cell lung cancer, nasopharyngeal carcinoma and prostate cancer^{79,80,81}.

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.(G12V) c.35G>T

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.(G12V) c.35G>T (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.

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.

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KRAS p.(G12V) c.35G>T

cetuximab

Cancer type: Colon Cancer

Variant class: KRAS G12 mutation

Summary:

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

- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]

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]

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]

KRAS p.(G12V) c.35G>T (continued)

panitumumab

Cancer type: Rectal Cancer

Variant class: KRAS G12 mutation

Summary:

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

- "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 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.(G12V) c.35G>T

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G12 mutation

Reference:

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

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.(G12V) c.35G>T

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, 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, DAXX, 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.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avutometinib + defactinib	○	○	✕	✕	✕
bevacizumab + CAPOX	✕	✕	✕	●	✕
bevacizumab + FOLFIRI	✕	✕	✕	●	✕
bevacizumab + FOLFOX	✕	✕	✕	●	✕
bevacizumab + FOLFOXIRI	✕	✕	✕	●	✕
bevacizumab, chemotherapy	✕	✕	✕	✕	● (III)
fruquintinib, chemotherapy	✕	✕	✕	✕	● (II)
afatinib, selumetinib	✕	✕	✕	✕	● (I/II)
almonertinib, palbociclib	✕	✕	✕	✕	● (I/II)
anti-KRAS G12V mTCR, chemotherapy, aldesleukin	✕	✕	✕	✕	● (I/II)
ERAS-0015	✕	✕	✕	✕	● (I/II)
YL-15293	✕	✕	✕	✕	● (I/II)
ASP-5834	✕	✕	✕	✕	● (I)
BPI-442096	✕	✕	✕	✕	● (I)
daraxonrasib	✕	✕	✕	✕	● (I)
imatinib, trametinib	✕	✕	✕	✕	● (I)
IX-001	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✕	✕	✕	✕	● (I)
Nest-1	✕	✕	✕	✕	● (I)
NW-301V	✕	✕	✕	✕	● (I)
toripalimab, chemotherapy, KRAS peptide vaccine	✕	✕	✕	✕	● (I)
ZEN-3694, binimetinib	✕	✕	✕	✕	● (I)

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

HRR Details

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

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

Thermo Fisher Scientific's Ion Torrent 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. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
3. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol.* 2013;31:529-61. PMID: 23298204
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
7. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. *Cancers (Basel).* 2020 Jul 2;12(7). PMID: 32630675
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
10. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer.* 2011 Oct 13;11(11):761-74. PMID: 21993244
11. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
12. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.000000000000187. PMID: 27341593
13. 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
14. 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
15. 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
16. 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
17. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214665Orig1s009correctedlbl.pdf
18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf
19. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219616s000lbl.pdf
21. <https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>
22. <https://ir.revmed.com/node/11881/pdf>
23. <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>
24. <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>
25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
26. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>
27. <https://www.businesswire.com/news/home/20250109170439/en/>
28. <https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy>
29. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375>
30. <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>
31. https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation_-_July_2021.pdf
32. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
33. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf

References (continued)

34. 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
35. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
36. 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
37. Nojadedeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
38. 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
39. 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
40. 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
41. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
42. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
43. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
44. 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
45. 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
46. 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
47. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
48. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
49. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
50. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
51. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
52. 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
53. 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
54. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
55. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
56. Yoshida et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature.* 2011 Sep 11;478(7367):64-9. PMID: 21909114
57. Liu et al. Mutations in the RNA Splicing Factor SF3B1 Promote Tumorigenesis through MYC Stabilization. *Cancer Discov.* 2020 Mar 18. PMID: 32188705
58. Patnaik et al. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management. *Am. J. Hematol.* 2017 Mar;92(3):297-310. PMID: 28188970
59. Patnaik et al. Spliceosome mutations involving SRSF2, SF3B1, and U2AF35 in chronic myelomonocytic leukemia: prevalence, clinical correlates, and prognostic relevance. *Am. J. Hematol.* 2013 Mar;88(3):201-6. PMID: 23335386
60. Ellis et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. *Nature.* 2012 Jun 10;486(7403):353-60. PMID: 22722193
61. Maguire et al. SF3B1 mutations constitute a novel therapeutic target in breast cancer. *J. Pathol.* 2015 Mar;235(4):571-80. PMID: 25424858
62. Harbour et al. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. *Nat. Genet.* 2013 Feb;45(2):133-5. PMID: 23313955

References (continued)

63. Martin et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. *Nat. Genet.* 2013 Aug;45(8):933-6. PMID: 23793026
64. Furney et al. SF3B1 mutations are associated with alternative splicing in uveal melanoma. *Cancer Discov.* 2013 Oct;3(10):1122-1129. PMID: 23861464
65. Dono et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: detection of an activating mutation in the TERT gene promoter in a single case of uveal melanoma. *Br. J. Cancer.* 2014 Feb 18;110(4):1058-65. PMID: 24423917
66. DeBoever et al. Transcriptome sequencing reveals potential mechanism of cryptic 3' splice site selection in SF3B1-mutated cancers. *PLoS Comput. Biol.* 2015 Mar;11(3):e1004105. PMID: 25768983
67. Darman et al. Cancer-Associated SF3B1 Hotspot Mutations Induce Cryptic 3' Splice Site Selection through Use of a Different Branch Point. *Cell Rep.* 2015 Nov 3;13(5):1033-45. PMID: 26565915
68. Alsafadi et al. Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage. *Nat Commun.* 2016 Feb 4;7:10615. doi: 10.1038/ncomms10615. PMID: 26842708
69. Wan et al. SF3B1 mutations in chronic lymphocytic leukemia. *Blood.* 2013 Jun 6;121(23):4627-34. PMID: 23568491
70. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood.* 2022 Sep 22;140(12):1345-1377. PMID: 35797463
71. NCCN Guidelines® - NCCN-Uveal Melanoma [Version 1.2025]
72. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
73. Seiler et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. *Nat. Med.* 2018 May;24(4):497-504. PMID: 29457796
74. Lee et al. Therapeutic targeting of splicing in cancer. *Nat. Med.* 2016 Sep 7;22(9):976-86. PMID: 27603132
75. Deng et al. The role of PPM1D in cancer and advances in studies of its inhibitors. *Biomed Pharmacother.* 2020 May;125:109956. PMID: 32006900
76. Le Guezennec et al. WIP1 phosphatase at the crossroads of cancer and aging. *Trends Biochem Sci.* 2010 Feb;35(2):109-14. PMID: 19879149
77. Hsu et al. PPM1D Mutations Drive Clonal Hematopoiesis in Response to Cytotoxic Chemotherapy. *Cell Stem Cell.* 2018 Nov 1;23(5):700-713.e6. PMID: 30388424
78. Miller et al. PPM1D modulates hematopoietic cell fitness and response to DNA damage and is a therapeutic target in myeloid malignancy. *Blood.* 2023 Dec 14;142(24):2079-2091. PMID: 37595362
79. Yang et al. PPM1D overexpression predicts poor prognosis in non-small cell lung cancer. *Tumour Biol.* 2015 Mar;36(3):2179-84. PMID: 25412952
80. Sun et al. Overexpression of Wild-Type p53-Induced Phosphatase 1 Confers Poor Prognosis of Patients with Nasopharyngeal Carcinoma. *Pathol Oncol Res.* 2015 Apr;21(2):283-91. PMID: 25060857
81. Wu et al. PPM1D exerts its oncogenic properties in human pancreatic cancer through multiple mechanisms. *Apoptosis.* 2016 Mar;21(3):365-78. PMID: 26714478
82. 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
83. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene.* 2006 Mar 13;25(11):1659-72. PMID: 16550166
84. 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
85. 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
86. 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
87. 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
88. Karas et al. *JCO Oncol Pract.* 2021 Dec 3:OP2100624. PMID: 34860573