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Patient Name: 이주남 Gender: M Sample ID: N25-176 Primary Tumor Site: colon
Collection Date: 2025.08.11

Sample Cancer Type: Colon Cancer

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Relevant Colon Cancer Findings

Gene	Finding		Gene	Finding	
BRAF	None detected		NTRK2	None detected	
ERBB2	None detected		NTRK3	None detected	
KRAS	KRAS p.(G12\	/) c.35G>T	POLD1	None detected	
NRAS	None detected		POLE	None detected	
NTRK1	None detected		RET	None detected	
Genomic Alte	eration	Finding			
Microsate	llite Status	Microsatellite stable			
Tumor Mu	tational Burden	4.76 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: 19.93% Locus: chr12:25398284 Transcript: NM_033360.4	bevacizumab + chemotherapy	None*	23
IIC	IDH1 p.(R132C) c.394C>T isocitrate dehydrogenase (NADP(+)) 1, cytosolic Allele Frequency: 14.05% Locus: chr2:209113113 Transcript: NM_005896.4	None*	ivosidenib ^{1, 2 / +} vorasidenib ^{1 / +}	0

 $[\]hbox{* Public data sources included in relevant the rapies: FDA1, NCCN, EMA2, ESMO}$

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

Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

^{*} Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

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Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	Microsatellite stable	None*	None*	1
IIC	PTEN deletion phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	1
IIC	TP53 p.(S99Rfs*23) c.294_297delTTCC tumor protein p53 Allele Frequency: 4.78% Locus: chr17:7579389 Transcript: NM_000546.6	None*	None*	1

^{*} Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

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

Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.



🛕 Alerts informed by public data sources: 🥝 Contraindicated, 🏮 Resistance, 🗳 Breakthrough, 🗚 Fast Track

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

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

APC p.(S1411Rfs*4) c.4233delT, CDH1 p.(D443Lfs*4) c.1323_1326dup, MLH1 p.(V384D) c.1151T>A, SMAD4 c.905-1G>A, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, HLA-B deletion, CSMD3 p.(R1228*) c.3682C>T, CIITA p.(R174Dfs*3) c.520delA, NQ01 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants Allele Gene **Amino Acid Change** Coding Variant ID Locus Transcript Variant Effect Frequency COSM520 **KRAS** p.(G12V) c.35G>T chr12:25398284 19.93% NM 033360.4 missense IDH1 p.(R132C) c.394C>T COSM28747 chr2:209113113 14.05% NM_005896.4 missense frameshift TP53 p.(S99Rfs*23) c.294_297delTTCC chr17:7579389 4.78% NM_000546.6 Deletion frameshift APC p.(S1411Rfs*4) c.4233delT COSM18948 chr5:112175523 34.46% NM_000038.6 Deletion CDH1 p.(D443Lfs*4) c.1323_1326dup chr16:68849418 30.28% NM_004360.5 frameshift Insertion MLH1 p.(V384D) chr3:37067240 51.30% NM_000249.4 c.1151T>A missense SMAD4 p.(?) c.905-1G>A chr18:48586235 5.06% NM 005359.6 unknown UGT1A1 p.(G71R) c.211G>A COSM4415616 chr2:234669144 99.75% NM_000463.3 missense CSMD3 p.(R1228*) chr8:113649079 c.3682C>T 3.95% NM_198123.2 nonsense

^{*} Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

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Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CIITA	p.(R174Dfs*3)	c.520delA		chr16:10995932	1.54%	NM_000246.3	frameshift Deletion
NQ01	p.(P187S)	c.559C>T		chr16:69745145	99.70%	NM_000903.3	missense
CNTNAP5	p.(L58R)	c.173T>G		chr2:124979372	18.86%	NM_130773.4	missense
CTNNB1	p.(G455D)	c.1364G>A		chr3:41275198	42.35%	NM_001904.4	missense
APC	p.(S590N)	c.1769G>A		chr5:112170673	30.32%	NM_000038.6	missense
HLA-A	p.(C125S)	c.373T>A		chr6:29911074	40.86%	NM_001242758.1	missense
PARP4	p.(?)	c.3285+6_3285+8delA AG		chr13:25021145	92.31%	NM_006437.4	unknown

Copy Number Variations						
Gene	Locus	Copy Number	CNV Ratio			
CDKN2A	chr9:21968178	0.93	0.63			
PTEN	chr10:89623659	0.93	0.62			
HLA-A	chr6:29910229	0.63	0.52			
HLA-B	chr6:31322252	0.77	0.57			
CD276	chr15:73991923	1.06	0.67			
ZNF217	chr20:52188253	0.83	0.59			

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 HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival^{21,22,23}.

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q619,24,25. Mutations at A59, K117, and A146 have also been observed but are less frequent 10,26.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib²⁷ (2021) and adagrasib²⁸ (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 adenocarcinoma²⁹. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036³⁰, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398³¹ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib³² was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520³³, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001³⁴, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib³⁵, 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, cetuximab³⁶ and

Biomarker Descriptions (continued)

panitumumab³⁷, 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)²⁶. Additionally, KRAS mutations are associated with poor prognosis in NSCLC³⁸.

IDH1 p.(R132C) c.394C>T

isocitrate dehydrogenase (NADP(+)) 1, cytosolic

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG) 1 . The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform 1 .

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies, including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)². Recurrent IDH1 variants include predominantly R132H/C plus other substitutions at lower frequencies³. These gain-of-function variants confer neomorphic enzyme activity⁴. Although wild-type enzymatic activity is ablated, recurrent IDH1 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair¹,⁵. Recurrent IDH1 mutations are present in 5-10% of patients with AML and 5% of patients with MDS^{6,7,8}. Recurrent IDH1 mutations are present in nearly 80% of lower-grade diffuse gliomas^{9,10}. Alterations in IDH1 are rare in pediatric cancers^{9,10}. Somatic mutations in IDH1 are observed in 2% of glioma and less than 1% of leukemia (2 in 311 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), embryonal tumor (1 in 332 cases), and Wilms tumor (1 in 710 cases)^{9,10}.

Potential relevance: The IDH1 and IDH2 inhibitor vorasidenib¹¹ is FDA-approved (2024) for the treatment of adults and children with Grade 2 astrocytoma and oligodendroglioma with IDH1 R132C/G/H/L/S mutations. Additionally, olutasidenib¹² (2022) and ivosidenib¹³ (2018) are FDA-approved for treating IDH1 R132C/G/H/L/S variants in AML. Ivosidenib is also approved for treating myelodysplastic syndrome (MDS) and cholangiocarcinoma patients with the same IDH1 variants¹⁴. IDH1 mutations are associated with favorable outcome in lower-grade gliomas, astrocytoma, and oligodendroglioma with 1p/19 codeletion^{15,16,17}. Conversely, IDH1 mutations are associated with inferior leukemia-free survival in primary myelofibrosis (PMF)^{18,19}. Mutations in IDH1 are diagnostic of IDH-mutated astrocytoma and oligodendroglioma with 1p/19q-codeletion subtypes of central nervous system (CNS) tumors^{15,20}.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression³⁹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)⁶². The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{63,64,65}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions⁶⁶. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation^{39,66,67}. CDKN2A aberrations commonly co-occur with CDKN2B⁶². Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation⁶⁸. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{69,70}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations⁷¹. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma^{9,10}. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{9,10}. Alterations in CDKN2A are also observed in pediatric cancers¹⁰. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors¹⁰. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)¹⁰.

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors^{72,73,74}. Additionally, deletion of CDKN2B is a molecular marker used in

Biomarker Descriptions (continued)

staging Grade 4 pediatric IDH-mutant astrocytoma⁷⁵. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib^{76,77,78}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁷⁹. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer^{80,81,82,83}.

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 genome¹⁶². Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{110,112}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2¹¹¹. 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 D17S250¹⁶³. 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)¹⁶³. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{113,164,165,166,167}. 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 genes¹¹². LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{110,112,113,114}.

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^{110,112,168,169}. 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^{168,169}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹²⁰ (2014) and nivolumab¹²¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹²⁰ 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 indication¹²⁰. Dostarlimab¹⁷⁰ (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^{165,171}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹²² (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^{165,172,173}. 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 patients¹⁷³. 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^{174,175}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{174,175}.

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities⁴³. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT^{44,45}. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency⁴⁶. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation⁴⁷. PTEN germline mutations are also associated with inherited cancer risk in several cancer types⁴⁸.

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer^{9,10}. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN^{45,49,50,51,52}. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer^{9,10}.

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors^{53,54}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁵⁵, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In

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Biomarker Descriptions (continued)

2023, the FDA approved the kinase inhibitor, capivasertib⁵⁶ in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

TP53 p.(S99Rfs*23) c.294_297delTTCC

tumor protein p53

<u>Background</u>: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair³⁹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis¹³⁷. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential¹³⁸. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{139,140}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)9.10.141.142.143.144. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R2829.10. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes145.146.147.148. Alterations in TP53 are also observed in pediatric cancers9.10. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)9.10. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)9.10.

Potential relevance: The small molecule p53 reactivator, PC14586¹⁴⁹ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt¹⁵⁰, (2019) and breakthrough designation¹⁵¹ (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{152,153}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma²⁰. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{154,155,156,157,158,159}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant¹⁶⁰. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system¹⁶¹.

APC p.(S1411Rfs*4) c.4233delT

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β -catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation¹⁷⁶. APC is an antagonist of WNT signaling as it targets β -catenin for proteasomal degradation^{177,178}. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine^{176,179}. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer¹⁸⁰.

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma^{9,10,130}. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation^{181,182}.

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

CDH1 p.(D443Lfs*4) c.1323_1326dup

cadherin 1

<u>Background</u>: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)^{39,97}. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-

Biomarker Descriptions (continued)

dependent transmembrane glycoproteins expressed in epithelial cells³⁹. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments⁹⁸. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis^{99,100}. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer¹⁰¹.

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function^{9,10,102,103}. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas^{9,10}. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma^{9,10}.

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

MLH1 p.(V384D) c.1151T>A

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein³⁹. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex¹⁰⁴. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2^{104,105}. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia^{106,107}. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway¹⁰⁴. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication¹⁰⁴. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes¹⁰⁸. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{109,110,111}. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes^{109,112}. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{110,112,113,114}. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer^{115,116,117,118}.

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma^{9,10}. Alterations in MLH1 are observed in pediatric cancers^{9,10}. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)^{9,10}.

Potential relevance: The PARP inhibitor, talazoparib¹¹⁹ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies¹²⁰. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment^{121,122}. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas^{123,124}.

SMAD4 c.905-1G>A

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7^{125,126}. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression^{126,127,128}. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC^{125,126}

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH) 125 . Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling 10,128,129 . Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers 9,10,130 .

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers^{126,128,131,132,133}. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy^{134,135}. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)¹³⁵. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors¹³⁶.

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^{39,84}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{84,85}. 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 resistance⁸⁶. 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^{86,87,88,89}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38⁹⁰.

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^{9,10}.

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, A^{39} . 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 cells⁹¹. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁹². 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^{93,94,95}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁹⁶.

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^{9,10}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{9,10}.

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B³⁹. 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 cells⁹¹. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁹². 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^{93,94,95}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B⁹⁶.

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^{9,10}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{9,10}.

Biomarker Descriptions (continued)

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

CSMD3 p.(R1228*) c.3682C>T

CUB and Sushi multiple domains 3

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2^{39,40}. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the transmembrane and extracellular proteins^{40,41}. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation^{40,41}. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)^{40,42}.

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma, 19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma^{9,10}. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma^{9,10}. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma^{9,10}.

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

CIITA p.(R174Dfs*3) c.520delA

class II major histocompatibility complex transactivator

Background: The CIITA gene encodes the class II major histocompatibility complex transactivator³⁹. CIITA, along with RFX, X2PB, and NF-Y, forms a multi-protein complex responsible for controlling the transcription of MHC class II expression⁵⁷. CIITA expression is regulated by cell-specific promoters in the first exon, with promoter I specific to dendritic cells and promoter III specific to B-cells^{58,59}. Promoter IV induces CIITA expression upon interferon-gamma stimulation in various cell types regardless of antigen presentation⁵⁷. MHC class II expression on tumor cells is driven by CIITA changes in the tumor microenvironment and promotes an adaptive immune response through the infiltration of macrophages and T-cells⁶⁰.

Alterations and prevalence: Somatic mutations are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 9% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of colorectal adenocarcinoma and stomach adenocarcinoma^{9,10}. CIITA alterations are rare in pediatric cancers, with somatic mutations observed in 3% of bone cancers and soft tissue sarcomas, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)^{9,10}. Biallelic deletions have been reported in less that 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)^{9,10}.

Potential relevance: Currently, no therapies are approved for CIITA aberrations. Alterations, amplification, or loss of CIITA is often observed in primary mediastinal large B-cell lymphoma^{57,61}.

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Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

FDA information is current as of 2025-05-14. 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:

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

Head and Neck Cancer

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

Colorectal Cancer

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

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

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

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

• in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

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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 irinotecancontaining chemotherapy.

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)*

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

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf

Current NCCN Information

Contraindicated

Not recommended



Breakthrough

A Fast Track

NCCN information is current as of 2025-05-01. To view the most recent and complete version of the guideline, go online to NCCN.org.

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

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

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

KRAS p.(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 3.2025]

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

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 3.2025]

cetuximab

Cancer type: Rectal Cancer Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]

panitumumab

Cancer type: Rectal Cancer Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]

Current EMA Information

EMA information is current as of 2025-05-14. 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

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Current ESMO Information

Contraindicated

Not recommended



Breakthrough

A Fast Track

ESMO information is current as of 2025-05-01. 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, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, 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, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI, FANCM, FAT1, FBXW7, FGF19, FGF23, 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, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, 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, FGR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRF11, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI, 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, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	×	×	×		×
bevacizumab + FOLFIRI	×	×	×	•	×
bevacizumab + FOLFOX	×	×	×	•	×
bevacizumab + FOLFOXIRI	×	×	×	•	×
bevacizumab, chemotherapy	×	×	×	×	(III)
fruquintinib, chemotherapy	×	×	×	×	(II)
KRAS TCR, chemotherapy, aldesleukin	×	×	×	×	(II)
regorafenib	×	×	×	×	(II)
tunlametinib, vemurafenib	×	×	×	×	(II)
afatinib, selumetinib	×	×	×	×	(1/11)
anti-KRAS G12V mTCR, chemotherapy, aldesleukin	×	×	×	×	(I/II)
APR-1051	×	×	×	×	(I/II)
ERAS-0015	×	×	×	×	(I/II)
IMM-1-104	×	×	×	×	(I/II)
YL-15293	×	×	×	×	(I/II)
AFNT-211	×	×	×	×	(I)
HMPL-415	×	×	×	×	(1)
IX-001	×	×	×	×	(1)
JAB-3312	×	×	×	×	(I)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	×	×	×	×	(1)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	×	×	×	×	(1)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	×	×	×	×	(I)
Nest-1	×	×	×	×	(1)
NW-301V	×	×	×	×	(I)
RMC-6236	×	×	×	×	(I)

IDH1 p.(R132C) c.394C>T					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ivosidenib	0	0	0	0	×

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

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Relevant Therapy Summary (continued)

■ In this cancer type □ In other cancer type □ In this cancer type and other cancer types □ No evidence

IDH1 p.(R13	2C) c.394C>T	(continued)
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Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
vorasidenib	0	0	×	×	×

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	(II)
palbociclib, abemaciclib	×	×	×	×	(II)
AMG 193	×	×	×	×	(1/11)

Microsatellite stable

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	×	×	×	×	(1)

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, gedatolisib	×	×	×	×	(I)

TP53 p.(S99Rfs*23) c.294_297delTTCC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
APR-1051	×	×	×	×	(I/II)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	13.1%
PALB2	LOH, 16p12.2(23614759-23652528)x2

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 lon Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). 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 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. 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.

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