

Patient Name: 김현미
Gender: Female
Sample ID: N26-81

Primary Tumor Site: colon
Collection Date: 2026.01.30

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.(G13D) c.38G>A	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	5.69 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.(G13D) c.38G>A KRAS proto-oncogene, GTPase Allele Frequency: 17.37% Locus: chr12:25398281 Transcript: NM_033360.4	bevacizumab + chemotherapy ^I	None*	9

* 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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	BRCA2 p.(C1200*) c.3599_3600delGT BRCA2, DNA repair associated Allele Frequency: 50.05% Locus: chr13:32912089 Transcript: NM_000059.4	None*	abiraterone + niraparib ^{1,2 / II+} bevacizumab + olaparib ^{1,2 / II+} niraparib ^{1 / II+} olaparib ^{1,2 / II+} rucaparib ^{1 / II+} talazoparib + hormone therapy ^{1 / II+} bevacizumab + niraparib ^{II+} talazoparib ^{II+} olaparib + hormone therapy	13
IIC	CCNE1 amplification cyclin E1 Locus: chr19:30303647	None*	None*	11
IIC	BRCA1 deletion BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	2
IIC	BRIP1 deletion BRCA1 interacting protein C-terminal helicase 1 Locus: chr17:59760627	None*	None*	1
IIC	CDK12 deletion cyclin dependent kinase 12 Locus: chr17:37618286	None*	None*	1
IIC	RAD51C deletion RAD51 paralog C Locus: chr17:56769933	None*	None*	1
IIC	RAD51D deletion RAD51 paralog D Locus: chr17:33427950	None*	None*	1

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

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

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

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

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

KRAS p.(G13D) c.38G>A **cetuximab**^{1,2}, **cetuximab + chemotherapy**², **panitumumab**¹, **panitumumab + chemotherapy**²

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

*AKT2 amplification, Microsatellite stable, RAD51B deletion, FAT1 p.(T2369Rfs*2) c.7105delA, HLA-A deletion, HLA-A p.(L180*) c.539T>A, HLA-B deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G13D)	c.38G>A	COSM532	chr12:25398281	17.37%	NM_033360.4	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA2	p.(C1200*)	c.3599_3600delGT	.	chr13:32912089	50.05%	NM_000059.4	nonsense
FAT1	p.(T2369Rfs*2)	c.7105delA	.	chr4:187540634	24.80%	NM_005245.4	frameshift Deletion
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	79.09%	NM_001242758.1	nonsense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	72.62%	NM_002439.5	nonframeshift Insertion
FANCE	p.(A20E)	c.59C>A	.	chr6:35420381	12.91%	NM_021922.3	missense
RB1	p.(?)	c.380+2T>G	.	chr13:48916852	13.58%	NM_000321.3	unknown
SMAD4	p.(C71F)	c.212G>T	.	chr18:48573628	20.45%	NM_005359.6	missense
MAP2K7	p.(L77F)	c.229C>T	.	chr19:7974744	42.56%	NM_145185.4	missense
ZRSR2	p.(Q115E)	c.343C>G	.	chrX:15822264	51.25%	NM_005089.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CCNE1	chr19:30303647	5.16	2.11
BRCA1	chr17:41197602	1	0.92
BRIP1	chr17:59760627	1	0.89
CDK12	chr17:37618286	1	0.9
RAD51C	chr17:56769933	1	1.0
RAD51D	chr17:33427950	1	0.96
AKT2	chr19:40739751	8.59	3.3
RAD51B	chr14:68290164	1	0.92
HLA-A	chr6:29910229	0.76	0.56
HLA-B	chr6:31322252	0.99	0.64

Biomarker Descriptions

KRAS p.(G13D) c.38G>A

KRAS proto-oncogene, GTPase

Background: The *KRAS* proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS¹. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival^{2,3,4}. Germline mutations in *KRAS* lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in heart and congenital defects, growth inhibition, and facial dysmorphic features⁵. Somatic mutations in *KRAS* are commonly altered in several cancers including non-small cell lung cancer, pancreatic cancer, and multiple myeloma⁵.

Alterations and prevalence: The majority of *KRAS* mutations consist of point mutations occurring at G12, G13, and Q61^{6,7,8}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{9,10}. Somatic mutations in *KRAS* are observed in 66% of pancreatic adenocarcinoma, 41% of colorectal adenocarcinoma, 30% of lung adenocarcinoma, 19% of uterine corpus

Biomarker Descriptions (continued)

endometrial carcinoma, 12% of uterine carcinosarcoma, 9% of stomach adenocarcinoma, 8% of testicular germ cell tumors, 6% of cholangiocarcinoma, 5% of cervical squamous cell carcinoma, acute myeloid leukemia, and diffuse large B-cell lymphoma, 4% of bladder urothelial carcinoma, and 2% of skin cutaneous melanoma and kidney renal papillary cell carcinoma^{6,9}. KRAS is amplified in 9% of ovarian serous cystadenocarcinoma and testicular germ cell tumors, 8% of stomach adenocarcinoma, 7% of esophageal adenocarcinoma and uterine carcinosarcoma, 6% of lung adenocarcinoma, 4% of pancreatic adenocarcinoma and bladder urothelial carcinoma, 3% of lung squamous cell carcinoma, and 2% of sarcoma, mesothelioma, brain lower grade glioma, and uterine corpus endometrial carcinoma^{6,9}. Alterations in KRAS are also observed in pediatric cancers⁹. Somatic mutations in KRAS are observed in 10% of B-lymphoblastic leukemia/lymphoma (24 in 252 cases), 8% of leukemia (29 in 354 cases), and in less than 1% of embryonal tumors (2 in 332 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)⁹. KRAS is amplified in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)⁹. Structural alterations in KRAS are observed in less than 1% of acute lymphoblastic leukemia (1 in 85 cases)⁹.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib¹¹ (2021) and adagrasib¹² (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma¹³. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib¹⁴ (2025), for the treatment of adult patients with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) after prior systemic therapy. The FDA has granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036¹⁵, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib¹⁶, and the KRAS G12C inhibitor, D3S-001¹⁷, were both granted breakthrough therapy designation (2025) for KRAS G12C-mutated locally advanced or metastatic NSCLC in adults previously treated with chemotherapy and immunotherapy, excluding KRAS G12C inhibitors. The KRAS-G12C inhibitor, olomorasib¹⁸, was granted breakthrough designation (2025) in combination with pembrolizumab¹⁹ for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression $\geq 50\%$. The RAF/MEK clamp, avutometinib²⁰ was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC in patients who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520²¹, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib²², was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375²³, was also granted fast track designation (2025) for first-line and previously treated KRAS G12D-mutated locally advanced or metastatic pancreatic adenocarcinoma. The KRAS G12C inhibitor, D3S-001²⁴, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib²⁵, was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab²⁶ and panitumumab²⁷, are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)¹⁰. Additionally, KRAS mutations are associated with poor prognosis in NSCLC²⁸.

BRCA2 p.(C1200*) c.3599_3600delGT

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{30,31}. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{30,31}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{32,33,34}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{32,35}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{36,37,38,39,40,41,42,43}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme^{6,9}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)⁴⁴. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{45,46}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁴⁷ (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary

Biomarker Descriptions (continued)

peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib⁴⁸ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib⁴⁹ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib⁴⁹ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA2. Niraparib⁵⁰ (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate⁵¹ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib⁵² received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁵³. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁵⁴. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. 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. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

CCNE1 amplification

cyclin E1

Background: The CCNE1 gene encodes the cyclin E1 protein, a member of the highly conserved E-cyclin family which also includes CCNE2⁵⁶. CCNE1 facilitates progression from G1 to the S phase of the cell cycle by binding to cyclin dependent kinase 2 (CDK2) which results in phosphorylation and inactivation of the retinoblastoma (RB1) protein⁵⁶. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition resulting in cell cycle progression, a common event observed in tumorigenesis^{57,58,59}. Additionally, CCNE1 is often deregulated in a variety of cancer types supporting an oncogenic role for CCNE1^{56,60}.

Alterations and prevalence: CCNE1 amplification is observed in about 40% of uterine carcinosarcoma, 20% of ovarian cancer, 11% of stomach cancer, 7-8% sarcoma, uterine, and esophageal cancers, 5-6%, adrenocortical carcinoma, squamous lung, and bladder cancers⁶. Additionally, CCNE1 overexpression has been observed in many different tumor types including in 70-80% of Hodgkin's lymphoma.^{56,60,61}

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib⁶², in combination with camonsertib for the treatment of adult patients with CCNE1 amplified endometrial cancer and platinum resistant ovarian cancer. CCNE1 amplification and overexpression has been associated with poor prognosis in certain cancer types including lung and breast cancers^{63,64,65}.

BRCA1 deletion

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{30,31}. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{30,31}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{32,33,34}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{32,35}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{36,37,38,39,40,41,42,43}. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme^{6,9}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)⁴⁴. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{45,46}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁴⁷ (2014) was the first PARPi to be approved by the FDA for BRCA1/2

Biomarker Descriptions (continued)

aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib⁴⁸ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib⁴⁹ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib⁴⁹ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA1. Niraparib⁵⁰ (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate⁵¹ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib⁵² received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁵³. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁵⁴. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. 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. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA⁸⁸. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control⁸⁹. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{75,83}. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)⁹⁰. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer^{90,91}. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer^{88,92}.

Alterations and prevalence: Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma^{6,9}.

Potential relevance: The PARP inhibitor, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy^{83,93}. 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.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability^{72,73,74}. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes^{72,73,74,75,76}. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype^{74,75}. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors⁷⁶. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene⁷⁶.

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma^{1,6}. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma^{1,6}.

Potential relevance: The PARP inhibitor, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib⁴⁹ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP

Biomarker Descriptions (continued)

inhibitors^{75,76}. 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.

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs⁷⁷. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)⁷⁸. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)⁷⁹. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing⁸⁰. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity^{81,82}. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{75,83}.

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers⁶.

Potential relevance: The PARP inhibitor, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib⁴⁹ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation⁸⁴. 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.

RAD51D deletion

RAD51 paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁷⁸. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁷⁹. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁸⁰. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{75,83}. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer⁸⁵.

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer⁶.

Potential relevance: The PARP inhibitor, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors⁸³. 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.

AKT2 amplification

AKT serine/threonine kinase 2

Background: The AKT2 gene encodes a serine/threonine kinase that belongs to a family of closely related protein kinases that also includes AKT1 and AKT3¹. Growth factor signaling leads to the activation of phosphatidylinositol 3-kinase (PI3K), recruitment of AKT to the plasma membrane, and subsequent activation of downstream effectors including MTOR¹¹⁵. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism^{115,116}. AKT2 is implicated in cancer cell invasion, survival, and metastasis in various cancers, including acute myeloid leukemia, neuroblastoma, bladder cancer, prostate cancer, and ovarian cancer^{117,118,119}.

Alterations and prevalence: Recurrent AKT2 activating mutations occur at E17K, L52R, and D324G/H¹²⁰. Somatic mutations in AKT2 are observed in 4% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, skin cutaneous melanoma, and cervical squamous cell carcinoma^{6,9}. AKT2 is amplified in 14% of uterine carcinosarcoma, 7% of pancreatic adenocarcinoma, 6% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 4% of sarcoma, 3% of cervical squamous cell carcinoma and uterine corpus endometrial carcinoma, and 2% of bladder urothelial carcinoma^{6,9}. A BCAM::AKT2 fusion

Biomarker Descriptions (continued)

has been identified in ovarian cancer¹²¹. Alterations in AKT2 are also observed in pediatric cancers⁹. Somatic mutations in AKT2 are observed in less than 1% of Wilms tumors (1 in 710 cases). AKT2 amplification is observed in 2% of Wilms tumors (3 in 136 cases)⁹.

Potential relevance: Currently, no therapies are approved specifically for AKT2 aberrations. Although the pan-AKT inhibitor capivasertib (AZD5363) targets all AKT isoforms, clinical evidence of supporting its efficacy in AKT2-aberrant cancers remains limited¹²².

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 genome⁹⁴. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{95,96}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁹⁷. 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 D17S250⁹⁸. 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)⁹⁸. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{99,100,101,102,103}. 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 genes⁹⁶. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{95,96,100,104}.

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^{95,96,105,106}. 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^{105,106}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹⁹ (2014) and nivolumab¹⁰⁷ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹⁹ is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication¹⁹. Dostarlimab¹⁰⁸ (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^{101,109}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹¹⁰ (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^{101,111,112}. 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 patients¹¹². 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^{113,114}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{113,114}.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁷⁸. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁷⁹. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁸⁰. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{75,83}. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents⁸⁶. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk⁸⁷.

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer^{6,9}. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk⁸⁷.

Potential relevance: The PARP inhibitor, olaparib⁴⁷ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. 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.

Biomarker Descriptions (continued)

FAT1 p.(T2369Rfs*2) c.7105delA

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats^{1,29}. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions²⁹. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion²⁹. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/ β -catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition²⁹. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1²⁹.

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot^{6,9}. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma^{6,9}. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma^{6,9}.

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

HLA-A deletion, HLA-A p.(L180*) c.539T>A

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 cells⁶⁶. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁶⁷. 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^{68,69,70}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁷¹.

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^{6,9}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{6,9}.

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, 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 cells⁶⁶. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁶⁷. 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^{68,69,70}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B⁷¹.

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^{6,9}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{6,9}.

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

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

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

KRAS p.(G13D) c.38G>A

cetuximab

Cancer type: Colorectal Cancer

Label as of: 2021-09-24

Variant class: KRAS G13 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.(G13D) c.38G>A (continued)

🚫 panitumumab

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G13 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

CCNE1 amplification

⚠️ camonsertib + lunresertib

Cancer type: Endometrial Carcinoma, Ovarian Cancer

Variant class: CCNE1 amplification

Supporting Statement:

- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated platinum resistant ovarian cancer.
- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated endometrial cancer.

Reference:

<https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda>

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.

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.(G13D) c.38G>A

cetuximab

Cancer type: Colon Cancer

Variant class: KRAS G13 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 G13 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 G13 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.(G13D) c.38G>A (continued)**🚫 panitumumab**

Cancer type: Rectal Cancer

Variant class: KRAS G13 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.(G13D) c.38G>A****🚫 cetuximab, cetuximab + oxaliplatin**

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G13 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 G13 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.(G13D) c.38G>A

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS G13 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 G13 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, CTNNA1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDN, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, 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, DAX1, 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 ① In this cancer type and other cancer types ✕ No evidence

KRAS p.(G13D) c.38G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	✕	✕	✕	●	✕
bevacizumab + FOLFIRI	✕	✕	✕	●	✕
bevacizumab + FOLFOX	✕	✕	✕	●	✕
bevacizumab + FOLFOXIRI	✕	✕	✕	●	✕
bevacizumab, chemotherapy	✕	✕	✕	✕	● (III)
fruquintinib, chemotherapy	✕	✕	✕	✕	● (II)
afatinib, selumetinib	✕	✕	✕	✕	● (I/II)
almonertinib, palbociclib	✕	✕	✕	✕	● (I/II)
ERAS-0015	✕	✕	✕	✕	● (I/II)
ASP-5834	✕	✕	✕	✕	● (I)
daraxonrasib	✕	✕	✕	✕	● (I)
Nest-1	✕	✕	✕	✕	● (I)
toripalimab, chemotherapy, KRAS peptide vaccine	✕	✕	✕	✕	● (I)

BRCA2 p.(C1200*) c.3599_3600delGT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	○	○	○	○	● (II)
bevacizumab + olaparib	○	○	○	○	✕
abiraterone + niraparib	○	○	○	✕	✕
niraparib	○	○	✕	○	✕
rucaparib	○	○	✕	○	✕
talazoparib + enzalutamide	○	○	✕	✕	✕
bevacizumab + niraparib	✕	○	✕	✕	✕
olaparib + abiraterone acetate	✕	○	✕	✕	✕
talazoparib	✕	✕	✕	○	● (II)
niraparib, dostarlimab	✕	✕	✕	✕	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✕	✕	✕	✕	● (II)
pamiparib, tislelizumab	✕	✕	✕	✕	● (II)
ZEN-3694, talazoparib	✕	✕	✕	✕	● (II)

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

Relevant Therapy Summary (continued)

In this cancer type
 In other cancer type
 In this cancer type and other cancer types
 ✕ No evidence

BRCA2 p.(C1200*) c.3599_3600delGT (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMXI-5001	✕	✕	✕	✕	● (I/II)
sacituzumab govitecan, berzosertib	✕	✕	✕	✕	● (I/II)
HS-10502	✕	✕	✕	✕	● (I)
niraparib, chemotherapy	✕	✕	✕	✕	● (I)
novobiocin	✕	✕	✕	✕	● (I)
olaparib, chemotherapy	✕	✕	✕	✕	● (I)
SNV-1521, trastuzumab deruxtecan	✕	✕	✕	✕	● (I)

CCNE1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✕	✕	✕	✕	● (II)
APR-1051	✕	✕	✕	✕	● (I/II)
ARTS-021	✕	✕	✕	✕	● (I/II)
ECI-830, hormone therapy, ribociclib	✕	✕	✕	✕	● (I/II)
INX-315, hormone therapy	✕	✕	✕	✕	● (I/II)
WJB-001	✕	✕	✕	✕	● (I/II)
ETX-197, hormone therapy	✕	✕	✕	✕	● (I)
lunresertib, camonsertib, Debio-0123	✕	✕	✕	✕	● (I)
nedisertib, tuvusertib	✕	✕	✕	✕	● (I)
NKT-3964	✕	✕	✕	✕	● (I)
NKT-5097	✕	✕	✕	✕	● (I)

BRCA1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✕	✕	✕	✕	● (II)
pamiparib, tislelizumab	✕	✕	✕	✕	● (II)

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

Relevant Therapy Summary (continued)

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

BRIP1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✗	✗	✗	✗	● (II)

CDK12 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✗	✗	✗	✗	● (II)

RAD51C deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✗	✗	✗	✗	● (II)

RAD51D deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✗	✗	✗	✗	● (II)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	28.14%
BRCA1	CNV, CN:1.0
BRCA1	LOH, 17q21.31(41197602-41276231)x1
BRIP1	CNV, CN:1.0
BRIP1	LOH, 17q23.2(59760627-59938976)x1
CDK12	CNV, CN:1.0
CDK12	LOH, 17q12(37618286-37687611)x1
RAD51B	CNV, CN:1.0
RAD51B	LOH, 14q24.1(68290164-69061406)x1
RAD51C	CNV, CN:1.0
RAD51C	LOH, 17q22(56769933-56811619)x1
RAD51D	CNV, CN:1.0
RAD51D	LOH, 17q12(33427950-33446720)x1

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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