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1 of 20



Primary Tumor Site: colon
Collection Date: 2024.07.30

Patient Name: 신봉호 Gender: M Sample ID: N25-8

Sample Cancer Type: Rectal Cancer

Table of Contents	Page
Variant Details	2
Biomarker Descriptions	3
Alert Details	8
Relevant Therapy Summary	13

Report Highlights 7 Relevant Biomarkers 4 Therapies Available 21 Clinical Trials

Relevant Rectal Cancer Findings

Gene	Finding		Gene	Finding
BRAF	None detected		NTRK2	None detected
ERBB2	None detected		NTRK3	None detected
KRAS	KRAS p.(G128	6) c.34G>A	POLD1	None detected
NRAS	None detected		POLE	None detected
NTRK1	None detected		RET	None detected
Genomic Alte	eration	Finding		
Tumor Mu	tational Burden	2.84 Mut/Mb measured		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	KRAS p.(G12S) c.34G>A KRAS proto-oncogene, GTPase Allele Frequency: 34.55% Locus: chr12:25398285 Transcript: NM_033360.4	bevacizumab + chemotherapy ^I	None*	11
IIC	PIK3CA p.(E542K) c.1624G>A phosphatidylinositol-4,5-bisphosphate 3- kinase catalytic subunit alpha Allele Frequency: 13.49% Locus: chr3:178936082 Transcript: NM_006218.4	None*	inavolisib + palbociclib + hormone therapy 1/1 alpelisib + hormone therapy 1,2/11+ capivasertib + hormone therapy 1,2/1 +	5
IIC	ATM deletion ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4

^{*} 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.

Report Date: 19 May 2025 2 of 20

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	TP53 p.(R248Q) c.743G>A tumor protein p53 Allele Frequency: 23.25% Locus: chr17:7577538 Transcript: NM_000546.6	None*	None*	2
IIC	CHEK1 deletion checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	MLH1 p.(V384D) c.1151T>A mutL homolog 1 Allele Frequency: 50.45% Locus: chr3:37067240 Transcript: NM_000249.4	None*	None*	1
IIC	Microsatellite stable	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.(G12S) c.34G>A

octuximab 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

APC p.(S1415Rfs*4) c.4245delT, FAT1 p.(T2369Rfs*2) c.7105delA, HLA-A deletion, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MLH1	p.(V384D)	c.1151T>A		chr3:37067240	50.45%	NM_000249.4	missense
PIK3CA	p.(E542K)	c.1624G>A	COSM760	chr3:178936082	13.49%	NM_006218.4	missense
FAT1	p.(T2369Rfs*2)	c.7105delA		chr4:187540634	23.38%	NM_005245.4	frameshift Deletion
APC	p.(S1415Rfs*4)	c.4245delT		chr5:112175535	35.63%	NM_000038.6	frameshift Deletion
KRAS	p.(G12S)	c.34G>A	COSM517	chr12:25398285	34.55%	NM_033360.4	missense
NQ01	p.(P187S)	c.559C>T		chr16:69745145	51.88%	NM_000903.3	missense
TP53	p.(R248Q)	c.743G>A	COSM10662	chr17:7577538	23.25%	NM_000546.6	missense
POLD1	p.(A215V)	c.644C>T		chr19:50905516	6.90%	NM_001256849.1	missense

Variant Details (continued)

Copy Number Variations							
Gene	Locus	Copy Number	CNV Ratio				
HLA-A	chr6:29910229	0.62	0.65				
ATM	chr11:108098341	1	0.85				
CHEK1	chr11:125496639	1	0.86				

Biomarker Descriptions

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2¹. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest². CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)³.4. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR³. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication³.5.

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases^{6,7}. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases^{6,7}.

Potential relevance: The PARP inhibitor, olaparib⁸ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

KRAS p.(G12S) c.34G>A

KRAS proto-oncogene, GTPase

<u>Background:</u> 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^{10,11,12}.

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 cancer⁶. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{6,13,14}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{15,16}.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib¹⁷ (2021) and adagrasib¹⁸ (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma¹⁹. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036²⁰, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398²¹ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib²² 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-8520²³, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. 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)¹⁶. Additionally, KRAS mutations are associated with poor prognosis in NSCLC²⁸.

Report Date: 19 May 2025 4 of 20

Biomarker Descriptions (continued)

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A1. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells²⁹. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M³⁰. 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^{31,32,33}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A³⁴.

<u>Alterations and prevalence:</u> 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^{6,15}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{6,15}.

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

ATM deletion

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)³⁵. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair³⁶. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB^{36,37}. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins³⁸. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss^{39,40}. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability⁴¹.

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer^{6,15}.

Potential relevance: The PARP inhibitor, olaparib⁸ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib⁴² in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors^{39,43,44}. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib⁴⁵. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein¹. 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 complex⁴⁶. 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^{46,47}. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates to mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia^{48,49}. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway⁴⁶. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. 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^{50,51,52}. 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^{50,53}. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{51,53,54,55}. Specifically, MLH1 mutations are associated with increased risk of ovarian and pancreatic cancer^{56,57,58,59}.

Biomarker Descriptions (continued)

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^{6,15}.

Potential relevance: The PARP inhibitor, talazoparib⁴² 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 therapies⁶⁰. 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^{61,62}.

TP53 p.(R248Q) c.743G>A

tumor protein p53

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential⁶³. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{64,65}.

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%)^{6,15,66,67,68,69}. 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 R282^{6,15}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{70,71,72,73}.

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation⁷⁴. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,⁷⁵ and breakthrough designation⁷⁶ (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^{77,78}. 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)^{79,80,81,82,83,84}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁸⁵. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system⁸⁶.

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 1,87 . 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 functions 87 . The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion 87 . 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 transition 87 . Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT187.

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot^{6,15}. 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^{6,15}. 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^{6,15}.

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

Biomarker Descriptions (continued)

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 genome⁸⁸. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{51,53}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁵². Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250⁸⁹. 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)⁸⁹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{54,90,91,92,93}. 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 genes⁵³. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{51,53,54,55}.

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^{51,53,94,95}. 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^{94,95}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁶⁰ (2014) and nivolumab⁶¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁶⁰ 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 indication⁶⁰. Dostarlimab⁹⁶ (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^{91,97}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁶² (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^{91,98,99}. 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 patients⁹⁹. 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^{100,101}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{100,101}.

PIK3CA p.(E542K) c.1624G>A

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme¹⁰². PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases^{103,104}. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively¹⁰³. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction^{105,106}. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism^{105,106,107,108}. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability^{109,110,111}.

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers^{6,15}. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)^{112,113}. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation^{114,115,116}. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers^{6,15}.

Potential relevance: The PI3K inhibitor, alpelisib 117 , is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase lb study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression \geq 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors 118 . Specifically, exon 20 H1047R mutations were associated

Report Date: 19 May 2025 7 of 20

Biomarker Descriptions (continued)

with more durable clinical responses in comparison to exon 9 E545K mutations¹¹⁸. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations¹¹⁹. The FDA also approved the kinase inhibitor, capivasertib (2023)¹²⁰ in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib¹²¹, is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers^{122,123}.

APC p.(S1415Rfs*4) c.4245delT

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 differentiation¹²⁴. APC is an antagonist of WNT signaling as it targets β -catenin for proteasomal degradation^{125,126}. 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^{124,127}. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer¹²⁸.

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^{6,15,129}. 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^{130,131}.

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

Report Date: 19 May 2025 8 of 20

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

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

KRAS p.(G12S) c.34G>A

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

Report Date: 19 May 2025 9 of 20

KRAS p.(G12S) c.34G>A (continued)

panitumumab

Cancer type: Colorectal Cancer Label as of: 2025-01-16 Variant class: KRAS G12 mutation

Indications and usage:

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

Adult patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test) Metastatic Colorectal Cancer (mCRC)*:

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and 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







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

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

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

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

KRAS p.(G12S) c.34G>A

cetuximab

Cancer type: Rectal Cancer Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2025]

Report Date: 19 May 2025 10 of 20

KRAS p.(G12S) c.34G>A (continued)

panitumumab

Cancer type: Rectal Cancer Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2025]

cetuximab

Cancer type: Colon Cancer Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2025]

panitumumab

Cancer type: Colon Cancer Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2025]

Current EMA Information

EMA information is current as of 2025-03-19. For the most up-to-date information, search www.ema.europa.eu.

KRAS p.(G12S) c.34G>A

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer Label as of: 2025-01-16 Variant class: KRAS G12 mutation

Reference:

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

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer Label as of: 2022-07-06 Variant class: KRAS G12 mutation

Reference:

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

Report Date: 19 May 2025 11 of 20

Current ESMO Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

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

KRAS p.(G12S) c.34G>A

cetuximab

Cancer type: Colorectal Cancer Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

panitumumab

Cancer type: Colorectal Cancer Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, 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

Report Date: 19 May 2025 12 of 20

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, 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, 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, FANCE, FANCG, FANCI, FANCI, FANCH, FA

Relevant Therapy Summary

■ In this cancer type
O In other cancer type
O 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)
regorafenib	×	×	×	×	(II)
APR-1051	×	×	×	×	(/)
IMM-1-104	×	×	×	×	(/)
HMPL-415	×	×	×	×	(I)
JAB-3312	×	×	×	×	(I)
KQB-365, cetuximab	×	×	×	×	(I)
LY-4066434, cetuximab, pembrolizumab, chemotherapy	×	×	×	×	(1)
Nest-1	×	×	×	×	(l)
RMC-6236	×	×	×	×	(I)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	0	0	0	0	×
capivasertib + fulvestrant	0	0	0	×	×
inavolisib + palbociclib + fulvestrant	0	0	×	×	×
HTL-0039732, atezolizumab	×	×	×	×	(/)
ipatasertib, atezolizumab	×	×	×	×	(/)
STX-478, hormone therapy	×	×	×	×	(/)
JS-105	×	×	×	×	(I)
SNV-4818, hormone therapy	×	×	×	×	(I)

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

Report Date: 19 May 2025 14 of 20

Relevant Therapy Summary (continued)

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

ATM deletion					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	×	×	×	×	(II)
pamiparib, tislelizumab	×	×	×	×	(II)
senaparib, IMP-9064	×	×	×	×	(1/11)

TP53 p.(R248Q) c.743G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
APR-1051	×	×	×	×	(1/11)
TP53-EphA-2-CAR-DC, anti-PD-1	×	×	×	×	(I)

CHEK1 deletion

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ipilimumab + nivolumab, atezolizumab + talazoparib	×	×	×	×	(II)

Microsatellite stable

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
HTL-0039732, atezolizumab	×	×	×	×	(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	15.8%
ATM	CNV, CN:1.0
ATM	LOH, 11q22.3(108098341-108236285)x1
CHEK1	CNV, CN:1.0
CHEK1	LOH, 11q24.2(125496639-125525271)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, RAD51D, and RAD54L.

Report Date: 19 May 2025

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 (6.0.2 data version 2025.04(004)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

Report Date: 19 May 2025

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