

Patient Name: 김지성
Gender: M
Sample ID: N25-321

Primary Tumor Site: lung
Collection Date: 20251118

Sample Cancer Type: Lung Cancer

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Report Highlights
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Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	<i>NTRK1 amplification</i>
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	<i>KRAS p.(Q61H) c.183A>C</i>	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	<i>6.62 Mut/Mb measured</i>

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>KRAS p.(Q61H) c.183A>C</i> KRAS proto-oncogene, GTPase Allele Frequency: 25.25% Locus: chr12:25380275 Transcript: NM_033360.4	None*	avutometinib + defactinib¹ / II+ bevacizumab + chemotherapy¹	7
IIC	<i>NTRK1 amplification</i> neurotrophic receptor tyrosine kinase 1 Locus: chr1:156834550	None*	None*	2
IIC	<i>DDR2 amplification</i> discoidin domain receptor tyrosine kinase 2 Locus: chr1:162724523	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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	NBN p.(S53Lfs*2) c.153delC	None*	None*	1
	nibrin			
	Allele Frequency: 50.53%			
	Locus: chr8:90994967			
	Transcript: NM_002485.5			

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

Microsatellite stable, STK11 p.(I172Rfs*108) c.514_535delATTGTGCACAAGGACATCAAGC, MCL1 amplification, RIT1 amplification, UGT1A1 p.(G71R) c.211G>A, ERAP2 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
KRAS	p.(Q61H)	c.183A>C	COSM554	chr12:25380275	25.25%	NM_033360.4	missense
NBN	p.(S53Lfs*2)	c.153delC	.	chr8:90994967	50.53%	NM_002485.5	frameshift Deletion
STK11	p.(I172Rfs*108)	c.514_535delATTGTGC . ACAAGGACATCAAGC	.	chr19:1220418	38.89%	NM_000455.5	frameshift Deletion
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	51.73%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.20%	NM_000903.3	missense
PCDHGA9	p.(G380D)	c.1139G>A	.	chr5:140783658	11.66%	NM_018921.2	missense
FANCI	p.(F430dup)	c.1288_1290dup	.	chr15:89820115	12.09%	NM_001113378.2	nonframeshift Insertion
RAD51D	p.(T27K)	c.80C>A	.	chr17:33446553	48.38%	NM_133629.3	missense
KEAP1	p.(R71P)	c.212G>C	.	chr19:10610498	36.83%	NM_203500.2	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
NTRK1	chr1:156834550	8.28	2.57
DDR2	chr1:162724523	6.86	2.21
MCL1	chr1:150549846	7.22	2.3
RIT1	chr1:155870154	7.7	2.43
ERAP2	chr5:96219500	0	0.47
SDHC	chr1:161284179	5.94	1.98

Biomarker Descriptions

KRAS p.(Q61H) c.183A>C

KRAS proto-oncogene, GTPase

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival^{24,25,26}.

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^{6,27,28}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{7,29}.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib³⁰ (2021) and adagrasib³¹ (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 adenocarcinoma³². The FDA has approved the combination of kinase inhibitors, avutemetinib and defactinib³³ (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-6036³⁴, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironasib³⁵, and the KRAS G12C inhibitor, D3S-001³⁶, 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, olomorasib³⁷, was granted breakthrough designation (2025) in combination with pembrolizumab³⁸ for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression $\geq 50\%$. The SHP2 inhibitor, BBP-398³⁹ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutemetinib⁴⁰ 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-8520⁴¹, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonasib⁴², was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375⁴³, 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-001⁴⁴, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib⁴⁵, 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, cetuximab⁴⁶ and panitumumab⁴⁷, 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)²⁹. Additionally, KRAS mutations are associated with poor prognosis in NSCLC⁴⁸.

NTRK1 amplification

neurotrophic receptor tyrosine kinase 1

Background: The NTRK genes encode a family of neurotrophic receptor tyrosine kinases that function as receptors for nerve growth factors⁹⁴. NTRKs are activated by different neurotrophins and are important for the development of the nervous system⁹⁴. The NTRK1, 2 and 3 proteins are also known as tropomyosin-related kinases (TrkA, TrkB, TrkC) because NTRK1 was originally discovered as part of a chimeric fusion gene with tropomyosin-3 isolated from a human colon carcinoma cell line⁹⁵. NTRKs are the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact tyrosine kinase domain combined with numerous fusion partner genes^{96,97}. NTRK fusion kinases are constitutively active and lead to increased signaling through the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, or PLC γ /PKC pathways, promoting cell growth and proliferation^{96,98}.

Alterations and prevalence: NTRK fusions are infrequently observed in diverse pediatric and adult cancer types including glioma, glioblastoma, lung adenocarcinoma, colorectal carcinoma, thyroid cancer, and sarcoma^{6,96,99,100,101,102,103}. In certain cancer subtypes, including melanoma, infantile fibrosarcoma, papillary thyroid carcinoma, and secretory carcinoma of the breast or salivary gland, NTRK fusions are more prevalent^{96,102,103,104,105,106}. NTRK1 is amplified in 11% of cholangiocarcinoma, 10% of liver hepatocellular carcinoma, 8% of breast invasive carcinoma, 7% of lung adenocarcinoma, 4% of sarcoma, bladder urothelial carcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, and uterine carcinosarcoma, 3% of adrenocortical carcinoma, lung squamous cell carcinoma, and esophageal adenocarcinoma, and 2% of skin cutaneous melanoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, thymoma, and stomach adenocarcinoma^{6,7}. Somatic mutations in NTRK1 are observed in 8% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, 3% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and colorectal adenocarcinoma^{6,7}. Alterations in NTRK1 are rare in pediatric cancers⁷. NTRK1 is amplified in 6% of Wilms tumor and less than 1% of B-lymphoblastic

Biomarker Descriptions (continued)

leukemia/lymphoma (5 in 731 cases)⁷. Somatic mutations in NTRK1 are observed in less than 1% of embryonal tumors (2 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)⁷.

Potential relevance: The first-generation selective tropomyosin receptor kinase (TRK) inhibitor, larotrectinib¹⁰⁷, is approved (2018) for the treatment of adults and pediatric patients with any solid tumors harboring NTRK gene fusions and is the first approved small molecule inhibitor with a tissue agnostic indication. Entrectinib¹⁰⁸ is another first-generation TRK inhibitor approved (2019) for adults and pediatric patients with NTRK fusion-positive solid tumors as well as for adult patients with ROS1-positive non-small cell lung cancer (NSCLC). However, acquired resistance to first-generation NTRK inhibition is often mediated by the acquisition of solvent-front and gatekeeper mutations in the kinase domain¹⁰⁹. Consequently, the second generation TRK inhibitor, repotrectinib¹¹⁰, is approved by the FDA (2024) for the treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion. NTRK fusion is diagnostic of NTRK-rearranged spindle cell carcinoma as defined by the World Health Organization (WHO)¹¹¹.

DDR2 amplification

discoidin domain receptor tyrosine kinase 2

Background: The DDR2 gene encodes the discoidin domain receptor tyrosine kinase 2 protein. In comparison to receptor tyrosine kinases (RTKs) such as EGFR and FGFR that display rapid and transient activation, DDR2 exhibits delayed and continued receptor activation⁴⁹. DDR2 binds to collagen and can impact cell adhesion and migration through extracellular matrix (ECM) remodeling^{50,51}. DDR2 activation stimulates oncogenic signaling including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways thereby promoting cell proliferation and metastasis⁵¹.

Alterations and prevalence: Somatic mutations are observed in up to 7% of uterine cancer, and up to 4% of melanoma, non-small lung cell carcinoma, stomach cancer, and colorectal cancer^{4,6,52}. DDR2 mutations have been found along the kinase and discoidin domains but do not appear to occur in hotspot fashion and are not mutually exclusive with other driver mutations^{7,51,53}. Amplification of DDR2 is found to occur in up to 15% of bladder cancer and 10-14% of cholangiocarcinoma, breast, lung adenocarcinoma, and liver cancers^{5,6,7,54}.

Potential relevance: Currently, no therapies are approved for DDR2 aberrations. Various pre-clinical studies have demonstrated the efficacy of dasatinib (an approved multi-targeted tyrosine kinase inhibitor) in DDR2 mutated cancers^{53,55,56}. However, clinical data is limited. In an early phase clinical trial, one squamous cell carcinoma patient with a DDR2 S768R mutation and without an EGFR mutation demonstrated a radiographic response to treatment with dasatinib and erlotinib⁵⁷.

NBN p.(S53Lfs*2) c.153delC

nibrin

Background: The NBN gene encodes nibrin, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) protein complex, which is necessary for the maintenance of genomic stability^{79,80}. The MRN complex is involved in repair of double-stranded breaks (DSB) by homologous recombination repair (HRR) and non-homologous end joining (NHEJ)^{81,82,83}. Specifically, NBN contains a nuclear localization signaling motif responsible for translocation of the MRN complex into the nucleus and contributes to DNA repair by mediating protein-protein interactions at the site of DNA damage⁷⁹. NBN is a tumor suppressor gene. Loss of function mutations in NBN are implicated in the BRCAness phenotype, which is characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{84,85}. Germline mutations in NBN are associated with Nijmegen breakage syndrome, an autosomal recessive disorder resulting in microcephaly at birth, immunodeficiency, radiosensitivity, and cancer predisposition^{86,87}.

Alterations and prevalence: Somatic mutations in NBN are observed in 7-8% of uterine cancer and 2-4% of melanoma, colorectal, esophageal, bladder and stomach cancers⁶.

Potential relevance: The PARP inhibitor, talazoparib⁸⁸ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Loss of function mutations in one or more HRR genes, including NBN, may confer sensitivity to platinum agents and PARP inhibitors^{84,85,89}. NBN overexpression has been shown to be associated with poor prognosis in uveal melanoma, head and neck cancer, and ovarian cancer^{90,91,92,93}.

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 genome⁵⁸. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{59,60}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁶¹. 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 D17S250⁶². Tumors with instability in one of the five markers were defined as

Biomarker Descriptions (continued)

MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)⁶². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{63,64,65,66,67}. 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 genes⁶⁰. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{59,60,64,68}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endometrial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{59,60,69,70}. 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^{69,70}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab³⁸ (2014) and nivolumab⁷¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab³⁸ 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 indication³⁸. Dostarlimab⁷² (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^{65,73}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁷⁴ (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^{65,75,76}. 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 patients⁷⁶. 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^{77,78}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{77,78}.

STK11 p.(I172Rfs*108) c.514_535delATTGTGCACAAGGACATCAAGC

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression¹. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development^{2,3}.

Alterations and prevalence: Somatic mutations in STK11 have been reported in 10% of lung cancer, 4% of cervical cancer, and up to 3% of cholangiocarcinoma and uterine cancer^{4,5,6,7}. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer^{6,7}. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others^{2,5,6,7,8}.

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260⁹ in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors¹⁰. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)¹¹.

MCL1 amplification

MCL1, BCL2 family apoptosis regulator

Background: MCL1 encodes the MCL1 apoptosis regulator and is a member of the BCL2 family^{12,13}. The BCL2 family of proteins includes anti-apoptotic proteins, such as MCL1, BCL-2, BCL-W, BCL-B, BCL-XL, and BFL-1/A1, and pro-apoptotic proteins, such as BAX, BAK, BIM, BID, BAD, NOXA, and PUMA. MCL1 blocks apoptosis by sequestering pro-apoptotic proteins such as BAK and BAX, thereby preventing the release of cytochrome c from mitochondria, which is responsible for macromolecular degradation during apoptosis¹⁴. High levels of MCL1 expression sustain cancer cell survival and promote chemotherapy resistance^{15,16,17,18}.

Alterations and prevalence: Somatic mutations in MCL1 are observed in 2% of skin cutaneous melanoma^{6,7}. Amplification of MCL1 are observed in 11% of Liver Hepatocellular Carcinoma and Bladder Urothelial Carcinoma, 10% of Lung Adenocarcinoma and Breast Invasive Carcinoma, 8% of Cholangiocarcinoma and Ovarian Serous Cystadenocarcinoma, 7% of Uterine Corpus Endometrial Carcinoma, and 5% of Uterine Carcinosarcoma, Sarcoma, and Lung Squamous Cell Carcinoma^{6,7}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for MCL1 aberrations.

RIT1 amplification

Ras like without CAAX 1

Background: The RIT1 gene encodes the ras-like without CAAX1 protein¹². RIT1 is a member of the Ras family, possessing intrinsic GTP hydrolysis activity¹⁹. Specifically, RIT1 is ubiquitously expressed and plays a role in neuron survival following oxidative stress and dendritic cell retraction^{19,20,21}. RIT1 mutations have been shown to activate PI3K and MEK signaling pathways and likely promotes tumorigenesis²². Hereditary mutations in RIT1 lead to constitutive activation of RAS and MAPK pathways resulting in Noonan syndrome, a type of RASopathy^{22,23}.

Alterations and prevalence: Somatic mutations in RIT1 are observed in 3% of cholangiocarcinoma, 2% of uterine corpus endometrial carcinoma and lung adenocarcinoma, and 1% of cervical squamous cell carcinoma, skin cutaneous melanoma, and acute myeloid leukemia (AML)^{6,7}. Amplifications in RIT1 are observed in 14% of uterine carcinosarcoma, 11% of liver hepatocellular and cholangiocarcinoma, 8% of lung adenocarcinoma, breast invasive carcinoma, uterine corpus endometrial carcinoma, and 6% of ovarian serous cystadenocarcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for RIT1 aberrations.

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily^{12,115}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{115,116}. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance¹¹⁷. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation^{117,118,119,120}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38¹²¹.

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma^{6,7}.

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

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway^{112,113}. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules^{112,114}. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic¹¹².

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma^{6,7}. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for ERAP2 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

KRAS p.(Q61H) c.183A>C

cetuximab

Cancer type: Colorectal Cancer Label as of: 2021-09-24 Variant class: KRAS Q61 mutation

Indications and usage:

Erbixux® 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: Erbixux® 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.(Q61H) c.183A>C (continued)**🚫 panitumumab****Cancer type:** Colorectal Cancer**Label as of:** 2025-01-16**Variant class:** KRAS Q61 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

Current NCCN Information**🚫** Contraindicated**⊖** Not recommended**🛡️** Resistance**🚀** Breakthrough**🏠** Fast Track

NCCN information is current as of 2025-09-02. To view the most recent and complete version of the guideline, go online to NCCN.org.

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

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

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KRAS p.(Q61H) c.183A>C**🚫 cetuximab****Cancer type:** Colon Cancer**Variant class:** KRAS Q61 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 4.2025]

KRAS p.(Q61H) c.183A>C (continued)**❌ cetuximab**

Cancer type: Rectal Cancer

Variant class: KRAS Q61 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 3.2025]

❌ panitumumab

Cancer type: Colon Cancer

Variant class: KRAS Q61 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 4.2025]

❌ panitumumab

Cancer type: Rectal Cancer

Variant class: KRAS Q61 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 3.2025]

Current EMA Information**❌** Contraindicated**⊖** Not recommended**🛡** Resistance**🚀** Breakthrough**A** Fast TrackEMA information is current as of 2025-09-17. For the most up-to-date information, search www.ema.europa.eu.**KRAS p.(Q61H) c.183A>C****❌ cetuximab, cetuximab + oxaliplatin**

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS Q61 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 Q61 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 2025-09-02. For the most up-to-date information, search www.esmo.org.

KRAS p.(Q61H) c.183A>C

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS Q61 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 Q61 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, 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, TGFB, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, 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, PXDN, 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, SLC01B3, 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, 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, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

Relevant Therapy Summary

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

KRAS p.(Q61H) c.183A>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avutometinib + defactinib					
bevacizumab + CAPOX					
bevacizumab + FOLFIRI					
bevacizumab + FOLFOX					
bevacizumab + FOLFOXIRI					
daraxonrasib					
regorafenib					
afatinib, selumetinib					
ERAS-0015					
zotatifin					
Nest-1					

NTRK1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
larotrectinib					

DDR2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib					

NBN p.(S53Lfs*2) c.153delC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib					

* 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
Not Detected	Not Applicable

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. 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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