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Patient Name: 곽하영
Gender: F
Sample ID: N25-308

Primary Tumor Site:
Collection Date: 2023.10.24

Sample Cancer Type: Liver Cancer

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Relevant Liver Cancer Findings

Gene	Finding
BRAF	None detected
NTRK1	***NTRK1 imbalance***
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***6.72 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*NTRK1 imbalance* neurotrophic receptor tyrosine kinase 1 Locus: chr1:156841457	**repotrectinib** [1, 2 / II+] entrectinib [II+] larotrectinib [II+]	entrectinib [I, II+] larotrectinib [I, II+] repotrectinib [I, II+]	8
IIC	*KRAS p.(G13D) c.38G>A* KRAS proto-oncogene, GTPase Allele Frequency: 15.90% Locus: chr12:25398281 Transcript: NM_033360.4	None*	bevacizumab + chemotherapy [I]	8
IIC	*RAD54L p.(R536*) c.1606C>T* RAD54 like (S. cerevisiae) Allele Frequency: 3.31% Locus: chr1:46739415 Transcript: NM_001142548.1	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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

DPYD p.(M166V) c.496A>G, MAP2K4 deletion, NF1 deletion, POLE deletion, RPA1 deletion, STAG2 p.(R146) c.436C>T, TP53 deletion, TP53 p.(R337L) c.1010G>T, MCL1 amplification, H3-3A amplification, MAP3K1 deletion, ADAMTS2 deletion, CYLD deletion, CTCF deletion, ZFHX3 deletion, NCOR1 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	15.90%	NM_033360.4	missense
RAD54L	p.(R536*)	c.1606C>T	.	chr1:46739415	3.31%	NM_001142548.1	nonsense
DPYD	p.(M166V)	c.496A>G	.	chr1:98165091	32.44%	NM_000110.4	missense
STAG2	p.(R146*)	c.436C>T	.	chrX:123176469	3.95%	NM_001042749.2	nonsense
TP53	p.(R337L)	c.1010G>T	.	chr17:7574017	29.30%	NM_000546.6	missense
SLC8A1	p.(E625K)	c.1873G>A	.	chr2:40405569	16.41%	NM_021097.4	missense
SETD2	p.(R1826C)	c.5476C>T	.	chr3:47125794	3.98%	NM_014159.7	missense
OPRM1	p.(P65H)	c.194C>A	.	chr6:154360873	4.09%	NM_001008505.2	missense
JAK2	p.(S472N)	c.1415G>A	.	chr9:5069110	4.55%	NM_004972.4	missense
ARMC4	p.(E246K)	c.736G>A	.	chr10:28272855	3.35%	NM_018076.5	missense
ETV6	p.(E441K)	c.1321G>A	.	chr12:12043942	6.73%	NM_001987.5	missense
ARID2	p.(D157V)	c.470A>T	.	chr12:46211504	39.64%	NM_152641.4	missense
DICER1	p.(S1747L)	c.5240C>T	.	chr14:95560349	2.45%	NM_030621.4	missense
FANCI	p.(Q961_F962insWQ)	c.2884_2885insGGCAAT	.	chr15:89843611	37.72%	NM_001113378.2	nonframeshift Insertion
CDH1	p.(S649C)	c.1946C>G	.	chr16:68857311	46.37%	NM_004360.5	missense
FANCA	p.(S861F)	c.2582C>T	.	chr16:89833568	19.03%	NM_000135.4	missense
NCOR1	p.(A2407V)	c.7220C>T	.	chr17:15935713	3.57%	NM_006311.4	missense
NOL4	p.(R458H)	c.1373G>A	.	chr18:31537345	3.36%	NM_003787.5	missense
XPNPEP2	p.(T142I)	c.425C>T	.	chrX:128880592	4.79%	NM_003399.6	missense

Gene Fusions

Genes	Variant ID	Locus
NTRK1	NTRK1	chr1:156841457

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MAP2K4	chr17:11924164	0.88	0.66
NF1	chr17:29422233	0.73	0.62
POLE	chr12:133201214	0.68	0.61

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RPA1	chr17:1733385	0.95	0.68
TP53	chr17:7572848	0.72	0.61
MCL1	chr1:150549846	6.88	2.46
H3-3A	chr1:226252022	6.15	2.24
MAP3K1	chr5:56111388	0.95	0.69
ADAMTS2	chr5:178549645	0.58	0.58
CYLD	chr16:50783549	0.97	0.69
CTCF	chr16:67644720	0.93	0.68
ZFHX3	chr16:72820995	0.4	0.52
NCOR1	chr17:15935586	0.58	0.57
ELF3	chr1:201980251	6.37	2.31
PARP1	chr1:226549124	4.73	1.82

Biomarker Descriptions

NTRK1 imbalance

neurotrophic receptor tyrosine kinase 1

Background: The NTRK genes encode a family of neurotrophic receptor tyrosine kinases that function as receptors for nerve growth factors[129]. NTRKs are activated by different neurotrophins and are important for the development of the nervous system[129]. 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 line[130]. NTRKs are the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact tyrosine kinase domain combined with numerous fusion partner genes[131,132]. NTRK fusion kinases are constitutively active and lead to increased signaling through the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, or PLCγ/PKC pathways, promoting cell growth and proliferation[131,133].

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[4,131,134,135,136,137,138]. 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[131,137,138,139,140,141]. 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[4,5]. 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[4,5]. Alterations in NTRK1 are rare in pediatric cancers[5]. NTRK1 is amplified in 6% of Wilms tumor and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[5]. 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)[5].

Potential relevance: The first-generation selective tropomyosin receptor kinase (TRK) inhibitor, larotrectinib[142], 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. Entrectinib[143] 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 domain[144]. Consequently, the second generation TRK inhibitor, repotrectinib[145], is approved

Biomarker Descriptions (continued)

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)[146].

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 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[12,13,14].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,15,16]. Mutations at A59, K117, and A146 have also been observed but are less frequent[5,17].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[18] (2021) and adagrasib[19] (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 adenocarcinoma[20]. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib[21] (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-6036[22], for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib[23], and the KRAS G12C inhibitor, D3S-001[24], 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, olomorasib[25], was granted breakthrough designation (2025) in combination with pembrolizumab[26] for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression ≥ 50%. The SHP2 inhibitor, BBP-398[27] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib[28] 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-8520[29], was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib[30], was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375[31], 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-001[32], was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib[33], 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, cetuximab[34] and panitumumab[35], 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)[17]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[36].

RAD54L p.(R536*) c.1606C>T

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B[90]. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair[90,91,92]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[90,93]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[94]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[95].

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[96] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[97], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

DPYD p.(M166V) c.496A>G

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DPYD.

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[61]. Activation of MAPK proteins occurs through a kinase signaling cascade[61,62,63]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[61,62,63]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[61,62,63]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[87].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[4,5]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[4,5]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[88,89].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

NF1 deletion

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[42]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[42,43]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[42]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[42,44,45].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[42]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[42,46]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[42,45].

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)[47].

Biomarker Descriptions (continued)

POLE deletion

DNA polymerase epsilon, catalytic subunit

Background: The POLE gene encodes the DNA polymerase epsilon, catalytic subunit protein[1]. POLE is one of the four-subunits in the DNA polymerase epsilon complex that also includes POLE2, POLE3, and POLE4[77,78]. The DNA polymerase epsilon complex mediates DNA repair, chromosomal replication, and genomic stability[77,78]. Specifically, POLE is the largest subunit in the complex and contains the catalytic and proofreading exonuclease active sites proposed to function in leading strand synthesis during homologous recombination repair (HRR)[78,79]. Mutations in POLE lead to increased mutation rates and subsequent tumor formation thereby impacting genomic stability[78,79]. Somatic POLE mutations are characterized by a hypermutated phenotype due to the increase in single-nucleotide substitutions[80]. Monoallelic POLE variants have also been associated with adenomatous polyposis and may confer an increased risk in colorectal cancer (CRC)[81,82,83,84,85]. Germline mutations in POLE exonuclease domains are associated with a predisposition to polymerase proofreading-associated polyposis[80].

Alterations and prevalence: Recurrent somatic mutations occur in 15% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of colorectal adenocarcinoma, stomach adenocarcinoma, and bladder urothelial carcinoma, as well as 5% of lung squamous cell carcinoma and lung adenocarcinoma[4,5]. Specifically, mutations in the proofreading domain of POLE occur in 7-12% of endometrial cancer and 1-2% of colorectal cancer[78,80]. POLE mutations are associated with high tumor mutational burden (TMB)[78,80,86].

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

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[60]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[60]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[60].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[4,5]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for RPA1 aberrations.

STAG2 p.(R146*) c.436C>T

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[48,49]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[50,51]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[50,52].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants[45]. Somatic mutations in STAG2 are observed in 14% of bladder cancer, 10% of uterine cancer, 5% of glioblastoma multiforme, 4% of lung adenocarcinoma and skin cutaneous melanoma, 3% of acute myeloid leukemia, stomach adenocarcinoma, kidney renal papillary cell carcinoma, and lung squamous cell carcinoma, and 2% of cholangiocarcinoma, diffuse large B-cell lymphoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, uterine carcinosarcoma, breast invasive carcinoma, and esophageal adenocarcinoma[5]. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia[5]. Alterations in STAG2 are also observed in pediatric cancers[5]. Somatic mutations in STAG2 are observed in 10% of bone cancer (34 in 327 cases), 5% of soft tissue sarcoma (2 in 38 cases), 2% of embryonal tumors (5 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases) and peripheral nervous system cancers (1 in 1158 cases)[5]. Structural variants in STAG2 are observed in 2% of leukemia (1 in 64 cases) and less than 1% of bone cancer (1 in 150 cases)[5]. Biallelic deletion of STAG2 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of leukemia (1 in 250 cases)[5].

Biomarker Descriptions (continued)

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and acute myeloid leukemia[45,53]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[54].

TP53 deletion, TP53 p.(R337L) c.1010G>T

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[98]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[99]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[100,101].

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%)[4,5,102,103,104,105]. 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[4,5]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[106,107,108,109]. Alterations in TP53 are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[4,5]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[4,5].

Potential relevance: The small molecule p53 reactivator, PC14586[110] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[111,112]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[113]. 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)[45,53,114,115,116]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[117]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[118].

MCL1 amplification

MCL1, BCL2 family apoptosis regulator

Background: MCL1 encodes the MCL1 apoptosis regulator and is a member of the BCL2 family[1,6]. 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 apoptosis[7]. High levels of MCL1 expression sustain cancer cell survival and promote chemotherapy resistance[8,9,10,11].

Alterations and prevalence: Somatic mutations in MCL1 are observed in 2% of skin cutaneous melanoma[4,5]. 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[4,5].

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

H3-3A amplification

H3.3 histone A

Background: The H3-3A gene encodes H3.3 histone A, also known as H3F3A, a sequence variant member of the histone H3 family and the predominant form of histone H3 in non-dividing cells[65]. Histone H3, along with histones H4, H2A, and H2B, form the nucleosome, which is a component of chromatin[66]. Histones play a role in transcription regulation, DNA repair, replication, and chromosome stability[66]. Specifically, H3-3A marks enhancers and affects the transcriptional potential of target genes depending on where it binds in

Biomarker Descriptions (continued)

the genome[67]. Mutations in H3 have been observed to impact global histone methylation and gene transcription, which may promote tumorigenesis[68].

Alterations and prevalence: Somatic mutations in H3-3A are rare but mutually exclusive to IDH1 mutations in glioblastoma (GBM)[69]. In a study of diffuse intrinsic pontine gliomas (DIPGs) and non-brainstem pediatric glioblastoma (non-BS-PG), 14% of non-BS-PGs harbored a somatic G34R mutation in H3F3A[70]. In the same study, 78% of DIPGs and 22% of non-BS-PGs contained a K27M mutation in either H3-3A or H3C2[70]. Somatic mutations are observed in adult malignancies, including 2% of diffuse large B-cell lymphoma and uterine corpus endometrial carcinoma[4,5]. H3-3A amplification is observed in 9% of breast invasive carcinoma, 6% of cholangiocarcinoma, 5% of liver hepatocellular carcinoma, uterine carcinosarcoma, and ovarian serous cystadenocarcinoma, 3% of thymoma, lung adenocarcinoma, and stomach adenocarcinoma, and 2% of pheochromocytoma and paraganglioma, lung squamous cell carcinoma, skin cutaneous melanoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, and esophageal adenocarcinoma[4,5]. Alterations in H3-3A have also been reported in pediatric cancers[4,5]. Somatic mutations are observed in 17% of gliomas, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), leukemia (1 in 311 cases), bone cancer (1 in 327 cases) and Wilms tumor (1 in 710 cases)[4,5]. Amplification of H3-3A is observed in 3% of Wilms tumor and less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[4,5].

Potential relevance: The H3-3A K27M mutation is a diagnostic marker for diffuse midline glioma H3 K27-altered (Grade 4) and is associated with an adverse prognosis[71]. The FDA has approved the protease activator, dordaviprone[72] (2025), for the treatment of adult and pediatric patients with diffuse midline glioma harboring an H3-3A K27M mutation. The FDA has also granted breakthrough designation to BCB-276[73], a CART-T cell therapy, for the treatment of pediatric patients with DIPG.

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[1]. Activation of MAPK proteins occurs through a kinase signaling cascade[61,62,63]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[61,62,63]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[61,62,63]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[64]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[64]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[64].

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[4,5]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[64]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

CYLD deletion

CYLD lysine 63 deubiquitinase

Background: The CYLD gene encodes CYLD lysine 63 deubiquitinase, which is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) family of deubiquitinases[1,37]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[38]. CLYD contains a USP domain with a catalytic triad formed by Cys601, His871, and Asp889 that selectively hydrolyses K63-linked ubiquitin chains from signaling molecules and regulates cell survival, proliferation, and tumorigenesis[39,40]. CYLD plays a tumor suppressor role by negatively regulating NF-κB activation by deubiquitinating multiple NF-κB signaling components, including NEMO, Tak1, TRAF2, TRAF6, and RIP1[41]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[40,41]. CYLD has also been found to be downregulated in melanoma, salivary gland tumors, head and neck cancer, colon and hepatocellular carcinoma, cervical cancer, lung cancer, and renal cell carcinoma[40].

Alterations and prevalence: Somatic mutations in CYLD have been observed in 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of thymoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[4,5]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[4,5].

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

Biomarker Descriptions (continued)

CTCF deletion

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[74]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[74,75,76]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[74].

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma[4,5].

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

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,119,120]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[120,121]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[122,123,124,125,126]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[122,125,127,128].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[4,5]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,55,56]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[55,56,57,58]. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[56]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types, including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[56,59].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[4,5]. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[4,5]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[4,5]. Alterations in NCOR1 are also observed in pediatric cancer[5]. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[5]. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)[5].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for NCOR1 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.(G13D) c.38G>A

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-09-24 **Variant class:** KRAS G13 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 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: 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

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

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.

NTRK1 imbalance

larotrectinib

Cancer type: Angiosarcoma, Pleomorphic Rhabdomyosarcoma **Variant class:** NTRK1 fusion

Summary:

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

- "Not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma."

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]

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 4.2025]

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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 3.2025]

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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 4.2025]

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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 3.2025]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2025-09-17. 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 2025-09-02. 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)]

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

⊘ 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, 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, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

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, 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 (continued)

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, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

NTRK1 imbalance

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
repotrectinib	●	◑	●	✖	● (I/II)
entrectinib	✖	◑	✖	○	● (II)
larotrectinib	✖	◑	✖	○	✖
taletrectinib	✖	✖	✖	✖	● (II)
TL-118	✖	✖	✖	✖	● (II)
BPI-28592	✖	✖	✖	✖	● (I)
LZ-001	✖	✖	✖	✖	● (I)
VMD-928	✖	✖	✖	✖	● (I)

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFIRI	✖	✖	✖	○	✖

* 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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + FOLFOX	✖	✖	✖	○	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	○	✖
regorafenib	✖	✖	✖	✖	● (II)
almonertinib, palbociclib	✖	✖	✖	✖	● (I/II)
ERAS-0015	✖	✖	✖	✖	● (I/II)
ASP-5834	✖	✖	✖	✖	● (I)
daraxonrasib	✖	✖	✖	✖	● (I)
Nest-1	✖	✖	✖	✖	● (I)
toripalimab, chemotherapy, KRAS peptide vaccine	✖	✖	✖	✖	● (I)
ZEN-3694, binimetinib	✖	✖	✖	✖	● (I)

RAD54L p.(R536*) c.1606C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(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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