

**Patient Name:** 주선옥  
**Gender:** Female  
**Sample ID:** N26-29

**Primary Tumor Site:** Lung  
**Collection Date:** 2026.01.13.

## Sample Cancer Type: Lung Cancer

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## Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	<b>KRAS p.(G12C) c.34G&gt;T</b>	ROS1	None detected
MET	None detected		

  

Genomic Alteration	Finding
Tumor Mutational Burden	<b>6.63 Mut/Mb measured</b>

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
<b>IA</b>	<b>KRAS p.(G12C) c.34G&gt;T</b> KRAS proto-oncogene, GTPase Allele Frequency: 14.52% Locus: chr12:25398285 Transcript: NM_033360.4	<b>adagrasib</b> <sup>1,2 / II+</sup> <b>sotorasib</b> <sup>1,2 / II+</sup>	<b>adagrasib + cetuximab</b> <sup>1 / I, II+</sup> <b>panitumumab + sotorasib</b> <sup>1 / I, II+</sup> adagrasib <sup>I, II+</sup> adagrasib + panitumumab <sup>I, II+</sup> cetuximab + sotorasib <sup>I, II+</sup> sotorasib <sup>I, II+</sup> bevacizumab + chemotherapy <sup>I</sup>	69
<b>IIC</b>	<b>BRIP1 p.(L449*) c.1346T&gt;G</b> BRCA1 interacting protein C-terminal helicase 1 Allele Frequency: 17.89% Locus: chr17:59871085 Transcript: NM_032043.3	None*	None*	1

\* Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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)

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

**KRAS p.(G12C) c.34G>T** **D3S-001**<sup>1</sup>, **divarasib**<sup>1</sup>, **elironrasib**<sup>1</sup>, **olomorasib + pembrolizumab**<sup>1</sup>  
 **avutemetinib + sotorasib**<sup>1</sup>, **BBO-8520**<sup>1</sup>

Public data sources included in alerts: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*MAP2K7 deletion, MLH1 p.(E558\*) c.1672G>T, Microsatellite stable, PTEN p.(P246L) c.737C>T, RAD51B deletion, XRCC3 deletion, MECOM p.(R915Q) c.2744G>A, HLA-A deletion, HLA-A p.(L180\*) c.539T>A, MGA p.(M1426Wfs\*15) c.4276delA, B2M p.(L15Ffs\*41) c.43\_44delCT, ARHGAP35 p.(R1145\*) c.3433C>T, Tumor Mutational Burden*

## Variant Details

### DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	14.52%	NM_033360.4	missense
BRIP1	p.(L449*)	c.1346T>G	.	chr17:59871085	17.89%	NM_032043.3	nonsense
MLH1	p.(E558*)	c.1672G>T	.	chr3:37083763	17.75%	NM_000249.4	nonsense
PTEN	p.(P246L)	c.737C>T	COSM5111	chr10:89717712	16.42%	NM_000314.8	missense
MECOM	p.(R915Q)	c.2744G>A	COSM3203560	chr3:168819875	56.25%	NM_004991.4	missense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	76.40%	NM_001242758.1	nonsense
MGA	p.(M1426Wfs*15)	c.4276delA	.	chr15:42028734	17.37%	NM_001164273.1	frameshift Deletion
B2M	p.(L15Ffs*41)	c.43_44delCT	COSM144579	chr15:45003780	17.37%	NM_004048.4	frameshift Deletion
ARHGAP35	p.(R1145*)	c.3433C>T	.	chr19:47425365	2.60%	NM_004491.5	nonsense
MIB2	p.(R30W)	c.88C>T	.	chr1:1551972	49.07%	NM_080875.3	missense
SCN9A	p.(E438G)	c.1313A>G	.	chr2:167144948	3.85%	NM_002977.3	missense
DCAF4L2	p.(G175V)	c.524G>T	.	chr8:88885676	2.35%	NM_152418.4	missense
SMAD4	p.(R531Q)	c.1592G>A	.	chr18:48604770	15.57%	NM_005359.6	missense

### Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MAP2K7	chr19:7968792	0.25	0.65
RAD51B	chr14:68290164	1	0.92
XRCC3	chr14:104165043	0.43	0.69
HLA-A	chr6:29910229	0.3	0.66
GATA2	chr3:128200046	0.3	0.66
FGFR3	chr4:1801456	0	0.56
AKT1	chr14:105236628	0	0.55

## Variant Details (continued)

### Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CD276	chr15:73991923	0.38	0.67

## Biomarker Descriptions

### KRAS p.(G12C) c.34G>T

*KRAS proto-oncogene, GTPase*

**Background:** The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS<sup>1</sup>. 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<sup>2,3,4</sup>. Germline mutations in KRAS lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in heart and congenital defects, growth inhibition, and facial dysmorphic features<sup>5</sup>. Somatic mutations in KRAS are commonly altered in several cancers including non-small cell lung cancer, pancreatic cancer, and multiple myeloma<sup>5</sup>.

**Alterations and prevalence:** The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61<sup>6,7,8</sup>. Mutations at A59, K117, and A146 have also been observed but are less frequent<sup>9,10</sup>. Somatic mutations in KRAS are observed in 66% of pancreatic adenocarcinoma, 41% of colorectal adenocarcinoma, 30% of lung adenocarcinoma, 19% of uterine corpus endometrial carcinoma, 12% of uterine carcinosarcoma, 9% of stomach adenocarcinoma, 8% of testicular germ cell tumors, 6% of cholangiocarcinoma, 5% of cervical squamous cell carcinoma, acute myeloid leukemia, and diffuse large B-cell lymphoma, 4% of bladder urothelial carcinoma, and 2% of skin cutaneous melanoma and kidney renal papillary cell carcinoma<sup>6,9</sup>. KRAS is amplified in 9% of ovarian serous cystadenocarcinoma and testicular germ cell tumors, 8% of stomach adenocarcinoma, 7% of esophageal adenocarcinoma and uterine carcinosarcoma, 6% of lung adenocarcinoma, 4% of pancreatic adenocarcinoma and bladder urothelial carcinoma, 3% of lung squamous cell carcinoma, and 2% of sarcoma, mesothelioma, brain lower grade glioma, and uterine corpus endometrial carcinoma<sup>6,9</sup>. Alterations in KRAS are also observed in pediatric cancers<sup>9</sup>. Somatic mutations in KRAS are observed in 10% of B-lymphoblastic leukemia/lymphoma (24 in 252 cases), 8% of leukemia (29 in 354 cases), and in less than 1% of embryonal tumors (2 in 332 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)<sup>9</sup>. KRAS is amplified in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)<sup>9</sup>. Structural alterations in KRAS are observed in less than 1% of acute lymphoblastic leukemia (1 in 85 cases)<sup>9</sup>.

**Potential relevance:** The FDA has approved the small molecule inhibitors, sotorasib<sup>11</sup> (2021) and adagrasib<sup>12</sup> (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<sup>13</sup>. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib<sup>14</sup> (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<sup>15</sup>, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib<sup>16</sup>, and the KRAS G12C inhibitor, D3S-001<sup>17</sup>, 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<sup>18</sup>, was granted breakthrough designation (2025) in combination with pembrolizumab<sup>19</sup> for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression  $\geq$  50%. The RAF/MEK clamp, avutometinib<sup>20</sup> 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<sup>21</sup>, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib<sup>22</sup>, was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375<sup>23</sup>, 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<sup>24</sup>, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib<sup>25</sup>, 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<sup>26</sup> and panitumumab<sup>27</sup>, 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)<sup>10</sup>. Additionally, KRAS mutations are associated with poor prognosis in NSCLC<sup>28</sup>.

## Biomarker Descriptions (continued)

### BRIP1 p.(L449\*) c.1346T>G

*BRCA1 interacting protein C-terminal helicase 1*

**Background:** The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA<sup>112</sup>. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control<sup>113</sup>. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss<sup>103,104</sup>. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)<sup>114</sup>. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer<sup>114,115</sup>. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer<sup>112,116</sup>.

**Alterations and prevalence:** Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma<sup>6,9</sup>.

**Potential relevance:** The PARP inhibitor, olaparib<sup>107</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy<sup>103,117</sup>. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>41</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

### MAP2K7 deletion

*mitogen-activated protein kinase kinase 7*

**Background:** The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7<sup>1</sup>. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10<sup>51,52,53</sup>. Activation of MAPK proteins occurs through a kinase signaling cascade<sup>51,52,54</sup>. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members<sup>51,52,54</sup>. 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<sup>51,52,54</sup>.

**Alterations and prevalence:** Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma<sup>6,9</sup>. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma<sup>6,9</sup>.

**Potential relevance:** Currently, no therapies are approved for MAP2K7 aberrations.

### MLH1 p.(E558\*) c.1672G>T

*mutL homolog 1*

**Background:** The MLH1 gene encodes the mutL homolog 1 protein<sup>1</sup>. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLa complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex<sup>76</sup>. The MutLa complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLa and degradation of PMS2<sup>76,77</sup>. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia<sup>78,79</sup>. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway<sup>76</sup>. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication<sup>76</sup>. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes<sup>80</sup>. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>81,82,83</sup>. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes<sup>81,84</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>82,84,85,86</sup>. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer<sup>87,88,89,90</sup>.

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

**Potential relevance:** The PARP inhibitor, talazoparib<sup>91</sup> in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior

## Biomarker Descriptions (continued)

therapies<sup>19</sup>. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment<sup>92,93</sup>. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas<sup>94,95</sup>.

### 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 genome<sup>118</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>82,84</sup>. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2<sup>83</sup>. 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 D17S250<sup>119</sup>. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)<sup>119</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>85,120,121,122,123</sup>. 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 genes<sup>84</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>82,84,85,86</sup>.

**Alterations and prevalence:** The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma<sup>82,84,124,125</sup>. 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<sup>124,125</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>19</sup> (2014) and nivolumab<sup>92</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>19</sup> 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 indication<sup>19</sup>. Dostarlimab<sup>126</sup> (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<sup>121,127</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>93</sup> (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<sup>121,128,129</sup>. 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 patients<sup>129</sup>. 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<sup>130,131</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>130,131</sup>.

### PTEN p.(P246L) c.737C>T

#### *phosphatase and tensin homolog*

**Background:** The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities<sup>29</sup>. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT<sup>30,31</sup>. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency<sup>32</sup>. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation<sup>33</sup>. PTEN germline mutations are also associated with inherited cancer risk in several cancer types<sup>34</sup>.

**Alterations and prevalence:** PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are observed in several cancers including 65% of uterine cancer, 34% of uterine corpus endometrial carcinoma, 20% of uterine carcinosarcoma, 11% of lung squamous cell carcinoma, and 5-10% of skin cutaneous melanoma, kidney chromophobe, stomach adenocarcinoma, stomach squamous cell carcinoma, and cervical squamous cell carcinoma<sup>6,9</sup>. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN<sup>31,35,36,37,38</sup>. PTEN gene deletion is observed in several cancers including 17% of prostate adenocarcinoma, 10% of lung squamous cell carcinoma and glioblastoma multiforme, 7% of skin cutaneous melanoma, 6% of diffuse large B-cell lymphoma, sarcoma, and 1-5% of breast invasive carcinoma, melanoma, sarcoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, and uterine corpus endometrial carcinoma<sup>6,9</sup>. Alterations in PTEN are also observed in pediatric cancers<sup>9</sup>. Somatic mutations in PTEN are observed in 10% of T-lymphoblastic leukemia/lymphoma (4 in 41 cases), 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of glioma (7 in 297 cases),

## Biomarker Descriptions (continued)

and 1% of bone cancer (4 in 327 cases) and embryonal tumors (4 in 332 cases)<sup>9</sup>. Biallelic deletion of PTEN is observed in 6% of glioma (1 in 16 cases), 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (10 in 250 cases), and less than 1% of embryonal tumors (5 in 731 cases)<sup>9</sup>. Structural alterations in PTEN are observed in less than 1% of bone cancer (1 in 150 cases)<sup>9</sup>.

**Potential relevance:** Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors<sup>39,40</sup>. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>41</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib<sup>42</sup> in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

### **RAD51B deletion**

#### *RAD51 paralog B*

**Background:** The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)<sup>100</sup>. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex<sup>101</sup>. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP<sup>102</sup>. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss<sup>103,104</sup>. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents<sup>105</sup>. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk<sup>106</sup>.

**Alterations and prevalence:** Somatic mutations in RAD51B are observed in up to 3% of uterine cancer<sup>6,9</sup>. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk<sup>106</sup>.

**Potential relevance:** The PARP inhibitor, olaparib<sup>107</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>41</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

### **XRCC3 deletion**

#### *X-ray repair cross complementing 3*

**Background:** The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs<sup>1,43</sup>. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)<sup>43,44</sup>. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability<sup>45</sup>.

**Alterations and prevalence:** Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma<sup>6,9</sup>. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma<sup>6,9</sup>.

**Potential relevance:** Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin<sup>45</sup>.

### **MECOM p.(R915Q) c.2744G>A**

#### *MDS1 and EVI1 complex locus*

**Background:** The MECOM gene encodes the MDS1 and EVI1 complex locus (MECOM), a zinc-finger transcriptional factor that regulates hematopoietic cell differentiation<sup>55</sup>. The MECOM locus encodes multiple alternative splice variants that result in MDS1-EVI1, MDS1, and EVI1 protein isoforms<sup>56</sup>. The EVI1 isoform is the most abundant and oncogenic form of MECOM that is expressed in various cancers including acute myeloid leukemia (AML)<sup>56,57</sup>. MECOM is a frequent target of chromosomal translocation which can lead to MECOM overexpression and leukemogenesis<sup>58</sup>.

**Alterations and prevalence:** Somatic mutations MECOM are observed in up to 22% of malignant melanoma; 75% of these mutations are missense and the remaining 25% are truncating mutations<sup>6,9,59</sup>. MECOM amplifications are observed in up to 35% of lung squamous cell carcinoma, 30% of ovarian serous cystadenocarcinoma, and 20% of esophageal adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma<sup>6,9</sup>. MECOM rearrangements occur with various partner genes including ETV6, RUNX1, and

## Biomarker Descriptions (continued)

H2AFY<sup>60</sup>. The t(3;21)(q26;q22) translocation that results in the MECOM::RUNX1 fusion is most commonly observed in chronic myeloid leukemia (CML) in blast crisis. The t(3;3)(q21.3;q26.2)/ inv(3)(q21.3;q26.3) translocation, also referred to as inv(3)/t(3;3), results in a GATA2::MECOM fusion and is observed in AML, primary myelofibrosis (PMF), and myelodysplastic syndrome (MDS)<sup>61,62,63</sup>. The inv(3)/t(3;3) translocation repositions the distal GATA enhancer element and activates MECOM expression while simultaneously causing GATA2 haploinsufficiency<sup>64</sup>.

**Potential relevance:** AML with MECOM rearrangement is considered a distinct molecular subtype of AML as defined by the World Health Organization (WHO)<sup>65</sup>. MECOM rearrangements, including GATA2::MECOM fusions, are associated with poor/adverse risk in AML<sup>61,66</sup>. Inv(3) is associated with poor cytogenetic risk in MDS as defined by the revised international prognostic scoring system (IPSS-R) scoring system<sup>63</sup>. In PMF, inv(3) is considered an unfavorable karyotype associated with intermediate risk as defined by the dynamic international prognostic scoring system (DIPSS)-Plus scoring system<sup>62</sup>. MECOM overexpression is observed in 10% of de novo AML associated with poor prognosis, and is commonly found in MLL-rearranged cases<sup>67,68</sup>. Amplification of MECOM is associated with favorable prognosis in ovarian cancer<sup>69</sup>.

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

*major histocompatibility complex, class I, A*

**Background:** The HLA-A gene encodes the major histocompatibility complex, class I, A<sup>1</sup>. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells<sup>70</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>71</sup>. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the  $\alpha$  polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self<sup>72,73,74</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A<sup>75</sup>.

**Alterations and prevalence:** Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma<sup>6,9</sup>. Biallelic loss of HLA-A is observed in 4% of DLBCL<sup>6,9</sup>.

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

### MGA p.(M1426Wfs\*15) c.4276delA

*MGA, MAX dimerization protein*

**Background:** The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily<sup>1,108</sup>. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT<sup>109</sup>. MGA is capable of heterodimerization with the MAX bHLHZ transcription factor, which results in DNA recognition and transcriptional regulation of target genes involved in cell growth and proliferation<sup>108</sup>. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation<sup>110</sup>. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair<sup>111</sup>.

**Alterations and prevalence:** Somatic mutations in MGA are predominantly missense or truncating and are observed in 16% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 8% of stomach adenocarcinoma and lung adenocarcinoma, and 6% of colorectal adenocarcinoma and bladder urothelial carcinoma<sup>6,9</sup>. MGA biallelic deletion is observed in 6% of diffuse large B-cell lymphoma (DLBCL), 3% of mesothelioma, and 2% of ovarian serous cystadenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma<sup>6,9</sup>.

**Potential relevance:** Currently, no therapies are approved for MGA aberrations. However, MGA mutation has been observed to be enriched in non-small cell lung cancer (NSCLC) patients with higher objective response rates to immune checkpoint inhibitor (ICI) therapy<sup>111</sup>.

### B2M p.(L15Ffs\*41) c.43\_44delCT

*beta-2-microglobulin*

**Background:** The B2M gene encodes the beta-2-microglobulin protein<sup>1</sup>. B2M is an extracellular component of the major histocompatibility class (MHC) class I and is important for proper folding and transport of MHC class I to the cell surface of nucleated cells<sup>96</sup>. MHC class I molecules are located on the cell surface and present antigens from within the cell for recognition by cytotoxic T cells<sup>70</sup>. Peptide antigen presentation by MHC class I requires B2M, and mutation or loss of B2M prevents presentation and results in escape from immune recognition<sup>97</sup>. In cancer, mutations or loss of B2M allows for immune evasion by tumor cells, thereby preventing their destruction and supporting a tumor suppressor role for B2M<sup>97</sup>.

## Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in B2M are observed in 22% of diffuse large B-cell lymphoma (DLBCL), 5% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of cervical squamous cell carcinoma and skin cutaneous melanoma<sup>6,9</sup>. Biallelic loss of B2M is observed in 8% of DLBCL 5% of mesothelioma, and 2% of lung adenocarcinoma and skin cutaneous melanoma<sup>6,9</sup>.

Potential relevance: Currently, no therapies are approved for B2M aberrations. Loss of B2M has been implicated in resistance to immunotherapy in melanoma<sup>97,98</sup>. However, B2M mutations in microsatellite instability-high colorectal carcinomas show response to immune checkpoint inhibitors<sup>99</sup>.

### **ARHGAP35 p.(R1145\*) c.3433C>T**

*Rho GTPase activating protein 35*

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription<sup>1</sup>. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell membrane<sup>46,47</sup>. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis<sup>48,49</sup>.

Alterations and prevalence: Somatic mutations of ARHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma<sup>6,9</sup>. In endometrial cancer, R997\* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain<sup>50</sup>. Amplification of ARHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma<sup>6,9</sup>. Biallelic loss of ARHGAP35 has been observed in 2% of sarcoma<sup>6,9</sup>.

Potential relevance: Currently, no therapies are approved for ARHGAP35 aberrations.

## Alerts Informed By Public Data Sources

### Current FDA Information

 Contraindicated    Not recommended    Resistance    Breakthrough    Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

### KRAS p.(G12C) c.34G>T

#### panitumumab, panitumumab + sotorasib

**Cancer type:** Colorectal Cancer

**Label as of:** 2025-01-16

**Variant class:** KRAS G12C 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf)

**KRAS p.(G12C) c.34G>T (continued)****🚫 cetuximab****Cancer type:** Colorectal Cancer**Label as of:** 2021-09-24**Variant class:** KRAS G12 mutation**Indications and usage:**

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

**Head and Neck Cancer**

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

**Colorectal Cancer**

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

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

**Limitations of Use:** Erbix® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.**BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)**

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

**Reference:**[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/125084s279lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf)**🦋 D3S-001****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** KRAS G12C mutation**Supporting Statement:**

The FDA has granted Breakthrough Therapy designation to the KRAS G12C inhibitor, D3S-001, for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have had prior treatment with platinum-based chemotherapy and anti-PD-(L)1 antibody but have not been previously treated with a KRAS G12C inhibitor.

**Reference:**<https://www.prnewswire.com/news-releases/d3-bio-inc-announces-fda-breakthrough-therapy-designation-and-orphan-drug-designation-for-d3s-001-for-the-treatment-of-patients-with-kras-g12c-mutated-cancers-302540808.html>**🦋 divarasib****Cancer type:** Non-Small Cell Lung Cancer**Variant class:** KRAS G12C mutation**Supporting Statement:**

The FDA has granted Breakthrough Therapy designation to KRAS G12C inhibitor, GDC-6036, for KRAS G12C mutation in non-small cell lung cancer.

**Reference:**<https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>

## KRAS p.(G12C) c.34G>T (continued)

### elironrasib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Breakthrough designation to KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib, for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer who have received prior chemotherapy and immunotherapy but have not been previously treated with a KRAS G12C inhibitor.

**Reference:**

<https://ir.revmed.com/node/11881/pdf>

### olomorasib + pembrolizumab

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** KRAS G12C mutation

**Other criteria:** PD-L1 overexpression

**Supporting Statement:**

The FDA has granted Breakthrough Therapy designation to the small molecule inhibitor, olomorasib, in combination with anti-PD-1 therapy pembrolizumab (KEYTRUDA®), for the first-line treatment of patients with unresectable advanced or metastatic non-small cell lung cancer with a KRAS G12C mutation and PD-L1 expression  $\geq$  50%.

**Reference:**

<https://www.prnewswire.com/news-releases/lillys-olomorasib-receives-us-fdas-breakthrough-therapy-designation-for-the-treatment-of-certain-newly-diagnosed-metastatic-kras-g12c-mutant-lung-cancers-302545643.html>

### daraxonrasib

**Cancer type:** Pancreatic Cancer

**Variant class:** KRAS G12 mutation

**Supporting Statement:**

The FDA has granted Breakthrough designation to the RAS inhibitor, daraxonrasib, for previously treated metastatic pancreatic adenocarcinoma (PDAC) in patients with KRAS G12 mutations.

**Reference:**

<https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy>

### avutometinib + sotorasib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Fast Track designation to Verastem Oncology's investigational RAF/MEK clamp, avutometinib, in combination with Amgen's KRAS G12C inhibitor, LUMAKRASTM (sotorasib), for the treatment of patients with KRAS G12C-mutant metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor.

**Reference:**

<https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>

## KRAS p.(G12C) c.34G>T (continued)

### **A** BBO-8520

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Fast Track designation to the KRAS G12C inhibitor, BBO-8520, for the treatment of adult patients with previously treated, KRAS<sup>G12C</sup>-mutated metastatic non-small cell lung cancer (NSCLC).

**Reference:**

<https://www.businesswire.com/news/home/20250109170439/en/>

### **A** D3S-001

**Cancer type:** Colorectal Cancer

**Variant class:** KRAS G12C mutation

**Supporting Statement:**

The FDA has granted Fast Track designation to the KRAS G12C inhibitor, D3S-001, for the treatment of KRAS G12C mutated patients with advanced unresectable or metastatic colorectal cancers.

**Reference:**

<https://www.d3bio.com/press-releases/d3-bios-d3s-001-receives-u-s-fda-fast-track-designation-for-the-treatment-of-colorectal-cancer-with-kras-g12c-mutation>

## Current NCCN Information

 Contraindicated    Not recommended    Resistance    Breakthrough    Fast Track

NCCN information is current as of 2025-11-03. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org).

For NCCN International Adaptations & Translations, search [www.nccn.org/global/what-we-do/international-adaptations](https://www.nccn.org/global/what-we-do/international-adaptations).

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

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

## KRAS p.(G12C) c.34G>T

### cetuximab

**Cancer type:** Colon Cancer

**Variant class:** KRAS G12 mutation

**Summary:**

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

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

**Reference:** NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]

## KRAS p.(G12C) c.34G>T (continued)

### cetuximab

Cancer type: Rectal Cancer

Variant class: KRAS G12 mutation

**Summary:**

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]

### panitumumab

Cancer type: Colon Cancer

Variant class: KRAS G12 mutation

**Summary:**

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

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

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]

### panitumumab

Cancer type: Rectal Cancer

Variant class: KRAS G12 mutation

**Summary:**

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]

## Current EMA Information

 Contraindicated    Not recommended    Resistance    Breakthrough    Fast Track

EMA information is current as of 2025-11-25. For the most up-to-date information, search [www.ema.europa.eu](http://www.ema.europa.eu).

## KRAS p.(G12C) c.34G>T

### cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G12 mutation

**Reference:**

[https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf)

### panitumumab + oxaliplatin

Cancer type: Colorectal Cancer

Label as of: 2025-05-07

Variant class: KRAS G12 mutation

**Reference:**

[https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf)

## Current ESMO Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

ESMO information is current as of 2025-11-03. For the most up-to-date information, search [www.esmo.org](http://www.esmo.org).

### KRAS p.(G12C) c.34G>T

#### cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

##### Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

#### panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

##### Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

## Genes Assayed

### Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, 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, 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, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

## Genes Assayed (continued)

### Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBF, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRF1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

### Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

### Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBF, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRF1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

## Relevant Therapy Summary

● In this cancer type    
 ○ In other cancer type    
 ◐ In this cancer type and other cancer types    
 ✕ No evidence

### KRAS p.(G12C) c.34G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
adagrasib	●	◐	●	●	● (II)
sotorasib	●	◐	●	●	● (II)
adagrasib + cetuximab	○	○	✕	✕	✕
panitumumab + sotorasib	⚠	○	✕	✕	✕
panitumumab	⚠	✕	✕	✕	✕
adagrasib + panitumumab	✕	○	✕	✕	✕
cetuximab + sotorasib	✕	○	✕	✕	✕
bevacizumab + CAPOX	✕	✕	✕	○	✕
bevacizumab + FOLFIRI	✕	✕	✕	○	✕
bevacizumab + FOLFOX	✕	✕	✕	○	✕
bevacizumab + FOLFOXIRI	✕	✕	✕	○	✕
adagrasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
ASKC-202, limetinib	✕	✕	✕	✕	● (III)
D-1553	✕	✕	✕	✕	● (III)
daraxonrasib	✕	✕	✕	✕	● (III)
divarasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
glecirasib, JAB-3312, tislelizumab, chemotherapy	✕	✕	✕	✕	● (III)
MK-1084, pembrolizumab	✕	✕	✕	✕	● (III)
olomorasib, durvalumab	✕	✕	✕	✕	● (III)
olomorasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
pembrolizumab + berahyaluronidase alfa, chemotherapy, MK-1084	✕	✕	✕	✕	● (III)
sotorasib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
adagrasib, radiation therapy	✕	✕	✕	✕	● (II)
daratumumab, TG-01 (Targovax), QS-21 Stimulon, nivolumab	✕	✕	✕	✕	● (II)
divarasib	✕	✕	✕	✕	● (II)
glecirasib	✕	✕	✕	✕	● (II)
sintilimab, catequentinib	✕	✕	✕	✕	● (II)
sotorasib, chemotherapy	✕	✕	✕	✕	● (II)

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

## Relevant Therapy Summary (continued)

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

### KRAS p.(G12C) c.34G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
afatinib, selumetinib	✕	✕	✕	✕	● (I/II)
almonertinib, palbociclib	✕	✕	✕	✕	● (I/II)
avutometinib, sotorasib, defactinib	✕	✕	✕	✕	● (I/II)
D-1553, ifebemtinib	✕	✕	✕	✕	● (I/II)
elironrasib, pembrolizumab, chemotherapy, daraxonrasib	✕	✕	✕	✕	● (I/II)
ERAS-0015	✕	✕	✕	✕	● (I/II)
FMC-376	✕	✕	✕	✕	● (I/II)
glecirasib, JAB-3312	✕	✕	✕	✕	● (I/II)
HBI 2376, D-1553	✕	✕	✕	✕	● (I/II)
HS-10370	✕	✕	✕	✕	● (I/II)
HYP-2090PTSA	✕	✕	✕	✕	● (I/II)
YL-15293	✕	✕	✕	✕	● (I/II)
zotatifin, sotorasib	✕	✕	✕	✕	● (I/II)
adagrasib, olaparib	✕	✕	✕	✕	● (I)
ASP-5834	✕	✕	✕	✕	● (I)
BAY-3498264, sotorasib	✕	✕	✕	✕	● (I)
BBO-8520, pembrolizumab	✕	✕	✕	✕	● (I)
BEBT-607	✕	✕	✕	✕	● (I)
BMS-986488, adagrasib	✕	✕	✕	✕	● (I)
BPI-421286	✕	✕	✕	✕	● (I)
BPI-442096	✕	✕	✕	✕	● (I)
carfilzomib, sotorasib	✕	✕	✕	✕	● (I)
darlifarnib, adagrasib	✕	✕	✕	✕	● (I)
elironrasib, daraxonrasib	✕	✕	✕	✕	● (I)
HRS-7058	✕	✕	✕	✕	● (I)
ifebemtinib, sosimerasib, chemotherapy	✕	✕	✕	✕	● (I)
imatinib, trametinib	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
JSKN-016	✕	✕	✕	✕	● (I)

\* 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.(G12C) c.34G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
KQB-365	✕	✕	✕	✕	● (I)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	✕	✕	✕	✕	● (I)
ladarixin, sotorasib	✕	✕	✕	✕	● (I)
MK-0472, MK-1084	✕	✕	✕	✕	● (I)
MK-1084	✕	✕	✕	✕	● (I)
Nest-1	✕	✕	✕	✕	● (I)
patritumab deruxtecan	✕	✕	✕	✕	● (I)
sotorasib, radiation therapy	✕	✕	✕	✕	● (I)
SY-5933	✕	✕	✕	✕	● (I)
SYS-6023	✕	✕	✕	✕	● (I)
toripalimab, chemotherapy, KRAS peptide vaccine	✕	✕	✕	✕	● (I)

### BRIP1 p.(L449\*) c.1346T>G

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.

## HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	<b>20.99%</b>
RAD51B	<b>CNV, CN:1.0</b>
RAD51B	<b>LOH, 14q24.1(68290164-69061406)x1</b>

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from [www.fda.gov](http://www.fda.gov) and is current as of 2025-11-25. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-11-03. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-11-25. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search [www.clinicaltrials.gov](http://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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