

**Patient Name:** 김창욱  
**Gender:** M  
**Sample ID:** N25-58

**Primary Tumor Site:** Pancreas  
**Collection Date:** 2025.05.27

Sample Cancer Type: Pancreatic Cancer

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Relevant Pancreatic Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	KRAS	<b>KRAS p.(G12C) c.34G&gt;T</b>
BRCA1	None detected	NRG1	None detected
BRCA2	None detected	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	PALB2	None detected
FGFR3	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	<b>2.85 Mut/Mb measured</b>

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<b>KRAS p.(G12C) c.34G&gt;T</b> KRAS proto-oncogene, GTPase Allele Frequency: 45.29% Locus: chr12:25398285 Transcript: NM_033360.4	adagrasib II+ sotorasib II+	<b>adagrasib</b> 1, 2 / I, II+ <b>adagrasib + cetuximab</b> 1 / I, II+ <b>panitumumab + sotorasib</b> 1 / I, II+ <b>sotorasib</b> 1, 2 / I, II+ adagrasib + panitumumab I, II+ cetuximab + sotorasib I, II+ bevacizumab + chemotherapy I	40
IIC	<b>MTAP deletion</b> methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	8

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>CDKN2A deletion</i> cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	<i>ARID1A p.(Q1708*) c.5122C&gt;T</i> AT-rich interaction domain 1A Allele Frequency: 26.94% Locus: chr1:27102196 Transcript: NM_006015.6	None*	None*	1
IIC	<i>CDKN2B deletion</i> cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	<i>SMAD4 deletion</i> SMAD family member 4 Locus: chr18:48573387	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.

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

KRAS p.(G12C) c.34G>T  BBP-398 + sotorasib <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  
Microsatellite stable, TP53 p.(G266R) c.796G>A, TPMT p.(Y240C) c.719A>G, HLA-A deletion, HLA-A p.(L180\*) c.539T>A, HLA-B deletion, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	45.29%	NM_033360.4	missense
ARID1A	p.(Q1708*)	c.5122C>T	.	chr1:27102196	26.94%	NM_006015.6	nonsense
TP53	p.(G266R)	c.796G>A	COSM10794	chr17:7577142	28.61%	NM_000546.6	missense
TPMT	p.(Y240C)	c.719A>G	COSM4986703	chr6:18130918	47.20%	NM_000367.5	missense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	99.95%	NM_001242758.1	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.92%	NM_000903.3	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGC GGCCGACGCGGC	.	chr5:79950707	54.94%	NM_002439.5	nonframeshift Deletion
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT CA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
PARP4	p.(?)	c.3285_3285+5delinsA GT	.	chr13:25021149	100.00%	NM_006437.4	unknown

Variant Details (continued)

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	0.3	0.57
CDKN2A	chr9:21968178	0	0.41
CDKN2B	chr9:22005728	0.32	0.58
SMAD4	chr18:48573387	0.2	0.55
HLA-A	chr6:29910229	0.12	0.53
HLA-B	chr6:31322252	0	0.43
SETBP1	chr18:42281265	0.32	0.58

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. 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>10,11,12</sup>.

**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<sup>8</sup>. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61<sup>8,13,14</sup>. Mutations at A59, K117, and A146 have also been observed but are less frequent<sup>9,15</sup>.

**Potential relevance:** The FDA has approved the small molecule inhibitors, sotorasib<sup>16</sup> (2021) and adagrasib<sup>17</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>18</sup>. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036<sup>19</sup>, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398<sup>20</sup> was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avotemetinib<sup>21</sup> was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520<sup>22</sup>, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001<sup>23</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>24</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>25</sup> and panitumumab<sup>26</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>15</sup>. Additionally, KRAS mutations are associated with poor prognosis in NSCLC<sup>27</sup>.

MTAP deletion

methylthioadenosine phosphorylase

**Background:** The MTAP gene encodes methylthioadenosine phosphorylase<sup>1</sup>. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate<sup>91,92</sup>. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation<sup>92</sup>.

**Alterations and prevalence:** MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers<sup>92,93</sup>. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell

## Biomarker Descriptions (continued)

lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma<sup>8,9</sup>. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma<sup>8,9</sup>.

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

### CDKN2A deletion

*cyclin dependent kinase inhibitor 2A*

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression<sup>1</sup>. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)<sup>100</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>101,102,103</sup>. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions<sup>104</sup>. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation<sup>1,104,105</sup>. CDKN2A aberrations commonly co-occur with CDKN2B<sup>100</sup>. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation<sup>106</sup>. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer<sup>107,108</sup>.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations<sup>109</sup>. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma<sup>8,9</sup>. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe<sup>8,9</sup>. Alterations in CDKN2A are also observed in pediatric cancers<sup>9</sup>. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors<sup>9</sup>. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)<sup>9</sup>.

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors<sup>110,111,112</sup>. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma<sup>113</sup>. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib<sup>114,115,116</sup>. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme<sup>117</sup>. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer<sup>118,119,120,121</sup>.

### ARID1A p.(Q1708\*) c.5122C>T

*AT-rich interaction domain 1A*

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein<sup>1</sup>. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes ARID1B<sup>1,94</sup>. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex<sup>94,95</sup>. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B<sup>95</sup>. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression<sup>95,96</sup>. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription<sup>94</sup>. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function<sup>94</sup>.

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors<sup>96</sup>. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations<sup>94</sup>. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma<sup>8,9,95</sup>. In microsatellite stable

## Biomarker Descriptions (continued)

(MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response<sup>97</sup>.

**Potential relevance:** Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800<sup>98</sup>, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulumimostat<sup>99</sup>, dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

### CDKN2B deletion

*cyclin dependent kinase inhibitor 2B*

**Background:** CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression<sup>1,100</sup>. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)<sup>100</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>101,102,103</sup>. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A<sup>100</sup>. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma<sup>1,122,123</sup>.

**Alterations and prevalence:** CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B-cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe<sup>8,9</sup>. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma<sup>8,9</sup>. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers<sup>8,9</sup>. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)<sup>8,9</sup>.

**Potential relevance:** Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma<sup>113</sup>.

### SMAD4 deletion

*SMAD family member 4*

**Background:** The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7<sup>28,29</sup>. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF- $\beta$  and BMP signaling pathways that are implicated in cancer initiation and progression<sup>29,30,31</sup>. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC<sup>28,29</sup>.

**Alterations and prevalence:** Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)<sup>28</sup>. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF- $\beta$  signaling<sup>9,31,32</sup>. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers<sup>8,9,33</sup>.

**Potential relevance:** Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers<sup>29,31,34,35,36</sup>. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy<sup>37,38</sup>. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)<sup>38</sup>. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors<sup>39</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>66</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>67,68</sup>. MSI is closely tied to the status of the mismatch repair (MMR)



## Biomarker Descriptions (continued)

genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2<sup>69</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>70</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>70</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>71,72,73,74,75</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>68</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>67,68,72,76</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>67,68,77,78</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>77,78</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>79</sup> (2014) and nivolumab<sup>80</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>79</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>79</sup>. Dostarlimab<sup>81</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>73,82</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>83</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>73,84,85</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>85</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>86,87</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>86,87</sup>.

### TP53 p.(G266R) c.796G>A

*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<sup>1</sup>. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis<sup>40</sup>. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential<sup>41</sup>. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers<sup>42,43</sup>.

**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%)<sup>8,9,44,45,46,47</sup>. 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<sup>8,9</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>48,49,50,51</sup>. Alterations in TP53 are also observed in pediatric cancers<sup>8,9</sup>. 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)<sup>8,9</sup>. 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)<sup>8,9</sup>.

**Potential relevance:** The small molecule p53 reactivator, PC14586<sup>52</sup> (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprentapopt<sup>53</sup>, (2019) and breakthrough designation<sup>54</sup> (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation<sup>55,56</sup>. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma<sup>57</sup>. 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)<sup>58,59,60,61,62,63</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>64</sup>. Mono- and bi-allelic mutations in TP53 confer unique

## Biomarker Descriptions (continued)

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<sup>65</sup>.

### TPMT p.(Y240C) c.719A>G

*thiopurine S-methyltransferase*

**Background:** The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines<sup>1,88,89</sup>. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine<sup>88,89,90</sup>. Inherited TPMT polymorphisms, including TPMT\*2, TPMT\*3A, TPMT\*3B, TPMT\*3C, and TPMT\*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure<sup>88,90</sup>.

**Alterations and prevalence:** Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma<sup>8,9</sup>. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma<sup>8,9</sup>. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma<sup>8,9</sup>.

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

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

*major histocompatibility complex, class I, A*

**Background:** The HLA-A gene encodes the major histocompatibility complex, class I, 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>2</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>3</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>4,5,6</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A<sup>7</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>8,9</sup>. Biallelic loss of HLA-A is observed in 4% of DLBCL<sup>8,9</sup>.

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

### HLA-B deletion

*major histocompatibility complex, class I, B*

**Background:** The HLA-B gene encodes the major histocompatibility complex, class I, B<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>2</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>3</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>4,5,6</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B<sup>7</sup>.

**Alterations and prevalence:** Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma<sup>8,9</sup>. Biallelic loss of HLA-B is observed in 5% of DLBCL<sup>8,9</sup>.

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated    Not recommended    Resistance    Breakthrough    Fast Track

FDA information is current as of 2025-04-16. 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)

### 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>

### BBP-398 + sotorasib

**Cancer type:** Non-Small Cell Lung Cancer,  
Solid Tumor

**Variant class:** KRAS G12C mutation

#### Supporting Statement:

The FDA has granted Fast Track designation to a SHP2 inhibitor, BBP-398, in combination with LUMAKRAS® for adult patients with previously treated KRAS G12C-mutated metastatic NSCLC.

#### Reference:

<https://bridgebio.com/news/bridgebio-pharma-announces-first-lung-cancer-patient-dosed-in-phase-1-2-trial-and-us-fda-fast-track-designation-for-shp2-inhibitor-bbp-398-in-combination-with-amgens-lumakras-sotorasib/>

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

### **A** 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>

### **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.

The FDA has also granted Fast Track designation to D3S-001, for the treatment of late-line non-small cell lung cancer (NSCLC) and colorectal cancer (CRC).

**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 2025-04-01. 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 2.2025]

#### 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 2.2025]

#### 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 2.2025]

**KRAS p.(G12C) c.34G>T (continued)****🚫 panitumumab**

Cancer type: Rectal Cancer

Variant class: KRAS G12 mutation

**Summary:**

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]

**Current EMA Information****🚫** Contraindicated**⊖** Not recommended**🛡** Resistance**🚀** Breakthrough**A** Fast TrackEMA information is current as of 2025-04-16. 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: 2022-07-06

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 2025-04-01. 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, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPM1, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

## Genes Assayed (continued)

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

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDN, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

### Genes Assayed for the Detection of Fusions

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

### Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2



## Relevant Therapy Summary

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
adagrasib	○	◐	○	○	● (I)
sotorasib	○	◐	○	○	×
adagrasib + cetuximab	○	○	×	×	×
panitumumab + sotorasib	⚠	○	×	×	×
panitumumab	⚠	×	×	×	×
adagrasib + panitumumab	×	○	×	×	×
cetuximab + sotorasib	×	○	×	×	×
bevacizumab + CAPOX	×	×	×	○	×
bevacizumab + FOLFIRI	×	×	×	○	×
bevacizumab + FOLFOX	×	×	×	○	×
bevacizumab + FOLFOXIRI	×	×	×	○	×
RMC-6236	×	×	×	×	● (III)
daratumumab, TG-01 (Targovax), QS-21 Stimulon, nivolumab	×	×	×	×	● (II)
divarasib	×	×	×	×	● (II)
glecirasib	×	×	×	×	● (II)
regorafenib	×	×	×	×	● (II)
D-1553, ifebemtinib	×	×	×	×	● (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)
IMM-1-104	×	×	×	×	● (I/II)
IMM-6-415	×	×	×	×	● (I/II)
MRTX0902, adagrasib	×	×	×	×	● (I/II)
olomorasib	×	×	×	×	● (I/II)
RMC-6291, pembrolizumab, chemotherapy, RMC-6236	×	×	×	×	● (I/II)
YL-15293	×	×	×	×	● (I/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*
ZG-19018	×	×	×	×	● (I/II)
adagrasib, olaparib	×	×	×	×	● (I)
BAY-3498264, sotorasib	×	×	×	×	● (I)
BEBT-607	×	×	×	×	● (I)
BPI-421286	×	×	×	×	● (I)
divarasib, bevacizumab, RLY-1971, inavolisib	×	×	×	×	● (I)
GEC-255	×	×	×	×	● (I)
HBI-2438	×	×	×	×	● (I)
HMPL-415	×	×	×	×	● (I)
HRS-7058	×	×	×	×	● (I)
JAB-3312	×	×	×	×	● (I)
KO-2806, adagrasib	×	×	×	×	● (I)
KQB-365	×	×	×	×	● (I)
KRAS peptide vaccine, poly-ICLC, nivolumab, ipilimumab	×	×	×	×	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	×	×	×	×	● (I)
MK-0472, MK-1084	×	×	×	×	● (I)
MK-1084	×	×	×	×	● (I)
Nest-1	×	×	×	×	● (I)
RMC-6291, RMC-6236	×	×	×	×	● (I)
SY-5933	×	×	×	×	● (I)

### MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	×	×	×	×	● (I/II)
MRTX-1719	×	×	×	×	● (I/II)
TNG-456, abemaciclib	×	×	×	×	● (I/II)
TNG-462	×	×	×	×	● (I/II)
GTA-182	×	×	×	×	● (I)
ISM-3412	×	×	×	×	● (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

### MTAP deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
S-095035	×	×	×	×	● (I)
SYH-2039	×	×	×	×	● (I)

### CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	● (II)
palbociclib, abemaciclib	×	×	×	×	● (II)
AMG 193	×	×	×	×	● (I/II)

### ARID1A p.(Q1708\*) c.5122C>T

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

### CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	×	×	×	×	● (II)

### SMAD4 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
regorafenib	×	×	×	×	● (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	16.37%
RAD54L	LOH, 1p34.1(46714017-46743978)x2

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.05(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 2025-04-16. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-04-01. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-04-16. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. 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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