

Patient Name: 김숙이
Gender: Female
Sample ID: N26-67

Primary Tumor Site: gallbladder
Collection Date: 2023.07.20

Sample Cancer Type: Gallbladder Carcinoma

Table of Contents	Page	Report Highlights
Variant Details	2	2 Relevant Biomarkers
Biomarker Descriptions	4	2 Therapies Available
Alert Details	10	31 Clinical Trials
Relevant Therapy Summary	16	

Relevant Gallbladder Carcinoma Findings

Gene	Finding
BRAF	None detected
ERBB2	None detected
KRAS	KRAS p.(G12D) c.35G>A
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	17.24 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	KRAS p.(G12D) c.35G>A KRAS proto-oncogene, GTPase Allele Frequency: 44.35% Locus: chr12:25398284 Transcript: NM_033360.4	None*	avutometinib + defactinib^{1 / II+} bevacizumab + chemotherapy ^I	26
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO

* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Line of therapy: I: First-line therapy, II+: Other line of therapy

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

ARID1B deletion, *KEAP1* p.(V604Wfs*68) c.1810delG, *LATS1* deletion, *Microsatellite stable*, *NFE2L2* p.(D77N) c.229G>A, *RAD54L* deletion, *STK11* deletion, *USP9X* p.(R118*) c.352C>T, *HCN1* p.(R590Q) c.1769G>A, *HDAC2* 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.(G12D)	c.35G>A	COSM521	chr12:25398284	44.35%	NM_033360.4	missense
KEAP1	p.(V604Wfs*68)	c.1810delG	.	chr19:10597392	21.79%	NM_203500.2	frameshift Deletion
NFE2L2	p.(D77N)	c.229G>A	COSM132959	chr2:178098816	15.41%	NM_006164.5	missense
USP9X	p.(R118*)	c.352C>T	.	chrX:40994007	3.10%	NM_001039590.3	nonsense
HCN1	p.(R590Q)	c.1769G>A	.	chr5:45267205	3.45%	NM_021072.4	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	98.44%	NM_000903.3	missense
MTOR	p.(?)	c.6663-3C>T	.	chr1:11182186	3.41%	NM_004958.4	unknown
TEX38	p.(I107T)	c.320T>C	.	chr1:47138827	64.42%	NM_001145474.4	missense
EFCAB7	p.(G252R)	c.754G>A	.	chr1:63999837	3.66%	NM_032437.4	missense
JAK1	p.(D1021V)	c.3062A>T	.	chr1:65303693	18.07%	NM_002227.4	missense
JAK1	p.(R681W)	c.2041C>T	.	chr1:65311270	2.67%	NM_002227.4	missense
LRRC7	p.(R391H)	c.1172G>A	.	chr1:70478694	3.79%	NM_001370785.2	missense
FUBP1	p.(R214Q)	c.641G>A	.	chr1:78430649	3.05%	NM_003902.5	missense
FUBP1	p.(R146K)	c.437G>A	.	chr1:78432414	4.26%	NM_003902.5	missense
NOTCH2	p.(M1605I)	c.4815G>A	.	chr1:120466304	4.90%	NM_024408.4	missense
NOTCH2NL C	p.(T142I)	c.425C>T	.	chr1:120539829	4.01%	NM_001364012.2	missense
NOTCH2	p.(T181I)	c.542C>T	.	chr1:120539829	4.01%	NM_024408.4	missense
OR2L8	p.(Y217R)	c.649_650delTAinsCG	.	chr1:248112808	2.30%	NM_001001963.1	missense
MSH2	p.(V620I)	c.1858G>A	.	chr2:47702262	4.94%	NM_000251.3	missense
MSH2	p.(M866I)	c.2598G>A	.	chr2:47707974	4.92%	NM_000251.3	missense
EHBP1	p.(A780V)	c.2339C>T	.	chr2:63176215	4.72%	NM_015252.5	missense
CASP8	p.(Y507H)	c.1519T>C	.	chr2:202151219	6.25%	NM_001080125.2	missense
FANCD2	p.(?)	c.2977-1G>A	.	chr3:10122783	4.16%	NM_033084.6	unknown
MLH1	p.(D376G)	c.1127A>G	.	chr3:37067216	50.96%	NM_000249.4	missense
RASA2	p.(?)	c.761+1G>A	.	chr3:141277805	3.52%	NM_006506.5	unknown
ATR	p.(?)	c.5738+1G>A	.	chr3:142215854	4.32%	NM_001184.4	unknown
PIK3CA	p.(G463E)	c.1388G>A	.	chr3:178928110	3.12%	NM_006218.4	missense
FBXW7	p.(E287K)	c.859G>A	.	chr4:153258956	3.47%	NM_033632.3	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FBXW7	p.(R278Q)	c.833G>A	.	chr4:153258982	5.24%	NM_033632.3	missense
ADAMTS12	p.(G661D)	c.1982G>A	.	chr5:33630925	5.07%	NM_030955.4	missense
C6	p.(D627N)	c.1879_1881delGACins AAT	.	chr5:41158863	1.72%	NM_000065.5	missense
MAP3K1	p.(S423L)	c.1268C>T	.	chr5:56161771	3.69%	NM_005921.2	missense
MSH3	p.(A299V)	c.896C>T	.	chr5:79968166	7.10%	NM_002439.5	missense
MSH3	p.(D868N)	c.2602G>A	.	chr5:80088610	4.69%	NM_002439.5	missense
DAXX	p.(L384Q)	c.1151T>A	.	chr6:33288293	41.45%	NM_001141970.2	missense
CEP85L	p.(S239N)	c.716G>A	.	chr6:118887005	3.61%	NM_001178035.1	missense
MAP3K4	p.(S456N)	c.1367G>A	.	chr6:161470671	3.81%	NM_005922.4	missense
GLI3	p.(R325C)	c.973C>T	.	chr7:42079692	2.97%	NM_000168.6	missense
ABCB1	p.(?)	c.827+1G>A	.	chr7:87190578	6.04%	NM_000927.4	unknown
RUNDC3B	p.(V301A)	c.902T>C	.	chr7:87407166	4.69%	NM_138290.3	missense
C8orf89	p.(P63S)	c.187C>T	.	chr8:74169302	4.51%	NM_001243237.1	missense
ARMC4	p.(E417K)	c.1249G>A	.	chr10:28250634	3.42%	NM_018076.5	missense
FGFR2	p.(V232=;V233A)	c.696_698delAGTinsG GC	.	chr10:123298156	2.14%	NM_000141.5	synonymous, missense
KMT2D	p.(R5238Q)	c.15713G>A	.	chr12:49420036	3.29%	NM_003482.4	missense
SACS	p.(S4108L)	c.12323C>T	.	chr13:23905692	6.11%	NM_014363.6	missense
BRCA2	p.(P3202L)	c.9605C>T	.	chr13:32971138	3.56%	NM_000059.4	missense
KLF5	p.(N264Hfs*11)	c.790_793delAACA	.	chr13:73636526	25.51%	NM_001730.5	frameshift Deletion
TPP2	p.(A1079T)	c.3235G>A	.	chr13:103317178	5.02%	NM_003291.4	missense
FANCM	p.(D1284G)	c.3851A>G	.	chr14:45645808	8.73%	NM_020937.4	missense
MGA	p.(E2974K)	c.8920G>A	.	chr15:42059200	2.65%	NM_001164273.1	missense
PALB2	p.(P615S)	c.1843C>T	.	chr16:23641632	3.36%	NM_024675.4	missense
CTCF	p.(R320C)	c.958C>T	.	chr16:67650653	2.55%	NM_006565.4	missense
CTCF	p.(G714R)	c.2140G>A	.	chr16:67671731	5.39%	NM_006565.4	missense
EFCAB5	p.(V249I)	c.745G>A	.	chr17:28296363	4.39%	NM_198529.4	missense
STK11	p.(S216F)	c.647C>T	.	chr19:1220629	19.50%	NM_000455.5	missense
CIC	p.(S1503F)	c.4508C>T	.	chr19:42799024	3.42%	NM_015125.5	missense
ASXL1	p.(G870S)	c.2608G>A	.	chr20:31023123	3.90%	NM_015338.6	missense
ASXL1	p.(T945I)	c.2834C>T	.	chr20:31023349	16.04%	NM_015338.6	missense
DYNLT3	p.(W43*)	c.129G>A	.	chrX:37701102	4.26%	NM_006520.3	nonsense
USP9X	p.(A2048V)	c.6143C>T	.	chrX:41076530	2.98%	NM_001039590.3	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KDM6A	p.(E1347K)	c.4039G>A	.	chrX:44969357	2.71%	NM_021140.3	missense
ZNF41	p.(C131Y)	c.392G>A	.	chrX:47308777	5.02%	NM_153380.3	missense
TEX11	p.(S448L)	c.1343C>T	.	chrX:69890309	4.57%	NM_001003811.2	missense
ATRX	p.(P599L)	c.1796C>T	.	chrX:76938952	4.37%	NM_000489.6	missense
AGTR2	p.(P200S)	c.598C>T	.	chrX:115304131	4.64%	NM_000686.5	missense
PHF6	p.(T102I)	c.305C>T	.	chrX:133527595	3.82%	NM_032458.3	missense
MPP1	p.(R107K)	c.320G>A	.	chrX:154020049	2.61%	NM_002436.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0	0.44
ARID1B	chr6:157099057	0.48	0.68
LATS1	chr6:149982844	0.38	0.66
RAD54L	chr1:46714017	1	0.75
STK11	chr19:1206847	0.43	0.67
HDAC2	chr6:114262171	0.1	0.6

Biomarker Descriptions

KRAS p.(G12D) c.35G>A

KRAS proto-oncogene, GTPase

Background: The *KRAS* proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS¹⁵. 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^{16,17,18}. 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 features¹⁹. Somatic mutations in *KRAS* are commonly altered in several cancers including non-small cell lung cancer, pancreatic cancer, and multiple myeloma¹⁹.

Alterations and prevalence: The majority of *KRAS* mutations consist of point mutations occurring at G12, G13, and Q61^{8,20,21}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{9,22}. 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^{8,9}. *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^{8,9}. Alterations in *KRAS* are also observed in pediatric cancers⁹. 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)⁹. *KRAS* is amplified in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)⁹. Structural alterations in *KRAS* are observed in less than 1% of acute lymphoblastic leukemia (1 in 85 cases)⁹.

Biomarker Descriptions (continued)

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib²³ (2021) and adagrasib²⁴ (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 adenocarcinoma²⁵. The FDA has approved the combination of kinase inhibitors, avutometinib and defactinib²⁶ (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-6036²⁷, for KRAS G12C-mutated NSCLC. The KRAS-G12C/NRAS-G12C dual inhibitor, elironrasib²⁸, and the KRAS G12C inhibitor, D3S-001²⁹, 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, olomorasi³⁰, was granted breakthrough designation (2025) in combination with pembrolizumab³¹ for unresectable advanced or metastatic NSCLC with a KRAS G12C mutation and PD-L1 expression \geq 50%. The RAF/MEK clamp, avutometinib³² 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-8520³³, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The RAS inhibitor, daraxonrasib³⁴, was granted breakthrough designation (2025) for previously treated metastatic pancreatic cancer with KRAS G12 mutations. The KRAS G12D (ON/OFF) inhibitor, GFH-375³⁵, 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-001³⁶, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib³⁷, 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, cetuximab³⁸ and panitumumab³⁹, 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)²². Additionally, KRAS mutations are associated with poor prognosis in NSCLC⁴⁰.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹⁵. 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)⁹⁴. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{95,96,97}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions⁹⁸. 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^{15,98,99}. CDKN2A aberrations commonly co-occur with CDKN2B⁹⁴. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation¹⁰⁰. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{101,102}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations¹⁰³. 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^{8,9}. 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^{8,9}. Alterations in CDKN2A are also observed in pediatric cancers⁹. 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 tumors⁹. 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)⁹.

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^{104,105,106}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma¹⁰⁷. 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^{108,109,110}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme¹¹¹. 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^{112,113,114,115}.

Biomarker Descriptions (continued)

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein¹⁵. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A^{15,41}. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex^{41,42}. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B⁴². The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{42,43}. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID1B functions as a tumor suppressor⁴¹.

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 tumors⁴³. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma^{8,9}. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma^{8,9}.

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases^{44,45}.

KEAP1 p.(V604Wfs*68) c.1810delG

kelch like ECH associated protein 1

Background: The KEAP1 gene encodes the kelch like ECH associated protein 1, a tumor suppressor and a member of the KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex^{15,46}. KEAP1 helps facilitate the negative regulation of the proto-oncogene NFE2L2 (NRF2) through ubiquitination, which leads to proteasomal degradation of NFE2L2⁴⁷. Aberrations in KEAP1 can result in loss of function leading to accumulation of NFE2L2, thereby altering the transcription genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation^{47,48,49}.

Alterations and prevalence: Somatic mutations in KEAP1 are observed in 18% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 6% of cholangiocarcinoma, 5% of liver hepatocellular carcinoma, 4% of uterine corpus endometrial carcinoma and head and neck squamous cell carcinoma, 3% of esophageal adenocarcinoma, and 2% of stomach adenocarcinoma, skin cutaneous melanoma, adrenocortical carcinoma, and bladder cancer⁹. Alterations in KEAP1 are also observed in pediatric cancers⁹. Somatic mutations in KEAP1 are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone cancer (1 in 327 cases), and embryonal tumors (1 in 332 cases)⁹. Biallelic deletion of KEAP1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases)⁹.

Potential relevance: Currently, no therapies are approved for KEAP1 aberrations.

LATS1 deletion

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1¹⁵. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members^{90,91}. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ⁹². Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes⁹². Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1⁹³.

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma^{8,9}. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma^{8,9}.

Potential relevance: Currently, no therapies are approved for LATS1 aberrations.

Biomarker Descriptions (continued)

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome⁶². Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{63,64}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁶⁵. 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 D17S250⁶⁶. 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)⁶⁶. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{67,68,69,70,71}. 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 genes⁶⁴. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{63,64,68,72}.

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^{63,64,73,74}. 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^{73,74}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab³¹ (2014) and nivolumab⁷⁵ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab³¹ 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 indication³¹. Dostarlimab⁷⁶ (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^{69,77}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁷⁸ (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^{69,79,80}. 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 patients⁸⁰. 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^{81,82}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{81,82}.

NFE2L2 p.(D77N) c.229G>A

nuclear factor, erythroid 2 like 2

Background: The NFE2L2 gene encodes the nuclear factor, erythroid 2 like 2 transcription factor, a member of the basic leucine zipper protein family¹⁵. NFE2L2, also known as NRF2, is a proto-oncogene that activates transcription of genes with antioxidant response elements (ARE)⁴⁹. NFE2L2 targets include genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation^{47,49}. NFE2L2 is negatively regulated by KEAP1, a Cul3 adaptor protein, that ubiquitinates NFE2L2⁴⁷.

Alterations and prevalence: Recurrent somatic mutations in NFE2L2 are observed in 14% of lung squamous cell carcinoma, 9% of esophageal adenocarcinoma, and 5% of head and neck squamous cell carcinoma^{8,9}. Deletion of NFE2L2 exon 2 or exon 2 and 3 result in an isoform leading to the lack of the KEAP1 interacting domain, NFE2L2 stabilization, and expression of NFE2L2 targets such as HMOX1, G6PD, PDGFC, FGF2, and NQO1^{49,60}.

Potential relevance: Currently, no therapies are approved for NFE2L2 aberrations. The FDA has granted fast track designation (2022) to the mTORC 1/2 inhibitor, sapanisertib (CB-228)⁶¹, for patients with NFE2L2 mutated, unresectable or metastatic squamous non-small cell lung cancer (NSCLC) who have received prior platinum-based chemotherapy and immune checkpoint inhibitor therapy.

RAD54L deletion

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B⁵⁰. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair^{50,51,52}. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases^{50,53}. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination⁵⁴. RAD54L is a

Biomarker Descriptions (continued)

tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss⁵⁵.

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer^{8,9}.

Potential relevance: The PARP inhibitor, olaparib⁵⁶ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁵⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression¹. STK11 preserves hematopoietic stem cell homeostasis, and its loss drives metabolic dysfunction and promotes leukemic progression in myeloproliferative neoplasms via ROS and HIF-1 α activation^{2,3}. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development^{4,5}.

Alterations and prevalence: Somatic mutations in STK11 are observed in 13% of lung adenocarcinoma, 4% of cervical squamous cell carcinoma, 3% of cholangiocarcinoma and uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, pancreatic adenocarcinoma, adrenocortical carcinoma, and esophageal adenocarcinoma^{6,7,8,9}. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer^{8,9}. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others^{4,7,8,9,10}. Biallelic loss of STK11 is observed in 3% of sarcoma, cervical squamous cell carcinoma, and ovarian serous cystadenocarcinoma^{8,9}. Alterations in STK11 are also observed in pediatric cancers¹¹. Biallelic loss of STK11 is observed in 6% of B-lymphoblastic leukemia/lymphoma (45 in 731 cases), 2% of leukemia (4 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)¹¹. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and glioma (1 in 297 cases)¹¹.

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260¹² in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors¹³. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)¹⁴.

USP9X p.(R118*) c.352C>T

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-linked protein¹⁵. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases⁵⁸. DUBs catalyze the removal of ubiquitin from target proteins, thereby counter-regulating post-translational ubiquitin modifications within the cell^{58,59}. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X⁵⁹. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its substrates⁵⁹. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair⁵⁹.

Alterations and prevalence: Somatic mutations are observed in 16% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of cholangiocarcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma^{8,9}. Biallelic deletion in USP9X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma, uterine carcinosarcoma, and lung squamous cell carcinoma^{8,9}. Alterations in USP9X are also observed in the pediatric population⁹. Somatic mutations are observed in 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (1 in 311 cases)⁹. Biallelic deletion in USP9X is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)⁹.

Potential relevance: Currently, no therapies are approved for USP9X aberrations.

Biomarker Descriptions (continued)

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein¹⁵. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)⁸³. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8⁸³. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation^{83,84}. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes⁸³. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells⁸³. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development^{83,85}.

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma^{8,9}. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma^{8,9}.

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies⁸⁶. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy⁸⁷. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL⁸⁸. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens⁸⁹.

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.

KRAS p.(G12D) c.35G>A

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

KRAS p.(G12D) c.35G>A (continued)

panitumumab

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G12 mutation

Indications and usage:

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

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

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

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>

GFH-375

Cancer type: Pancreatic Cancer

Variant class: KRAS G12D mutation

Supporting Statement:

The FDA has granted Fast Track designation to an oral KRAS G12D (ON/OFF) inhibitor, GFH-375 (VS-7375), for the first-line treatment of patients with KRAS G12D-mutated locally advanced or metastatic adenocarcinoma of the pancreas (PDAC) and for the treatment of patients with KRAS G12D-mutated locally advanced or metastatic PDAC who have received at least one prior line of standard systemic therapy.

Reference:

<https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375>

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.

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

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

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

KRAS p.(G12D) c.35G>A

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]

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]

KRAS p.(G12D) c.35G>A (continued)**⊘ panitumumab**

Cancer type: Rectal Cancer

Variant class: KRAS G12 mutation

Summary:

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

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

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 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.**KRAS p.(G12D) c.35G>A****⊘ cetuximab, cetuximab + oxaliplatin**

Cancer type: Colorectal Cancer

Label as of: 2025-01-16

Variant class: KRAS G12 mutation

Reference:https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf**⊘ panitumumab + oxaliplatin**

Cancer type: Colorectal Cancer

Label as of: 2025-05-07

Variant class: KRAS G12 mutation

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

Current ESMO Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

ESMO information is current as of 2025-11-03. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12D) c.35G>A

cetuximab

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

panitumumab

Cancer type: Colorectal Cancer

Variant class: KRAS G12 mutation

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

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

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, 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, 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, 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, DAX1, 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 ① In this cancer type and other cancer types ✕ No evidence

KRAS p.(G12D) c.35G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avutometinib + defactinib	○	○	✕	✕	✕
bevacizumab + CAPOX	✕	✕	✕	○	✕
bevacizumab + FOLFIRI	✕	✕	✕	○	✕
bevacizumab + FOLFOX	✕	✕	✕	○	✕
bevacizumab + FOLFOXIRI	✕	✕	✕	○	✕
almonertinib, palbociclib	✕	✕	✕	✕	● (I/II)
ARV-806	✕	✕	✕	✕	● (I/II)
DN-022150	✕	✕	✕	✕	● (I/II)
ERAS-0015	✕	✕	✕	✕	● (I/II)
GFH-375	✕	✕	✕	✕	● (I/II)
HRS-4642, SHR-A1904, SHR-1921	✕	✕	✕	✕	● (I/II)
QLC-1101, QL1203, pembrolizumab (Qilu Pharmaceutical), iparomlimab and tuvonralimab, chemotherapy	✕	✕	✕	✕	● (I/II)
RNK-08954	✕	✕	✕	✕	● (I/II)
TSN-1611	✕	✕	✕	✕	● (I/II)
YL-15293	✕	✕	✕	✕	● (I/II)
ASP-4396	✕	✕	✕	✕	● (I)
ASP-5834	✕	✕	✕	✕	● (I)
AST-NS2101	✕	✕	✕	✕	● (I)
BPI-442096	✕	✕	✕	✕	● (I)
daraxonrasib	✕	✕	✕	✕	● (I)
GDC-7035	✕	✕	✕	✕	● (I)
HS-10529	✕	✕	✕	✕	● (I)
imatinib, trametinib	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✕	✕	✕	✕	● (I)
Nest-1	✕	✕	✕	✕	● (I)
NT-112, AZD-0240	✕	✕	✕	✕	● (I)
PT-0253	✕	✕	✕	✕	● (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.(G12D) c.35G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
QLC-1101	✗	✗	✗	✗	● (I)
RMC-9805, daraxonrasib	✗	✗	✗	✗	● (I)
toripalimab, chemotherapy, KRAS peptide vaccine	✗	✗	✗	✗	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✗	✗	✗	✗	● (II)
palbociclib, abemaciclib	✗	✗	✗	✗	● (II)
AMG 193	✗	✗	✗	✗	● (I/II)
ABSK-131	✗	✗	✗	✗	● (I)
CID-078	✗	✗	✗	✗	● (I)

* 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	39.38%
RAD54L	CNV, CN:1.0
RAD54L	LOH, 1p34.1(46714017-46743978)x1

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, 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 and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from 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 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.

References

1. Li et al. Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells (Review). *Oncol. Rep.* 2015 Dec;34(6):2821-6. PMID: 26398719
2. Gan et al. Lkb1 regulates quiescence and metabolic homeostasis of haematopoietic stem cells. *Nature.* 2010 Dec 2;468(7324):701-4. PMID: 21124456
3. Marinaccio et al. LKB1/ STK11 Is a Tumor Suppressor in the Progression of Myeloproliferative Neoplasms. *Cancer Discov.* 2021 Jun;11(6):1398-1410. PMID: 33579786
4. Zhou et al. LKB1 Tumor Suppressor: Therapeutic Opportunities Knock when LKB1 Is Inactivated. *Genes Dis.* 2014 Sep 1;1(1):64-74. PMID: 25679014
5. Hemminki et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* 1998 Jan 8;391(6663):184-7. PMID: 9428765
6. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat. Genet.* 2016 Jun;48(6):607-16. PMID: 27158780
7. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature.* 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
10. Sanchez-Cespedes et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res.* 2002 Jul 1;62(13):3659-62. PMID: 12097271
11. De Braekeleer et al. ETV6 fusion genes in hematological malignancies: a review. *Leuk. Res.* 2012 Aug;36(8):945-61. PMID: 22578774
12. <https://ir.tangotx.com//news-releases/news-release-details/tango-therapeutics-announces-first-patient-dosed-tng260-phase-12>
13. Koyama et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. *Cancer Res.* 2016 Mar 1;76(5):999-1008. PMID: 26833127
14. Skoulidis et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discov.* 2018 Jul;8(7):822-835. PMID: 29773717
15. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
16. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer.* 2011 Oct 13;11(11):761-74. PMID: 21993244
17. Karnoub et al. Ras oncogenes: split personalities. *Nat. Rev. Mol. Cell Biol.* 2008 Jul;9(7):517-31. PMID: 18568040
18. Scott et al. Therapeutic Approaches to RAS Mutation. *Cancer J.* 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.000000000000187. PMID: 27341593
19. Johnson et al. Classification of KRAS-Activating Mutations and the Implications for Therapeutic Intervention. *Cancer Discov.* 2022 Apr 1;12(4):913-923. PMID: 35373279
20. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. *Mol Cancer.* 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
21. Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. *J Med Life.* 2014 Oct-Dec;7(4):581-7. PMID: 25713627
22. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J. Clin. Oncol.* 2016 Jan 10;34(2):179-85. PMID: 26438111
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214665Orig1s009correctedlbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216340s005lbl.pdf
25. NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2025]
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219616s000lbl.pdf
27. <https://assets.cwp.roche.com/f/126832/x/5738a7538b/irp230202.pdf>
28. <https://ir.revmed.com/node/11881/pdf>
29. <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>
30. <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>

References (continued)

31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
32. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-combination>
33. <https://www.businesswire.com/news/home/20250109170439/en/>
34. <https://ir.revmed.com/news-releases/news-release-details/revolution-medicines-announces-fda-breakthrough-therapy>
35. <https://investor.verastem.com/news-releases/news-release-details/verastem-oncology-granted-fast-track-designation-vs-7375>
36. <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>
37. https://cardiffoncology.com/wp-content/uploads/2021/07/Cardiff_Oncology_Investor_Presentation-_July_2021.pdf
38. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf
40. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N. Engl. J. Med.* 1990 Aug 30;323(9):561-5. PMID: 2199829
41. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. *Cancer Discov.* 2013 Jan;3(1):35-43. PMID: 23208470
42. Wilson et al. SWI/SNF nucleosome remodellers and cancer. *Nat. Rev. Cancer.* 2011 Jun 9;11(7):481-92. PMID: 21654818
43. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. *Nat Commun.* 8;14648. PMID: 28262751
44. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
45. McKinney et al. The Genetic Basis of Hepatosplenic T-cell Lymphoma. *Cancer Discov.* 2017 Apr;7(4):369-379. PMID: 28122867
46. Baird et al. The Molecular Mechanisms Regulating the KEAP1-NRF2 Pathway. *Mol Cell Biol.* 2020 Jun 15;40(13). PMID: 32284348
47. Suzuki et al. Toward clinical application of the Keap1-Nrf2 pathway. *Trends Pharmacol. Sci.* 2013 Jun;34(6):340-6. PMID: 23664668
48. Ohta et al. Loss of Keap1 function activates Nrf2 and provides advantages for lung cancer cell growth. *Cancer Res.* 2008 Mar 1;68(5):1303-9. PMID: 18316592
49. Rojo de la Vega et al. NRF2 and the Hallmarks of Cancer. *Cancer Cell.* 2018 Jul 9;34(1):21-43. PMID: 29731393
50. Heyer et al. Rad54: the Swiss Army knife of homologous recombination?. *Nucleic Acids Res.* 2006;34(15):4115-25. PMID: 16935872
51. Ryan et al. Snf2-family proteins: chromatin remodellers for any occasion. *Curr Opin Chem Biol.* 2011 Oct;15(5):649-56. PMID: 21862382
52. Matsuda et al. Mutations in the RAD54 recombination gene in primary cancers. *Oncogene.* 1999 Jun 3;18(22):3427-30. PMID: 10362365
53. Bugreev et al. Rad54 protein promotes branch migration of Holliday junctions. *Nature.* 2006 Aug 3;442(7102):590-3. PMID: 16862129
54. Mason et al. RAD54 family translocases counter genotoxic effects of RAD51 in human tumor cells. *Nucleic Acids Res.* 2015 Mar 31;43(6):3180-96. PMID: 25765654
55. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. *Endocr. Relat. Cancer.* 2016 Jun;23(6):R267-85. PMID: 27226207
56. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
57. <https://www.senhwbio.com/en/news/20220125>
58. Dufner et al. Ubiquitin-specific protease 8 (USP8/UBPy): a prototypic multidomain deubiquitinating enzyme with pleiotropic functions. *Biochem Soc Trans.* 2019 Dec 20;47(6):1867-1879. PMID: 31845722
59. Lu et al. USP9X stabilizes BRCA1 and confers resistance to DNA-damaging agents in human cancer cells. *Cancer Med.* 2019 Nov;8(15):6730-6740. PMID: 31512408
60. Goldstein et al. Recurrent Loss of NFE2L2 Exon 2 Is a Mechanism for Nrf2 Pathway Activation in Human Cancers. *Cell Rep.* 2016 Sep 6;16(10):2605-2617. PMID: 27568559
61. <https://ir.calithera.com/news-releases/news-release-details/calithera-receives-fda-fast-track-designation-sapanisertib>
62. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011

References (continued)

63. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol.* 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
64. Nojadedh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
65. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. *Front Microbiol.* 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
66. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998 Nov 15;58(22):5248-57. PMID: 9823339
67. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. *Cancer Res.* 2002 Jan 1;62(1):53-7. PMID: 11782358
68. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
69. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
70. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
71. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. *Medicine (Baltimore).* 2015 Dec;94(50):e2260. PMID: 26683947
72. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J. Clin. Oncol.* 2019 Feb 1;37(4):286-295. PMID: 30376427
73. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
74. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
75. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
76. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
77. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
78. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
79. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003 Jul 17;349(3):247-57. PMID: 12867608
80. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann. Oncol.* 2015 Jan;26(1):126-32. PMID: 25361982
81. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
82. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
83. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. *Nat Rev Drug Discov.* 2014 Sep;13(9):673-91. PMID: 25131830
84. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. *Biomed Pharmacother.* 2016 Dec;84:284-290. PMID: 27665474
85. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. *Cold Spring Harb Perspect Med.* 2016 Oct 3;6(10). PMID: 27599530
86. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf
87. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf
88. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
89. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf
90. Furth et al. The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway. *Cell Death Differ.* 2017 Sep;24(9):1488-1501. PMID: 28644436
91. Leroux et al. AGC kinases, mechanisms of regulation #and innovative drug development. *Semin Cancer Biol.* 2018 Feb;48:1-17. PMID: 28591657
92. Meng et al. Mechanisms of Hippo pathway regulation. *Genes Dev.* 2016 Jan 1;30(1):1-17. PMID: 26728553
93. Yu et al. Mutation analysis of large tumor suppressor genes LATS1 and LATS2 supports a tumor suppressor role in human cancer. *Protein Cell.* 2015 Jan;6(1):6-11. PMID: 25482410

References (continued)

94. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. *Nat Commun.* 2021 Apr 6;12(1):2047. PMID: 33824349
95. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. *Am. J. Respir. Cell Mol. Biol.* 2018 Aug;59(2):200-214. PMID: 29420051
96. Roussel. The INK4 family of cell cycle inhibitors in cancer. *Oncogene.* 1999 Sep 20;18(38):5311-7. PMID: 10498883
97. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). *Biochem. Biophys. Res. Commun.* 1999 Aug 27;262(2):534-8. PMID: 10462509
98. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet.* 2013;14:257-79. PMID: 23875803
99. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell.* 2006 Oct 20;127(2):265-75. PMID: 17055429
100. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
101. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
102. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
103. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. *Clin Cancer Res.* 2021 Jul 15;27(14):4025-4035. PMID: 34074656
104. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2026]
105. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2026]
106. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
107. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol.* 2020 Jul;30(4):844-856. PMID: 32307792
108. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med.* 2019 Jul 29;17(1):245. PMID: 31358010
109. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. *Anticancer Res.* 2013 Aug;33(8):2997-3004. PMID: 23898052
110. von Witzleben et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway. *Cancer Res.* 2015 Sep 15;75(18):3823-31. PMID: 26183925
111. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. *Neuro-oncology.* 2012 Jul;14(7):870-81. PMID: 22711607
112. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. *Oncotarget.* 2018 Sep 7;9(70):33247-33248. PMID: 30279955
113. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J. Clin. Oncol.* 2014 Dec 10;32(35):3930-8. PMID: 25267748
114. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. *J. Natl. Cancer Inst.* 2018 Dec 1;110(12):1393-1399. PMID: 29878161
115. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. *Cancer Clin Oncol.* 2013;2(1):51-61. PMID: 23935769