

Patient Name: 김혜연
 Gender: Female
 Sample ID: N26-1

Primary Tumor Site: Lung
 Collection Date: 2025.12.22

Sample Cancer Type: Lung Cancer

Table of Contents

	Page
Variant Details	2
Biomarker Descriptions	2
Alert Details	5
Relevant Therapy Summary	6

Report Highlights

3 Relevant Biomarkers
 5 Therapies Available
 35 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	<i>EZR::ROS1 fusion</i>
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	1.89 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<i>EZR::ROS1 fusion</i> ezrin - ROS proto-oncogene 1, receptor tyrosine kinase Locus: chr6:159191796 - chr6:117645578, chr6:159191796 - chr6:117642557 (2 variants)	crizotinib 1, 2 / I, II+ entrectinib 1, 2 / I, II+ repotrectinib 1, 2 / I, II+ taletrectinib 1 / I, II+ lorlatinib II+	crizotinib II+ entrectinib II+	31
IIC	<i>CDKN2A deletion</i> 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.

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

EZR::ROS1 fusion

⚡ ***zidesamtinib***¹

Public data sources included in alerts: FDA1, NCCN, EMA2, ESMO

Disclaimer: The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. The data version is 2025.12(007). The content of this report has not been evaluated or approved by the FDA, EMA or other regulatory agencies.

Prevalent cancer biomarkers without relevant evidence based on included data sources

Microsatellite stable, TP53 p.(R337C) c.1009C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TP53	p.(R337C)	c.1009C>T	.	chr17:7574018	6.31%	NM_000546.6	missense
CDC7	p.(T330A)	c.988_990delACAinsG CG	.	chr1:91980445	39.85%	NM_001134419.1	missense
NOTCH1	p.(?)	c.2588-4_2588-2delins ACG	.	chr9:139405259	1.71%	NM_017617.5	unknown
COG1	p.(W399C)	c.1197G>T	.	chr17:71196831	24.34%	NM_018714.3	missense
STAG2	p.(M1267V)	c.3799A>G	.	chrX:123234439	61.24%	NM_001042749.2	missense

Gene Fusions

Genes	Variant ID	Locus
EZR::ROS1	EZR-ROS1.E10R34.COSF1267	chr6:159191796 - chr6:117645578
EZR::ROS1	EZR-ROS1.E10R35.1	chr6:159191796 - chr6:117642557

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0.92	0.67

Biomarker Descriptions

EZR::ROS1 fusion

ROS proto-oncogene 1, receptor tyrosine kinase, ezrin

Background: The ROS1 gene encodes the ROS proto-oncogene receptor tyrosine kinase 1, which exhibits structural similarity to anaplastic lymphoma kinase (ALK)^{1,2}. Like ALK, ROS1 is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact ROS1 tyrosine kinase domain combined with numerous fusion partner genes³. ROS1 fusion kinases are constitutively activated and drive oncogenic transformation⁴.

Alterations and prevalence: Somatic mutations in ROS1 are observed in 24% of skin cutaneous melanoma, 13% of uterine corpus endometrial carcinoma, 8% of lung squamous cell carcinoma, 7% of colorectal adenocarcinoma, 6% of stomach adenocarcinoma, 5% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and diffuse large B-cell lymphoma, 4% of lung adenocarcinoma and uterine carcinosarcoma, 3% of adrenocortical carcinoma, esophageal adenocarcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, and glioblastoma multiforme, and 2% of mesothelioma, brain lower grade glioma, breast invasive carcinoma, and acute myeloid leukemia^{5,6}. ROS1 fusions are observed in cholangiocarcinoma, gastric cancer, and ovarian cancer and have been reported in approximately 1-2% of non-small cell lung cancer (NSCLC) and glioblastoma^{1,7,8,9,10,11}. ROS1 amplification is observed in 3% of sarcoma^{5,6}. Alterations in ROS1 are rare in pediatric cancers^{5,6}. Somatic mutations are observed in 2% of bone cancer and embryonal tumors, and 1% or less in B-lymphoblastic leukemia/lymphoma (3 in 252 cases), glioma (3 in 297 cases), leukemia (1 in 311 cases), peripheral nervous system tumors (3 in 1158 cases), and Wilms tumor (1 in 710 cases)^{5,6}. Amplification of ROS1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)^{5,6}.

Potential relevance: The tyrosine kinase inhibitor (TKI), entrectinib¹² (2019), is approved for the treatment of ROS1 fusion-positive metastatic NSCLC. Tafetrectinib¹³ (2025) is a kinase inhibitor approved for the treatment of adult patients with locally advanced or

Biomarker Descriptions (continued)

metastatic ROS1-positive NSCLC. Crizotinib¹⁴ (2011), originally approved for the treatment of ALK-positive NSCLC, is also approved (2016) for the treatment of ROS1-positive NSCLC¹⁵. Acquired resistance to crizotinib in ROS1-positive NSCLC is associated with kinase domain mutations S1986F/Y, G2032R, D2033N, and L2155S^{16,17,18}. Repotrectinib¹⁹ (2023) is a kinase inhibitor approved for the treatment of locally advanced or metastatic ROS1-positive NSCLC. In 2024, zidesamtinib²⁰ received breakthrough designation for the treatment of patients with ROS1-positive NSCLC who have been previously treated with two or more ROS1 TKIs. Ceritinib²¹ (2017) is a second-generation ALK inhibitor approved for ALK-positive NSCLC that has also shown efficacy in ROS1-positive NSCLC²². In a phase II study, ceritinib demonstrated systemic and intra-cranial activity with an objective response rate (ORR) of 62% in patients with advanced ROS1-positive NSCLC²². Lorlatinib²³, a CNS-penetrant third-generation ALK and ROS1 inhibitor, is FDA approved (2018) for ALK-positive metastatic NSCLC. Emerging pre-clinical evidence suggests that lorlatinib may target almost all known ALK and ROS1 resistance mutations^{24,25}. In a phase I/II study of lorlatinib in advanced ROS1-positive NSCLC, objective responses were observed in both TKI-naïve and those previously treated with crizotinib, regardless of CNS metastasis²⁶. Lorlatinib is recommended for subsequent therapy in ROS1 fusion-positive NSCLC patients who have progressed after treatment with crizotinib, entrectinib, or ceritinib²⁷.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression²⁸. 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)⁷⁴. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{75,76,77}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions⁷⁸. 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^{28,78,79}. CDKN2A aberrations commonly co-occur with CDKN2B⁷⁴. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation⁸⁰. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{81,82}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations⁸³. 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^{5,6}. 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^{5,6}. Alterations in CDKN2A are also observed in pediatric cancers⁶. 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 tumors⁶. 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)⁶.

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^{84,85,86}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma⁸⁷. 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^{88,89,90}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁹¹. 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^{92,93,94,95}.

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 genome⁵². Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{53,54}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁵⁵. 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 D17S250⁵⁶. 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)⁵⁶. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{57,58,59,60,61}. MSI-H is a hallmark of Lynch

Biomarker Descriptions (continued)

syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes⁵⁴. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{53,54,58,62}.

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^{53,54,63,64}. 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^{63,64}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁶⁵ (2014) and nivolumab⁶⁶ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁶⁵ 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 indication⁶⁵. Dostarlimab⁶⁷ (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^{59,68}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁶⁹ (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^{59,70,71}. 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 patients⁷¹. 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^{72,73}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{72,73}.

TP53 p.(R337C) c.1009C>T

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair²⁸. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis²⁹. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential³⁰. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{31,32}.

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%)^{5,6,33,34,35,36}. 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^{5,6}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{37,38,39,40}. Alterations in TP53 are also observed in pediatric cancers^{5,6}. 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)^{5,6}. 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)^{5,6}.

Potential relevance: The small molecule p53 reactivator, PC14586⁴¹ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{42,43}. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma⁴⁴. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{45,46,47,48,49}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁵⁰. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system⁵¹.

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.

EZR::ROS1 fusion

zidesamtinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Supporting Statement:

The FDA has granted Breakthrough Therapy designation to the brain-penetrant ROS1-selective tyrosine kinase inhibitor (TKI), zidesamtinib (NVL-520), for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have been previously treated with two or more ROS1 TKIs.

Reference:

<https://investors.nuvalent.com/2024-02-27-Nuvalent-Received-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-520>

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, MYD88L, 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, SNCAP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, 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, ERF1, 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, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBBM10, 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, TGFBR2,

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations (continued)

TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed 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, RSP02, RSP03, 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, 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, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

EZR::ROS1 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
entrectinib	●	○	●	●	● (II/III)
crizotinib	●	○	●	●	● (II)
repotrectinib	●	●	●	●	● (II)
taletrectinib	●	●	✗	✗	✗
lorlatinib	✗	●	✗	✗	✗
ASKC-202, limertinib	✗	✗	✗	✗	● (III)
entrectinib, crizotinib	✗	✗	✗	✗	● (III)
taletrectinib, crizotinib	✗	✗	✗	✗	● (III)
cabozantinib	✗	✗	✗	✗	● (II)
ICP-723	✗	✗	✗	✗	● (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

EZR::ROS1 fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
JS-207, chemotherapy	✗	✗	✗	✗	● (II)
amivantamab, lorlatinib, entrectinib	✗	✗	✗	✗	● (I/II)
furetinib	✗	✗	✗	✗	● (I/II)
XZP-5955	✗	✗	✗	✗	● (I/II)
zidesamtinib	✗	✗	✗	✗	● (I/II)
APG-2449	✗	✗	✗	✗	● (I)
HG 030	✗	✗	✗	✗	● (I)
JYP-0322	✗	✗	✗	✗	● (I)
LZ-001	✗	✗	✗	✗	● (I)
SYS-6023	✗	✗	✗	✗	● (I)
talazoparib, crizotinib	✗	✗	✗	✗	● (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	7.65%
BRCA2	LOH, 13q13.1(32890491-32972932)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 Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.2.4 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. Bergethon et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012 Mar 10;30(8):863-70. doi: 10.1200/JCO.2011.35.6345. Epub 2012 Jan 3. PMID: 22215748
2. Davare et al. Structural insight into selectivity and resistance profiles of ROS1 tyrosine kinase inhibitors. *Proc Natl Acad Sci U S A*. 2015 Sep 29;112(39):E5381-90. doi: 10.1073/pnas.1515281112. Epub 2015 Sep 8. PMID: 26372962
3. Kohno et al. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. *Transl Lung Cancer Res*. 2015 Apr;4(2):156-64. PMID: 25870798
4. Lin et al. Recent Advances in Targeting ROS1 in Lung Cancer. *J Thorac Oncol*. 2017 Nov;12(11):1611-1625. PMID: 28818606
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet*. 2013 Oct;45(10):1113-20. PMID: 24071849
6. 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
7. Shaw et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014 Nov 20;371(21):1963-71. doi: 10.1056/NEJMoa1406766. Epub 2014 Sep 27. PMID: 25264305
8. Gu et al. Survey of tyrosine kinase signaling reveals ROS kinase fusions in human cholangiocarcinoma. *PLoS ONE*. 2011 Jan 6;6(1):e15640. PMID: 21253578
9. Charest et al. Fusion of FIG to the receptor tyrosine kinase ROS in a glioblastoma with an interstitial del(6)(q21q21). *Genes Chromosomes Cancer*. 2003 May;37(1):58-71. PMID: 12661006
10. Birch et al. Chromosome 3 anomalies investigated by genome wide SNP analysis of benign, low malignant potential and low grade ovarian serous tumours. *PLoS ONE*. 2011;6(12):e28250. PMID: 22163003
11. Lee et al. Identification of ROS1 rearrangement in gastric adenocarcinoma. *Cancer*. 2013 May 1;119(9):1627-35. PMID: 23400546
12. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212725s011lbl.pdf
13. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219713s000lbl.pdf
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202570s036lbl.pdf
15. Kazandjian et al. Benefit-Risk Summary of Crizotinib for the Treatment of Patients With ROS1 Alteration-Positive, Metastatic Non-Small Cell Lung Cancer. *Oncologist*. 2016 Aug;21(8):974-80. doi: 10.1634/theoncologist.2016-0101. Epub 2016 Jun 21. PMID: 27328934
16. Song et al. Molecular Changes Associated with Acquired Resistance to Crizotinib in ROS1-Rearranged Non-Small Cell Lung Cancer. *Clin Cancer Res*. 2015 May 15;21(10):2379-87. doi: 10.1158/1078-0432.CCR-14-1350. Epub 2015 Feb 16. PMID: 25688157
17. Drilon et al. A Novel Crizotinib-Resistant Solvent-Front Mutation Responsive to Cabozantinib Therapy in a Patient with ROS1-Rearranged Lung Cancer. *Clin Cancer Res*. 2016 May 15;22(10):2351-8. doi: 10.1158/1078-0432.CCR-15-2013. Epub 2015 Dec 16. PMID: 26673800
18. Facchinetto et al. Crizotinib-Resistant ROS1 Mutations Reveal a Predictive Kinase Inhibitor Sensitivity Model for ROS1- and ALK-Rearranged Lung Cancers. *Clin Cancer Res*. 2016 Dec 15;22(24):5983-5991. Epub 2016 Jul 11. PMID: 27401242
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218213s001lbl.pdf
20. <https://investors.nuvalent.com/2024-02-27-Nuvalent-Receives-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-520>
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf
22. Lim et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. *J Clin Oncol*. 2017 Aug 10;35(23):2613-2618. doi: 10.1200/JCO.2016.71.3701. Epub 2017 May 18. PMID: 28520527
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf
24. Zou et al. PF-06463922, an ALK/ROS1 Inhibitor, Overcomes Resistance to First and Second Generation ALK Inhibitors in Preclinical Models. *Cancer Cell*. 2015 Jul 13;28(1):70-81. PMID: 26144315
25. Zou et al. PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations. *Proc. Natl. Acad. Sci. U.S.A.* 2015 Mar 17;112(11):3493-8. PMID: 25733882
26. Shaw et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2019 Dec;20(12):1691-1701. PMID: 31669155
27. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2025]
28. 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
29. Nag et al. The MDM2-p53 pathway revisited. *J Biomed Res*. 2013 Jul;27(4):254-71. PMID: 23885265

References (continued)

30. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell*. 2014 Mar 17;25(3):304-17. PMID: 24651012
31. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol*. 2010 Jan;2(1):a001008. PMID: 20182602
32. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med*. 2017 Apr 3;7(4). PMID: 28270529
33. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012 Sep 27;489(7417):519-25. PMID: 22960745
34. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015 Jan 29;517(7536):576-82. PMID: 25631445
35. 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
36. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
37. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. *Hum. Mutat.* 2002 Jun;19(6):607-14. PMID: 12007217
38. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. *Genes Cancer*. 2011 Apr;2(4):466-74. PMID: 21779514
39. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene*. 2007 Apr 2;26(15):2157-65. PMID: 17401424
40. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. *Hum. Mutat.* 2014 Jun;35(6):766-78. PMID: 24729566
41. <https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html>
42. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. *Front Oncol*. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
43. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci.* 2017 Nov;74(22):4171-4187. PMID: 28643165
44. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021 Aug 2;23(8):1231-1251. PMID: 34185076
45. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
46. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
47. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
48. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
49. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
50. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
51. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat. Med.* 2020 Aug 3. PMID: 32747829
52. Lander et al. Initial sequencing and analysis of the human genome. *Nature*. 2001 Feb 15;409(6822):860-921. PMID: 11237011
53. 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
54. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J*. 2018;17:159-168. PMID: 29743854
55. 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
56. 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
57. 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

References (continued)

58. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis*. 2008 Apr;29(4):673-80. PMID: 17942460
59. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
60. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers*. 2004;20(4-5):199-206. PMID: 15528785
61. 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
62. 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
63. 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
64. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol*. 2017;2017. PMID: 29850653
65. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
66. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
67. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
68. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
69. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
70. 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
71. 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
72. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med*. 2019 Jan 16;9(1). PMID: 30654522
73. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
74. 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
75. 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
76. Roussel. The INK4 family of cell cycle inhibitors in cancer. *Oncogene*. 1999 Sep 20;18(38):5311-7. PMID: 10498883
77. 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
78. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet*. 2013;14:257-79. PMID: 23875803
79. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell*. 2006 Oct 20;127(2):265-75. PMID: 17055429
80. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
81. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
82. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
83. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. *Clin Cancer Res*. 2021 Jul 15;27(14):4025-4035. PMID: 34074656
84. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2026]
85. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2026]
86. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
87. 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
88. 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
89. 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

References (continued)

90. 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
91. 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
92. 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
93. 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
94. 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
95. 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