삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Patient Name: 신서연
Gender: F
Sample ID: N25-195

Primary Tumor Site: endometrium
Collection Date: 2025.08.22

Sample Cancer Type: Endometrial Carcinoma

Table of Contents	Page

Report Highlights

2 Relevant Biomarkers
1 Therapies Available
1 Clinical Trials

Relevant Endometrial Carcinoma Findings

Gene	Finding
BRAF	None detected
ERBB2	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Microsatellite Status	***Microsatellite stable***
Tumor Mutational Burden	***6.63 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*ESR1 p.(V392I) c.1174G>A* estrogen receptor 1 Allele Frequency: 47.44% Locus: chr6:152332868 Transcript: NM_001122740.2	None*	**elacestrant** [1, 2 / I, II+]	0
IIC	*ARID1A p.(R1446*) c.4336C>T* AT-rich interaction domain 1A Allele Frequency: 51.68% Locus: chr1:27101054 Transcript: NM_006015.6	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

CCND1 p.(P287S) c.859C>T, FGFR2 p.(N549K) c.1647T>A, Microsatellite stable, PTEN p.(Y16) c.48T>A, HLA-B deletion, CTCF p.(V434Gfs*9) c.1301_1302delTG, 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
ESR1	p.(V392I)	c.1174G>A	COSM1545070	chr6:152332868	47.44%	NM_001122740.2	missense
ARID1A	p.(R1446*)	c.4336C>T	COSM907726	chr1:27101054	51.68%	NM_006015.6	nonsense
CCND1	p.(P287S)	c.859C>T	COSM931396	chr11:69466021	25.98%	NM_053056.3	missense
FGFR2	p.(N549K)	c.1647T>A	COSM36912	chr10:123258034	55.45%	NM_000141.5	missense
PTEN	p.(Y16*)	c.48T>A	.	chr10:89624274	52.07%	NM_000314.8	nonsense
CTCF	p.(V434Gfs*9)	c.1301_1302delTG	.	chr16:67655437	19.31%	NM_006565.4	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	47.85%	NM_000903.3	missense
DNMT3A	p.(R181H)	c.542G>A	.	chr2:25497907	9.92%	NM_022552.5	missense
MAP3K1	p.(A241T)	c.721G>A	.	chr5:56155629	48.10%	NM_005921.2	missense
CTCF	p.(?)	c.1518+1G>A	.	chr16:67660619	4.60%	NM_006565.4	unknown

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0.71	0.69

Biomarker Descriptions

ESR1 p.(V392I) c.1174G>A

estrogen receptor 1

Background: The ESR1 gene encodes estrogen receptor 1 (ERα), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses. A related gene, ESR2, encodes the cognate ERβ protein. ERα is a ligand-activated transcription factor regulated by the hormone estrogen[27,28]. Estrogen binding to ERα results in receptor dimerization, nuclear translocation, and target gene transcription. In addition, estrogen binding to the ERα results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival[29].

Alterations and prevalence: Approximately 70% of breast cancers express ERα and ERβ positivity. Mutations in the ERα ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance[30,31,32,33]. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease[34,35,36,37,38].

Potential relevance: The FDA has approved elacestrant[39] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer[40]. The FDA has also granted fast track designations to the following therapies: AC699[41] (2024) and lasofoxifene[42] (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizaestrant[43] for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel[44] (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[45] (1977), fulvestrant[46] (2002), letrozole[47] (1995), and exemestane[48] (2005) are FDA approved for ER-positive metastatic breast cancers[49,50]. Although ERα and ERβ positivity predicts

Biomarker Descriptions (continued)

response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance[51,52,53].

ARID1A p.(R1446*) c.4336C>T

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,95]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[95,96]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[96]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[96,97]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[95]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[95].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[97]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[95]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[8,9,96]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[98].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[99], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[100], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

CCND1 p.(P287S) c.859C>T

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[101,102,103]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[101,102]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[101,102,104]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[103,105].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[8,9,106,107]. These mutations block phosphorylation-dependent nuclear export and proteolysis[108,109,110,111]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[8,9,112]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[113,114].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma[115].

FGFR2 p.(N549K) c.1647T>A

fibroblast growth factor receptor 2

Background: The FGFR2 gene encodes fibroblast growth receptor 2, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR1, 3, and 4[1]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[1]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[54,55,56].

Biomarker Descriptions (continued)

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function[57]. Somatic mutations in FGFR2 are observed in 15% of uterine corpus endometrial carcinomas, 10% of skin cutaneous melanoma, 6% of cholangiocarcinoma, 4% of stomach adenocarcinoma, 3% of colorectal adenocarcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, lung adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[8,9]. In endometrial cancers, missense mutations are the most prevalent alterations in FGFR2[58]. These mutations are predominantly activating, most often involve substitutions at S252 and P253, and confer sensitivity to pan-FGFR2 inhibitors[58,59]. FGFR2 amplification occurs in up to 4% of stomach adenocarcinoma, and 2% of ovarian serous cystadenocarcinoma, uterine carcinosarcoma, and uterine corpus endometrial carcinoma[8,9]. FGFR2 fusions have also been reported in up to 14% of cholangiocarcinoma and confer sensitivity to select FGFR inhibitors[8,60,61]. Aberrations in FGFR2 are rare in pediatric cancers[8,9]. Somatic mutations in FGFR2 occur in 2% of T-lymphoblastic leukemia/lymphoma and FGFR2 is amplified in 2% of bone cancer[8,9].

Potential relevance: Several pan-FGFR inhibitors have been approved for FGFR2 aberrations in cancer. Futibatinib[62] (2022) is approved for FGFR2 fusion-positive locally advanced or metastatic intrahepatic cholangiocarcinoma and has been granted breakthrough designation[63] (2022) for FGFR2-fusion positive cholangiocarcinoma. Erdafitinib[64] (2019) is approved for the treatment of locally advanced or metastatic urothelial cancer with FGFR2 fusions, including FGFR2::BICC1 and FGFR2::CASP7. Pemigatinib[65] (2020) is approved for previously treated, advanced, or unresectable cholangiocarcinoma harboring FGFR2 fusions. The FDA has granted fast track designation to the pan-FGFR inhibitor, KIN-3248[66](2023), for unresectable, locally advanced, or metastatic cholangiocarcinoma with FGFR2 fusions or other alterations after receiving at least one prior systemic therapy. The FDA has also granted fast track designation to the FGFR2 inhibitor, 3HP-2827[67] (2024), for the treatment of patients with cholangiocarcinoma harboring FGFR2 mutations. The FDA has granted breakthrough designation to the FGFR2 inhibitor, lirafugratinib[68] (2024), for the treatment of FGFR2-driven cholangiocarcinoma and other FGFR2-altered solid tumors. The FDA also granted fast track designation to the small molecule inhibitor, Debio 1347[69] (2018), for solid tumors harboring FGFR1, FGFR2, or FGFR3 aberrations. The FDA has granted breakthrough designation to bemarituzumab[70] (2021), in combination with modified FOLFOX6 (fluoropyrimidine, leucovorin, and oxaliplatin), for treating FGFR2b-overexpressing, HER2-negative metastatic and locally advanced gastric and gastroesophageal adenocarcinoma. Additional FGFR inhibitors are under clinical evaluation for FGFR2 aberrations[71,72]. In a phase II study of patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma, the pan-kinase inhibitor derazantinib, demonstrated an overall response rate (ORR) of 20.7% with progression-free survival (PFS) of 5.7 months[71]. Likewise, results of a phase II trial testing the pan-FGFR inhibitor, infigratinib (BGJ398) demonstrated an ORR of 14.8% (18.8% FGFR2 fusions only), disease control rate (DCR) of 75.4% (83.3% FGFR2 fusions only), and a median PFS of 5.8 months[72].

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[73]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[74,75]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[76]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[77]. 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)[77]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[78,79,80,81,82]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[75]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[74,75,79,83].

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[74,75,84,85]. 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[84,85].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[86] (2014) and nivolumab[87] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[86] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[86]. Dostarlimab[88] (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[80,89]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[90] (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[80,91,92]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[92]. The majority of patients with tumors

Biomarker Descriptions (continued)

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[93,94]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[93,94].

PTEN p.(Y16*) c.48T>A

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[13]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[14,15]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[16]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[17]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[18].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[8,9]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[15,19,20,21,22]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[8,9].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[23,24]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[25], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[26] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[2]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[3]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[4,5,6]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[7].

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

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

CTCF p.(V434Gfs*9) c.1301_1302delTG

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[10]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[10,11,12]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[10].

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma[8,9].

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Genes Assayed (continued)

Genes Assayed with Full Exon Coverage (continued)

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

ESR1 p.(V392I) c.1174G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
elacestrant	○	○	○	✖	✖

ARID1A p.(R1446*) c.4336C>T

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***2.87%***
RAD54L	***LOH, 1p34.1(46714017-46743978)x2***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. 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. 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
2. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
3. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. Annu Rev Immunol. 2013;31:529-61. PMID: 23298204
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
7. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7). PMID: 32630675
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. Debaugny et al. CTCF and CTCFL in cancer. Curr Opin Genet Dev. 2020 Apr;61:44-52. PMID: 32334335
11. Lutz et al. Transcriptional repression by the insulator protein CTCF involves histone deacetylases. Nucleic Acids Res. 2000 Apr 15;28(8):1707-13. PMID: 10734189
12. Holwerda et al. CTCF: the protein, the binding partners, the binding sites and their chromatin loops. Philos Trans R Soc Lond B Biol Sci. 2013;368(1620):20120369. PMID: 23650640
13. Milella et al. PTEN: Multiple Functions in Human Malignant Tumors. Front Oncol. 2015 Feb 16;5:24. doi: 10.3389/fonc.2015.00024. eCollection 2015. PMID: 25763354
14. Song et al. The functions and regulation of the PTEN tumour suppressor. Nat. Rev. Mol. Cell Biol. 2012 Apr 4;13(5):283-96. PMID: 22473468
15. Chalhoub et al. PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol. 2009;4:127-50. PMID: 18767981
16. Mansour et al. Loss of PTEN-assisted G2/M checkpoint impedes homologous recombination repair and enhances radio-curability and PARP inhibitor treatment response in prostate cancer. Sci Rep. 2018 Mar 2;8(1):3947. PMID: 29500400
17. Leslie et al. Inherited PTEN mutations and the prediction of phenotype. Semin. Cell Dev. Biol. 2016 Apr;52:30-8. PMID: 26827793
18. Tan et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin. Cancer Res. 2012 Jan 15;18(2):400-7. PMID: 22252256
19. Dillon et al. Therapeutic targeting of cancers with loss of PTEN function. Curr Drug Targets. 2014 Jan;15(1):65-79. PMID: 24387334
20. Papa et al. Cancer-associated PTEN mutants act in a dominant-negative manner to suppress PTEN protein function. Cell. 2014 Apr 24;157(3):595-610. PMID: 24766807
21. Kato et al. Functional evaluation of p53 and PTEN gene mutations in gliomas. Clin. Cancer Res. 2000 Oct;6(10):3937-43. PMID: 11051241
22. Han et al. Functional evaluation of PTEN missense mutations using in vitro phosphoinositide phosphatase assay. Cancer Res. 2000 Jun 15;60(12):3147-51. PMID: 10866302
23. Mendes-Pereira et al. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med. 2009 Sep;1(6-7):315-22. PMID: 20049735
24. Bian et al. PTEN deficiency sensitizes endometrioid endometrial cancer to compound PARP-PI3K inhibition but not PARP inhibition as monotherapy. Oncogene. 2018 Jan 18;37(3):341-351. PMID: 28945226
25. https://www.senhwabio.com//en/news/20220125
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf
27. Paterni et al. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014 Nov;90:13-29. PMID: 24971815
28. Dahlman-Wright et al. International Union of Pharmacology. LXIV. Estrogen receptors. Pharmacol. Rev. 2006 Dec;58(4):773-81. PMID: 17132854
29. Marino et al. Estrogen signaling multiple pathways to impact gene transcription. Curr. Genomics. 2006;7(8):497-508. PMID: 18369406
30. Chang. Tamoxifen resistance in breast cancer. Biomol Ther (Seoul). 2012 May;20(3):256-67. PMID: 24130921

References (continued)

31. Toy et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat. Genet. 2013 Dec;45(12):1439-45. PMID: 24185512
32. Jeselsohn et al. Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen Receptor-Positive Breast Cancer. Clin. Cancer Res. 2014 Apr 1;20(7):1757-1767. PMID: 24398047
33. Robinson et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet. 2013 Dec;45(12):1446-51. doi: 10.1038/ng.2823. Epub 2013 Nov 3. PMID: 24185510
34. Hartmaier et al. Recurrent hyperactive ESR1 fusion proteins in endocrine therapy-resistant breast cancer. Ann. Oncol. 2018 Apr 1;29(4):872-880. PMID: 29360925
35. Matissek et al. Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor-Positive Breast Cancer. Cancer Discov. 2018 Mar;8(3):336-353. PMID: 29242214
36. Lei et al. ESR1 fusions drive endocrine therapy resistance and metastasis in breast cancer. Mol Cell Oncol. 2018;5(6):e1526005. PMID: 30525098
37. Lei et al. Functional Annotation of ESR1 Gene Fusions in Estrogen Receptor-Positive Breast Cancer. Cell Rep. 2018 Aug 7;24(6):1434-1444.e7. PMID: 30089255
38. Basudan et al. Frequent ESR1 and CDK Pathway Copy-Number Alterations in Metastatic Breast Cancer. Mol. Cancer Res. 2019 Feb;17(2):457-468. PMID: 30355675
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639Orig1s001lbl.pdf
40. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2025]
41. https://www.accutarbio.com/accutar-biotechnology-receives-fda-fast-track-designation-for-ac699-in-er-her2-breast-cancer/
42. https://sermonixpharma.com/sermonix-receives-fda-fast-track-designation-for-investigational-drug-lasofoxifene/
43. https://www.astrazeneca.com/content/dam/az/PDF/2022/h1-2022/H1-2022-results-announcement.pdf
44. https://www.businesswire.com/news/home/20160106006206/en/Innocrin-Pharmaceuticals-Granted-Fast-Track-Designation-FDA
45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/17970s37s44s49lbl.pdf
46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021344s044lbl.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020726s043lbl.pdf
48. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020753s025lbl.pdf
49. Tamoxifen--an update on current data and where it can now be used. Breast Cancer Res. Treat. 2002 Oct;75 Suppl 1:S7-12; discussion S33-5. PMID: 12353826
50. Kim et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. J. Clin. Oncol. 2011 Nov 1;29(31):4160-7. PMID: 21947828
51. Jeselsohn et al. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol. 2015 Oct;12(10):573-83. PMID: 26122181
52. Angus et al. ESR1 mutations: Moving towards guiding treatment decision-making in metastatic breast cancer patients. Cancer Treat. Rev. 2017 Jan;52:33-40. PMID: 27886589
53. Reinert et al. Clinical Implications of ESR1 Mutations in Hormone Receptor-Positive Advanced Breast Cancer. . Front Oncol. 2017 Mar 15;7:26. PMID: 28361033
54. Babina et al. Advances and challenges in targeting FGFR signalling in cancer. Nat. Rev. Cancer. 2017 May;17(5):318-332. PMID: 28303906
55. Ahmad et al. Mechanisms of FGFR-mediated carcinogenesis. Biochim. Biophys. Acta. 2012 Apr;1823(4):850-60. PMID: 22273505
56. Sarabipour et al. Mechanism of FGF receptor dimerization and activation. Nat Commun. 2016 Jan 4;7:10262. doi: 10.1038/ncomms10262. PMID: 26725515
57. Helsten et al. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. Clin. Cancer Res. 2016 Jan 1;22(1):259-67. PMID: 26373574
58. Touat et al. Targeting FGFR Signaling in Cancer. Clin. Cancer Res. 2015 Jun 15;21(12):2684-94. PMID: 26078430
59. Byron et al. The N550K/H mutations in FGFR2 confer differential resistance to PD173074, dovitinib, and ponatinib ATP-competitive inhibitors . Neoplasia. 2013 Aug;15(8):975-88. PMID: 23908597
60. Borad et al. Fibroblast growth factor receptor 2 fusions as a target for treating cholangiocarcinoma. Curr. Opin. Gastroenterol. 2015 May;31(3):264-8. PMID: 25763789

References (continued)

61. Ghedini et al. Future applications of FGF/FGFR inhibitors in cancer. Expert Rev Anticancer Ther. 2018 Sep;18(9):861-872. PMID: 29936878
62. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/214801s002lbl.pdf
63. https://www.taihooncology.com/us/news/2021-04-01_toi_tpc_futibatinib_btd/
64. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212018s010lbl.pdf
65. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213736s002lbl.pdf
66. https://www.globenewswire.com/news-release/2023/02/14/2608131/0/en/Kinnate-Biopharma-Inc-Receives-Fast-Track-Designation-from-the-U-S-Food-and-Drug-Administration-for-KIN-3248-an-Investigational-Pan-FGFR-Inhibitor.html
67. https://synapse.patsnap.com/blog/pharma-frontiers-daily-digest-of-global-pharmaceutical-news-%E2%80%93-jul-5
68. https://ir.relaytx.com/news-releases/news-release-details/relay-therapeutics-and-elevar-therapeutics-announce-exclusive
69. https://www.debiopharm.com/drug-development/press-releases/fda-grants-fast-track-designation-to-debiopharm-internationals-debio-1347-for-the-treatment-of-patients-with-unresectable-or-metastatic-tumors-with-a-specific-fgfr-gene-alteration/
70. https://www.amgen.com/newsroom/press-releases/2021/04/amgens-investigational-targeted-treatment-bemarituzumab-granted-breakthrough-therapy-designation
71. Mazzaferro et al. Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. Br. J. Cancer. 2019 Jan;120(2):165-171. PMID: 30420614
72. Javle et al. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. J. Clin. Oncol. 2018 Jan 20;36(3):276-282. PMID: 29182496
73. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
74. 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
75. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
76. 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
77. 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
78. 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
79. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
80. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
81. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
82. 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
83. 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
84. 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
85. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
86. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
87. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
88. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
89. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
90. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
91. 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
92. 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

References (continued)

93. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
94. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
95. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. Cancer Discov. 2013 Jan;3(1):35-43. PMID: 23208470
96. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818
97. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. Nat Commun. 8;14648. PMID: 28262751
98. Mehrvarz et al. ARID1A Mutation May Define an Immunologically Active Subgroup in Patients with Microsatellite Stable Colorectal Cancer. Clin Cancer Res. 2021 Mar 15;27(6):1663-1670. PMID: 33414133
99. https://nuvectis.com/press-release-view/?i=114174
100. https://www.morphosys.com/en/news/morphosys-receives-us-fda-fast-track-designation-tulmimetostat-endometrial-cancer
101. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
102. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. Oncogene. 2013 Aug 15;32(33):3840-5. PMID: 22964630
103. Ding et al. Prognostic role of cyclin D2/D3 in multiple human malignant neoplasms: A systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):2717-2729. PMID: 30950241
104. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. FEBS Lett. 2001 Feb 16;490(3):117-22. PMID: 11223026
105. Shan et al. Cyclin D1 overexpression correlates with poor tumor differentiation and prognosis in gastric cancer. Oncol Lett. 2017 Oct;14(4):4517-4526. PMID: 28943959
106. Cancer et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73. PMID: 23636398
107. Beà et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. Proc. Natl. Acad. Sci. U.S.A. 2013 Nov 5;110(45):18250-5. PMID: 24145436
108. Diehl et al. Glycogen synthase kinase-3beta regulates cyclin D1 proteolysis and subcellular localization. Genes Dev. 1998 Nov 15;12(22):3499-511. PMID: 9832503
109. Alt et al. Phosphorylation-dependent regulation of cyclin D1 nuclear export and cyclin D1-dependent cellular transformation. Genes Dev. 2000 Dec 15;14(24):3102-14. PMID: 11124803
110. Moreno-Bueno et al. Cyclin D1 gene (CCND1) mutations in endometrial cancer. Oncogene. 2003 Sep 4;22(38):6115-8. PMID: 12955092
111. Benzeno et al. Identification of mutations that disrupt phosphorylation-dependent nuclear export of cyclin D1. Oncogene. 2006 Oct 12;25(47):6291-303. PMID: 16732330
112. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
113. Kim et al. Nuclear cyclin D1: an oncogenic driver in human cancer. J. Cell. Physiol. 2009 Aug;220(2):292-6. PMID: 19415697
114. Jares et al. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat. Rev. Cancer. 2007 Oct;7(10):750-62. PMID: 17891190
115. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]