

Patient Name: 전영균
Gender: M
Sample ID: N25-349

Primary Tumor Site: urinary bladder
Collection Date: 2024.09.30

Sample Cancer Type: Bladder Urothelial Carcinoma

Table of Contents

Variant Details 2
Biomarker Descriptions 3
Relevant Therapy Summary 8

Page

Report Highlights

1 Relevant Biomarkers
0 Therapies Available
6 Clinical Trials

Relevant Bladder Urothelial Carcinoma Findings

Gene	Finding
BRAF	None detected
FGFR2	None detected
FGFR3	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	14.24 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	6

* 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 p.(Q1522*) c.4564_4568delCAGACinsTG, ERBB2 p.(D277Y) c.829G>T, Microsatellite stable, TP53 p.(R248W) c.742C>T, XRCC2 p.(L227Pfs*3) c.679_680insC, TPMT amplification, 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
ARID1B	p.(Q1522*)	c.4564_4568delCAGAC . insTG		chr6:157522043	37.55%	NM_001371656.1	nonsense
ERBB2	p.(D277Y)	c.829G>T	.	chr17:37866662	33.54%	NM_004448.4	missense
TP53	p.(R248W)	c.742C>T	COSM10656	chr17:7577539	32.40%	NM_000546.6	missense
XRCC2	p.(L227Pfs*3)	c.679_680insC	.	chr7:152345890	18.17%	NM_005431.2	frameshift Insertion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.15%	NM_000903.3	missense
PIK3C2B	p.(K818M)	c.2453A>T	.	chr1:204416600	26.22%	NM_002646.4	missense
ASXL2	p.(E363Q)	c.1087G>C	.	chr2:25976458	21.58%	NM_018263.6	missense
MSH2	p.(A72G)	c.215C>G	.	chr2:47635543	17.65%	NM_000251.3	missense
APC	p.(E56Q)	c.166G>C	.	chr5:112102053	13.13%	NM_000038.6	missense
RAD50	p.(Q104H)	c.312G>C	.	chr5:131911567	10.49%	NM_005732.4	missense
TPMT	p.(D162Y)	c.484G>T	.	chr6:18139204	4.31%	NM_000367.5	missense
HLA-A	p.(I121R)	c.362_363delTAinsGG	.	chr6:29911063	41.65%	NM_001242758.1	missense
NBN	p.(D555N)	c.1663G>A	.	chr8:90965654	15.76%	NM_002485.5	missense
TSC1	p.(?)	c.2209-1G>C	.	chr9:135778175	33.77%	NM_000368.5	unknown
KMT2D	p.(Q2553E)	c.7657C>G	.	chr12:49433896	3.14%	NM_003482.4	missense
KMT2D	p.(S2455L)	c.7364C>T	.	chr12:49434189	6.72%	NM_003482.4	missense
KMT2D	p.(P2390S)	c.7168C>T	.	chr12:49434385	8.50%	NM_003482.4	missense
KMT2D	p.(S2312L)	c.6935C>T	.	chr12:49434618	9.67%	NM_003482.4	missense
MLH3	p.(E787Q)	c.2359G>C	.	chr14:75514000	22.76%	NM_001040108.2	missense
CD276	p.(S233R)	c.699C>G	.	chr15:73995393	7.50%	NM_001024736.2	missense
SMAD4	p.(R38T)	c.113G>C	.	chr18:48573529	5.48%	NM_005359.6	missense
SMARCA4	p.(D1127V)	c.3380A>T	.	chr19:11138624	14.19%	NM_001128849.3	missense
CCNE1	p.(R31S)	c.93G>T	.	chr19:30303665	5.01%	NM_001238.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0.48	0.69
TPMT	chr6:18130879	8.43	2.28
FOXA1	chr14:38060550	0.4	0.68

Biomarker Descriptions

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹. 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)⁶². The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{63,64,65}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions⁶⁶. 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^{1,66,67}. CDKN2A aberrations commonly co-occur with CDKN2B⁶². Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation⁶⁸. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{69,70}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations⁷¹. 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^{6,7}. 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^{6,7}. Alterations in CDKN2A are also observed in pediatric cancers⁷. 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 tumors⁷. 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)⁷.

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^{72,73,74}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma⁷⁵. 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^{76,77,78}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁷⁹. 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^{80,81,82,83}.

ARID1B p.(Q1522*) c.4564_4568delCAGACinsTG

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein¹. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A⁹. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex^{9,10}. The BAF complex is a multisubunit protein that consists of SMARCB1/INI1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B¹⁰. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{10,11}. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor⁹.

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 tumors¹¹. 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^{6,7}. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma^{6,7}.

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^{12,13}.

Biomarker Descriptions (continued)

ERBB2 p.(D277Y) c.829G>T

erb-b2 receptor tyrosine kinase 2

Background: The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family¹. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family⁸⁴. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases⁸⁵. However, ERBB2/HER2 is an orphan receptor with no known ligand⁸⁵. ERBB2 preferentially binds other ligand-bound ERBB/HER family members to form heterodimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival⁸⁶. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types⁸⁶. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding^{87,88,89}.

Alterations and prevalence: ERBB2 gene amplification occurs in 10-25% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers^{6,7,90,91,92,93,94,95}. ERBB2 gene amplification in pediatric population is observed in 2% of peripheral nervous system cancers (2 in 91 patients) and less than 1% of leukemia (1 in 250 cases)⁷. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types^{7,96,97}. In breast, bladder, and colorectal cancers, the most common recurrent ERBB2 activating mutations include kinase domain mutations L755S and V777L and the extracellular domain mutation S310F. In lung cancer, the most common recurrent ERBB2 activating mutations include in-frame exon 20 insertions, particularly Y772_A775dup.

Potential relevance: The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987 led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2^{98,99}. Trastuzumab¹⁰⁰ was FDA approved for the treatment of HER2 positive breast cancer in 1998, and subsequently in HER2 positive metastatic gastric and gastroesophageal junction adenocarcinoma in 2010. Additional monoclonal antibody therapies have been approved by the FDA for HER2-positive breast cancer including pertuzumab¹⁰¹ (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine¹⁰² (2013), a conjugate of trastuzumab and a potent antimicrotubule agent. The combination of pertuzumab, trastuzumab, and a taxane is the preferred front-line regimen for HER2-positive metastatic breast cancer¹⁰³. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib¹⁰⁴, with specificity for both EGFR and ERBB2, was FDA approved (2007) for the treatment of patients with advanced HER2-positive breast cancer who have received prior therapy including trastuzumab. In 2017, the FDA approved the use of neratinib¹⁰⁵, an irreversible kinase inhibitor of EGFR, ERBB2/HER2, and ERBB4, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer. In 2020, the FDA approved neratinib¹⁰⁵ in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. Also in 2020, the TKI irbiniatinib¹⁰⁶ was FDA approved for HER2 overexpressing or amplified breast cancer in combination with trastuzumab and capecitabine. In 2021, the PD-1 blocking antibody, pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy, was approved for HER2 amplified gastric or gastroesophageal (GEJ) adenocarcinoma in the first line⁵⁰. In 2024, a bispecific HER2 antibody, zanidatamab¹⁰⁷, was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. In 2018 fast track designation was granted to the monoclonal antibody margetuximab¹⁰⁸ in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. Additionally, in 2019, zanidatamab¹⁰⁹, received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). The humanized anti-HER2 antibody drug conjugate disitamab vedotin¹¹⁰ (2020) received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment. In 2021, the antibody-drug conjugate ARX788¹¹¹ received fast track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies^{112,113,114,115,116}. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies^{117,118}. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy¹¹⁹. However, this was shown to be overcome by neratinib in combination with therapies targeting ER¹¹⁹. Additionally, in 2025, FDA approved the kinase inhibitors zongertinib¹²⁰ and sevabertinib¹²¹ for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 tyrosine kinase domain activating mutations. In 2025, a 9 amino acid transmembrane peptide of the HER2/neu protein, GLS1-100 (GP-2)¹²², received fast track designation for the prevention of breast cancer recurrence following surgery.

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 genome³⁷. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{38,39}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁴⁰. 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 D17S250⁴¹. Tumors with instability in one of the five markers were defined as

Biomarker Descriptions (continued)

MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)⁴¹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{42,43,44,45,46}. 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 genes³⁹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{38,39,43,47}.

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^{38,39,48,49}. 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^{48,49}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁵⁰ (2014) and nivolumab⁵¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁵⁰ 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 indication⁵⁰. Dostarlimab⁵² (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^{44,53}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁵⁴ (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^{44,55,56}. 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 patients⁵⁶. 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^{57,58}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{57,58}.

TP53 p.(R248W) c.742C>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 repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis¹⁴. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential¹⁵. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{16,17}.

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%)^{6,7,18,19,20,21}. 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^{6,7}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{22,23,24,25}. Alterations in TP53 are also observed in pediatric cancers^{6,7}. 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)^{6,7}. 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)^{6,7}.

Potential relevance: The small molecule p53 reactivator, PC14586²⁶ (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^{27,28}. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma²⁹. 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)^{30,31,32,33,34}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant³⁵. 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 system³⁶.

Biomarker Descriptions (continued)

XRCC2 p.(L227Pfs*3) c.679_680insC

X-ray repair cross complementing 2

Background: The XRCC2 gene encodes the X-ray repair cross complementing 2 protein, also known as FANCU, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC3 paralogs^{1,2,3}. XRCC2 forms the BCDX2 complex with other RAD51 paralogs, RAD51B, RAD51C, and RAD51D^{2,3}. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁴. XRCC2 regulates the assembly of RAD51 filaments to assist in strand-exchange activity during homologous recombination repair (HRR)^{2,3}. XRCC2 germline biallelic mutations result in Fanconi Anemia (FA) complementation group U, an atypical form of FA associated with defects in HRR⁵.

Alterations and prevalence: Somatic mutations in XRCC2 are observed in 3% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma^{6,7}. Biallelic deletions in XRCC2 are observed in 2% of acute myeloid leukemia (AML), sarcoma, and esophageal adenocarcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for XRCC2 aberrations. Pre-clinical evidence suggests that XRCC2 biallelic mutations may demonstrate sensitivity to the PARP inhibitor olaparib⁸.

TPMT amplification

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines^{1,59,60}. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine^{59,60,61}. Inherited TPMT polymorphisms, including TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, and TPMT*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure^{59,61}.

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma^{6,7}. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma^{6,7}. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma^{6,7}. Alterations in TPMT are also observed in pediatric cancers⁷. Somatic mutations are observed in less than 1% of peripheral nervous system tumors (1 in 1158 cases)⁷. Amplification of TPMT is observed in 1% of peripheral nervous system tumors (1 in 91 cases)⁷.

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, 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, 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 (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, 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, 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, SLC01B3, 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, 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, CBF, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERF1, 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, TP53, 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

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)
tislelizumab, palbociclib	✖	✖	✖	✖	● (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	18.93%
RAD51B	LOH, 14q24.1(68290164-69061406)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. 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. Andreassen et al. XRCC2 (X-ray repair cross complementing 2). *Atlas Genet Cytogenet Oncol Haematol.* 2019 Jan;23(1):1-7. PMID: 31275435
3. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. *Cold Spring Harb Perspect Biol.* 2015 Apr 1;7(4):a016600. PMID: 25833843
4. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. *Mol. Cell. Biol.* 2013 Jan;33(2):387-95. PMID: 23149936
5. Shamseldin et al. Exome sequencing reveals a novel Fanconi group defined by XRCC2 mutation. *J Med Genet.* 2012 Mar;49(3):184-6. PMID: 22232082
6. Weinstein et al. The Cancer Genome Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
7. 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
8. Park et al. Complementation of hypersensitivity to DNA interstrand crosslinking agents demonstrates that XRCC2 is a Fanconi anaemia gene. *J Med Genet.* 2016 Oct;53(10):672-680. PMID: 27208205
9. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. *Cancer Discov.* 2013 Jan;3(1):35-43. PMID: 23208470
10. Wilson et al. SWI/SNF nucleosome remodelers and cancer. *Nat. Rev. Cancer.* 2011 Jun 9;11(7):481-92. PMID: 21654818
11. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. *Nat Commun.* 8;14648. PMID: 28262751
12. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
13. McKinney et al. The Genetic Basis of Hepatosplenic T-cell Lymphoma. *Cancer Discov.* 2017 Apr;7(4):369-379. PMID: 28122867
14. Nag et al. The MDM2-p53 pathway revisited. *J Biomed Res.* 2013 Jul;27(4):254-71. PMID: 23885265
15. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell.* 2014 Mar 17;25(3):304-17. PMID: 24651012
16. 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
17. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med.* 2017 Apr 3;7(4). PMID: 28270529
18. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012 Sep 27;489(7417):519-25. PMID: 22960745
19. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
20. 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
21. 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
22. 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
23. 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
24. 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
25. 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
26. <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>
27. 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
28. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci.* 2017 Nov;74(22):4171-4187. PMID: 28643165

References (continued)

29. 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
30. 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
31. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
32. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
33. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
34. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
35. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]
36. 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
37. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
38. 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
39. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
40. 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
41. 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
42. 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
43. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
44. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
45. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
46. 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
47. 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
48. 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
49. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
51. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
52. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
53. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
54. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
55. 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
56. 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
57. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
58. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
59. Katara et al. TPMT Polymorphism: When Shield Becomes Weakness. *Interdiscip Sci.* 2016 Jun;8(2):150-155. PMID: 26297310
60. Yong et al. The role of pharmacogenetics in cancer therapeutics. *Br J Clin Pharmacol.* 2006 Jul;62(1):35-46. PMID: 16842377

References (continued)

61. McLeod et al. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. *Leukemia*. 2000 Apr;14(4):567-72. PMID: 10764140
62. 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
63. 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
64. Roussel. The INK4 family of cell cycle inhibitors in cancer. *Oncogene*. 1999 Sep 20;18(38):5311-7. PMID: 10498883
65. 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
66. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet*. 2013;14:257-79. PMID: 23875803
67. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell*. 2006 Oct 20;127(2):265-75. PMID: 17055429
68. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
69. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
70. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
71. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. *Clin Cancer Res*. 2021 Jul 15;27(14):4025-4035. PMID: 34074656
72. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2026]
73. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2026]
74. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
75. 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
76. 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
77. 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
78. 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
79. 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
80. 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
81. 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
82. 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
83. 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
84. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985 Sep 6;239(4717):974-6. PMID: 2992089
85. Hsu et al. The role of HER2, EGFR, and other receptor tyrosine kinases in breast cancer. *Cancer Metastasis Rev*. 2016 Dec;35(4):575-588. PMID: 27913999
86. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
87. Di Fiore et al. erbB-2 is a potent oncogene when overexpressed in NIH/3T3 cells. *Science*. 1987 Jul 10;237(4811):178-82. PMID: 2885917
88. Hudziak et al. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. *Proc. Natl. Acad. Sci. U.S.A.* 1987 Oct;84(20):7159-63. PMID: 2890160

References (continued)

89. Lonardo et al. The normal erbB-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. *New Biol.* 1990 Nov;2(11):992-1003. PMID: 1983208
90. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell.* 2015 Oct 8;163(2):506-19. PMID: 26451490
91. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature.* 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
92. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature.* 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
93. Donna M et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature.* 2012 Jul 18;487(7407):330-7. PMID: 22810696
94. 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
95. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011 Jun 29;474(7353):609-15. PMID: 21720365
96. Petrelli et al. Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. *Breast Cancer Res. Treat.* 2017 Nov;166(2):339-349. PMID: 28762010
97. Bose et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov.* 2013 Feb;3(2):224-37. doi: 10.1158/2159-8290.CD-12-0349. Epub 2012 Dec 7. PMID: 23220880
98. Hudis. Trastuzumab--mechanism of action and use in clinical practice. *N. Engl. J. Med.* 2007 Jul 5;357(1):39-51. PMID: 17611206
99. Slamon et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987 Jan 9;235(4785):177-82. PMID: 3798106
100. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/103792s5354lbl.pdf
101. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125409s139lbl.pdf
102. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125427s121lbl.pdf
103. NCCN Guidelines® - NCCN-Breast Cancer [Version 5.2025]
104. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022059s031lbl.pdf
105. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208051s009lbl.pdf
106. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213411s004lbl.pdf
107. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/761416Orig1s000lbl.pdf
108. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761150s005lbl.pdf
109. <https://www.targetedonc.com/view/her2targeted-antibody-zw25-earns-fda-fast-track-designation-in-gea>
110. <https://www.prnewswire.com/news-releases/remegen-announces-us-fda-has-granted-breakthrough-therapy-designation-for-disitamab-vedotin-rc48-in-urothelial-cancer-301138315.html>
111. <https://ir.ambrx.com/news/news-details/2023/ACE-Breast-02-Pivotal-Phase-3-Study-of-Ambrxs-ARX788-for-the-Treatment-of-HER2-Positive-Metastatic-Breast-Cancer-Achieves-Positive-Results/default.aspx>
112. Ma et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. *Clin. Cancer Res.* 2017 Oct 1;23(19):5687-5695. PMID: 28679771
113. De Grève et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer.* 2012 Apr;76(1):123-7. PMID: 22325357
114. Kris et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann. Oncol.* 2015 Jul;26(7):1421-7. PMID: 25899785
115. Falchook et al. Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. *J Thorac Oncol.* 2013 Feb;8(2):e19-20. PMID: 23328556
116. David M et al. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study. *AACR* 2017. Abstract CT001
117. Lin et al. Response to Afatinib in a Patient with Non-Small Cell Lung Cancer Harboring HER2 R896G Mutation: A Case Report. *Onco Targets Ther.* 2019;12:10897-10902. PMID: 31849493
118. Chang et al. Sustained Partial Response to Afatinib in a Patient With Lung Adenocarcinoma Harboring HER2V659E Mutation. *JCO Precis Oncol.* 2020 Aug; 912-915. PMID: 35050762

References (continued)

119. Nayar et al. Acquired HER2 mutations in ER+ metastatic breast cancer confer resistance to estrogen receptor-directed therapies. *Nat. Genet.* 2019 Feb;51(2):207-216. PMID: 30531871
120. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219042s000lbl.pdf
121. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219972s000lblCorrected.pdf
122. <https://investor.greenwichlifesciences.com/news-events/press-releases/detail/102/us-fda-fast-track-designation>