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Patient Name: 박효성
Gender: M
Sample ID: N25-292

Primary Tumor Site: bladder
Collection Date: 2025.10.28

Sample Cancer Type: Bladder Cancer

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Relevant Bladder Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR2	None detected	NTRK3	None detected
FGFR3	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***24.66 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PIK3CA p.(E545K) c.1633G>A* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 32.25% Locus: chr3:178936091 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1 / I] **alpelisib + hormone therapy** [1, 2 / II+] **capivasertib + hormone therapy** [1, 2 / II+] aspirin [II+]	5
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	15
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5
IIC	*CCND1 amplification* cyclin D1 Locus: chr11:69455949	None*	None*	2

*** 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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	2
IIC	*CDK12 p.(Q1088*) c.3262C>T* cyclin dependent kinase 12 Allele Frequency: 3.70% Locus: chr17:37681093 Transcript: NM_016507.4	None*	None*	1
IIC	*MYCL amplification* MYCL proto-oncogene, bHLH transcription factor Locus: chr1:40362966	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

KMT2D p.(Q5387) c.16159C>T, Microsatellite stable, PBRM1 p.(E372*) c.1114G>T, SLX4 p.(E335*) c.1003G>T, MPL amplification, ELF3 p.(K69*) c.205A>T, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, HLA-B deletion, EMSY amplification, NQO1 p.(P187S) c.559C>T, NCOR1 p.(R2018*) c.6052C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(E545K)	c.1633G>A	COSM763	chr3:178936091	32.25%	NM_006218.4	missense
CDK12	p.(Q1088*)	c.3262C>T	.	chr17:37681093	3.70%	NM_016507.4	nonsense
KMT2D	p.(Q5387*)	c.16159C>T	.	chr12:49416552	6.95%	NM_003482.4	nonsense
PBRM1	p.(E372*)	c.1114G>T	.	chr3:52668805	3.76%	NM_018313.5	nonsense
SLX4	p.(E335*)	c.1003G>T	.	chr16:3651140	5.26%	NM_032444.4	nonsense
ELF3	p.(K69*)	c.205A>T	.	chr1:201981126	45.83%	NM_004433.5	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.70%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.60%	NM_000903.3	missense
NCOR1	p.(R2018*)	c.6052C>T	.	chr17:15961337	52.53%	NM_006311.4	nonsense
ARID1A	p.(E1683D)	c.5049G>C	.	chr1:27102123	5.85%	NM_006015.6	missense
MSH6	p.(S63C)	c.188C>G	.	chr2:48010560	28.27%	NM_000179.3	missense
UGT1A1	p.(D63Y)	c.187G>T	.	chr2:234669120	6.11%	NM_000463.3	missense
CNTN6	p.(P433T)	c.1297C>A	.	chr3:1371552	51.88%	NM_014461.4	missense
TGFBR2	p.(?)	c.530-1G>C	.	chr3:30713129	4.82%	NM_001024847.2	unknown
TGFBR2	p.(N179K)	c.537C>A	.	chr3:30713137	4.77%	NM_001024847.2	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CB	p.(P546S)	c.1636C>T	.	chr3:138417883	6.93%	NM_006219.3	missense
ATR	p.(E1146Q)	c.3436G>C	.	chr3:142261521	33.27%	NM_001184.4	missense
FAT1	p.(?)	c.10350+1G>A	.	chr4:187527223	41.13%	NM_005245.4	unknown
IRF4	p.(E65K)	c.193G>A	.	chr6:393345	4.37%	NM_002460.4	missense
DDR1	p.(S142*)	c.425C>G	.	chr6:30858757	28.41%	NM_001954.4	nonsense
NOTCH4	p.(D1952N)	c.5854G>A	.	chr6:32163372	5.62%	NM_004557.4	missense
NOTCH4	p.(R1933I)	c.5798G>T	.	chr6:32163428	6.51%	NM_004557.4	missense
CEP85L	p.(R244T)	c.731G>C	.	chr6:118886990	8.04%	NM_001178035.1	missense
MAP3K4	p.(S1108L)	c.3323C>T	.	chr6:161514063	26.53%	NM_005922.4	missense
ABCB1	p.(R680K)	c.2039G>A	.	chr7:87174164	33.92%	NM_000927.4	missense
GATA3	p.(P394L)	c.1181C>T	.	chr10:8115832	6.35%	NM_001002295.2	missense
ATM	p.(E257K)	c.769G>A	.	chr11:108115621	19.40%	NM_000051.4	missense
ATM	p.(E1009K)	c.3025G>A	.	chr11:108142081	21.15%	NM_000051.4	missense
ATM	p.(A2040P)	c.6118G>C	.	chr11:108186760	33.30%	NM_000051.4	missense
DBX2	p.(S325F)	c.974C>T	.	chr12:45410115	4.29%	NM_001004329.3	missense
KMT2D	p.(E2660Q)	c.7978G>C	.	chr12:49433575	4.80%	NM_003482.4	missense
TBX3	p.(D101H)	c.301G>C	.	chr12:115120705	9.80%	NM_016569.4	missense
HNF1A	p.(S256Y)	c.767C>A	.	chr12:121432020	10.89%	NM_000545.8	missense
PARP4	p.(?)	c.3285_3285+5delinsAGT	.	chr13:25021149	100.00%	NM_006437.4	unknown
FOXA1	p.(S409L)	c.1226C>T	.	chr14:38060763	2.85%	NM_004496.5	missense
CYLD	p.(A807G)	c.2420C>G	.	chr16:50827535	5.26%	NM_001042355.2	missense
CDK12	p.(E888Q)	c.2662G>C	.	chr17:37666010	7.16%	NM_016507.4	missense
SMAD2	p.(?)	c.785-3C>T	.	chr18:45375061	15.90%	NM_001003652.4	unknown
NOTCH3	p.(G1347R)	c.4039G>C	.	chr19:15288700	60.97%	NM_000435.3	missense
APOE	p.(S157F)	c.470C>T	.	chr19:45412023	8.33%	NM_000041.4	missense
BID	p.(E60K)	c.178G>A	.	chr22:18226752	10.85%	NM_197966.2	missense
DDX3X	p.([V448=;E449K])	c.1344_1345delGGinsAA	.	chrX:41205510	5.85%	NM_001356.5	synonymous, missense
ZMYM3	p.(P821S)	c.2461C>T	.	chrX:70466314	33.33%	NM_201599.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	0	0.42
CDKN2A	chr9:21968178	0	0.38

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CCND1	chr11:69455949	6.15	1.83
CDKN2B	chr9:22005728	0	0.44
MYCL	chr1:40362966	16.15	3.83
MPL	chr1:43803495	12.1	3.02
HLA-A	chr6:29910229	0	0.55
HLA-B	chr6:31322252	0	0.56
EMSY	chr11:76157926	5.15	1.63
ZFHX3	chr16:72820995	4.88	1.57

Biomarker Descriptions

PIK3CA p.(E545K) c.1633G>A

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[100]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[101,102]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[101]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[103,104]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[103,104,105,106]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[107,108,109].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[4,5]. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[110,111]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[112,113,114]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[4,5].

Potential relevance: The PI3K inhibitor, alpelisib[115], is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[116]. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations[116]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[117]. The FDA also approved the kinase inhibitor, capivasertib (2023)[118] in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib[119], is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[120,121]. In colorectal cancers, PIK3CA mutations predict significantly improved survival and reduced disease recurrence with adjuvant aspirin therapy, compared to no benefit in wild-type PIK3CA tumors[85,94,122,123].

Biomarker Descriptions (continued)

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[14,15]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[15].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[15,16]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. 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)[22]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[23,24,25]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[26]. 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[1,26,27]. CDKN2A aberrations commonly co-occur with CDKN2B[22]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[28]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[29,30].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[31]. 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[4,5]. 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[4,5]. Alterations in CDKN2A are also observed in pediatric cancers[5]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[5]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[5].

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[32,33,34]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[35]. 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[36,37,38]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[39]. 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[40,41,42,43].

Biomarker Descriptions (continued)

CCND1 amplification

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[124,125,126]. 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[124,125]. 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[124,125,127]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[126,128].

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)[4,5,129,130]. These mutations block phosphorylation-dependent nuclear export and proteolysis[131,132,133,134]. 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[4,5,135]. 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[136,137].

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[138].

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,22]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[22]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[23,24,25]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[22]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,49,50].

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

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma[35].

CDK12 p.(Q1088*) c.3262C>T

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[64,65,66]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[64,65,66,67,68]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[66,67]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[68]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[68].

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma[1,4].

Biomarker Descriptions (continued)

CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma[1,4].

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[70] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors[67,68]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[71], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

MYCL amplification

MYCL proto-oncogene, bHLH transcription factor

Background: The MYCL gene encodes MYCL proto-oncogene, a basic helix-loop-helix transcription factor[1]. MYCL is a member of MYC oncogene family that includes related transcription factors, MYC and MYCN which regulate transcription in 10-15% of promoter regions[1,75]. MYCL, along with MYC and MYCN, control cell proliferation, replication, evasion of growth suppression and cell death[76].

Alterations and prevalence: Amplification of MYCL was first discovered in small cell lung cancer (SCLC) cell lines and is observed in 8% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma and esophageal squamous cell carcinoma, as well as 3% uterine corpus endometrial carcinoma[4,5,77].

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

KMT2D p.(Q5387*) c.16159C>T

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2D belongs to the SET domain protein methyltransferase superfamily[44]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[44]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[44].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for KMT2D aberrations.

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[78]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[79,80]. 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[81]. 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[82]. 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)[82]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[83,84,85,86,87]. 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[80]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[79,80,84,88].

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[79,80,89,90]. 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[89,90].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[91] (2014) and nivolumab[92] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[91] 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

Biomarker Descriptions (continued)

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[91]. Dostarlimab[93] (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[85,94]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[95] (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[85,96,97]. 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[97]. 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[98,99]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[98,99].

PBRM1 p.(E372*) c.1114G>T

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[17]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[17,18]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[17,19]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[20,21].

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[4,5]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for PBRM1 aberrations.

SLX4 p.(E335*) c.1003G>T

SLX4 structure-specific endonuclease subunit

Background: The SLX4 gene encodes the SLX4 structure-specific endonuclease subunit[1]. SLX4, also known as FANCP, is a tumor suppressor protein that functions as a scaffold for DNA repair endonucleases[72]. SLX4 functions in DNA repair mechanisms including double-strand break (DSB) repair and interstrand crosslink repair[72,73,74]. Specifically, SLX4 localizes at DSB sites and recruits and interacts with other repair proteins such as ERCC1-XPF, MUS81-EME1, and SLX1[72,73,74]. Germline SLX4 mutations are associated with Fanconi Anemia, a genetic condition characterized by genomic instability and congenital abnormalities, including bone marrow failure and cancer predisposition[73].

Alterations and prevalence: Recurrent somatic mutations in SLX4 are observed in 11% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of stomach adenocarcinoma, and 4% of bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for SLX4 aberrations.

MPL amplification

MPL proto-oncogene, thrombopoietin receptor

Background: The MPL gene encodes the MPL proto-oncogene, a transmembrane thrombopoietin receptor. Binding of the cytokine thrombopoietin to MPL leads to JAK2 activation and subsequent signaling that regulates stem cell homeostasis, cell survival, and proliferation[45]. Mutations in MPL typically disrupt normal auto-inhibitory functions and result in subsequent ligand-independent thrombopoietin receptor activation[45]. Gain-of-function mutations in MPL are associated with myeloproliferative neoplasms (MPN) and hereditary thrombocytosis. Loss-of-function mutations are linked to bone marrow failure syndromes, due to the regulation of thrombopoiesis by thrombopoietin[46].

Alterations and prevalence: Somatic mutations in MPL are present in 3-5% of primary myelofibrosis (PMF)[45,47]. Specifically, MPL W515L/K mutations are reported in 5-8% of myelofibrosis (MF) and 1-4% of essential thrombocythemia (ET)[48]. Other observed MPL mutations include V501A, Y252H, and S204P[45].

Biomarker Descriptions (continued)

Potential relevance: MPL W515K/L mutations confer intermediate prognosis in MPN[48].

ELF3 p.(K69*) c.205A>T

E74 like ETS transcription factor 3

Background: The ELF3 gene encodes the E74 like ETS transcription factor 3 protein[1]. ELF3 is a transcription factor that has been observed to function as a negative regulator of the epithelial-mesenchymal transition (EMT) process, specifically in ovarian cancer cells[2]. ELF3 has also been proposed to act as an antagonist of oncogenic-signaling induced ZEB1 expression in colorectal cancer, supporting a tumor suppressor role for ELF3[2,3].

Alterations and prevalence: Somatic mutations in ELF3 are observed in 13% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 3% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine corpus endometrial carcinoma, and cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ELF3 aberrations.

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,51]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[51,52]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[53]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[53,54,55,56]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[57].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[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[58]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[59]. 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[60,61,62]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[63].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[4,5]. Biallelic loss of HLA-A is observed in 4% of DLBCL[4,5].

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[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[58]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[59]. 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,

Biomarker Descriptions (continued)

to the immune system to distinguish self from non-self[60,61,62]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[63].

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[4,5]. Biallelic loss of HLA-B is observed in 5% of DLBCL[4,5].

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

EMSY amplification

EMSY transcriptional repressor, BRCA2 interacting

Background: The EMSY gene encodes the EMSY transcriptional repressor, BRCA2 interacting[1]. EMSY is a nuclear protein that interacts with the transactivation domain of BRCA2, resulting in the suppression of BRCA2 transcriptional activity.[11,12]. EMSY colocalizes with γ-H2AX at DNA damage sites, regulates chromatin remodeling, and suppresses interferon-stimulated genes in a BRCA2 dependent manner[11,13]. Overexpression of EMSY inactivates BRCA2 leading to chromosomal instability and tumorigenesis[11,13].

Alterations and prevalence: Somatic mutations in EMSY are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, colorectal adenocarcinoma, and 2% of lung adenocarcinoma, uterine carcinosarcoma, and stomach adenocarcinoma[4,5]. Amplification of EMSY is observed in 8% of ovarian serous cystadenocarcinoma, 6% of breast invasive carcinoma and esophageal adenocarcinoma, and 4% of head and neck squamous cell carcinoma and skin cutaneous melanoma[4,5].

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

NCOR1 p.(R2018*) c.6052C>T

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,6,7]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[6,7,8,9]. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[7]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types, including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[7,10].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[4,5]. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[4,5]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[4,5]. Alterations in NCOR1 are also observed in pediatric cancer[5]. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[5]. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)[5].

Potential relevance: Currently, no therapies are approved for NCOR1 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, 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

PIK3CA p.(E545K) c.1633G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✖
capivasertib + fulvestrant	○	○	○	✖	✖
inavolisib + palbociclib + fulvestrant	○	○	✖	✖	✖
aspirin	✖	○	✖	✖	✖
ETX-636	✖	✖	✖	✖	● (I/II)
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
RLY-2608	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (I)

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
etrumadenant, zimberelimab, chemotherapy	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)
CTS-3497	✖	✖	✖	✖	● (I/II)
IDE397	✖	✖	✖	✖	● (I/II)
MRTX-1719	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462, pembrolizumab	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)
GH-56	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
HSK-41959	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

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)

CCND1 amplification

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

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
tislelizumab, palbociclib	✖	✖	✖	✖	● (I/II)

CDK12 p.(Q1088*) c.3262C>T

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

MYCL amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
MRT-2359	✖	✖	✖	✖	● (I/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
ATM	***SNV, E257K, AF:0.19***
ATM	***SNV, E1009K, AF:0.21***
ATM	***SNV, A2040P, AF:0.33***
CDK12	***SNV, E888Q, AF:0.07***

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 2025.10(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 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. 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.

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