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Patient Name: 이성기
Gender: M
Sample ID: N25-17
Primary Tumor Site: lung
Collection Date: 2025.04.17

Sample Cancer Type: Lung Cancer

Table of Contents	Page

Report Highlights
12 Relevant Biomarkers
3 Therapies Available
5 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***7.56 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	*BRCA1 deletion* BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	2
IIC	*BARD1 deletion* BRCA1 associated RING domain 1 Locus: chr2:215593375	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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	*BRIP1 deletion* BRCA1 interacting protein C-terminal helicase 1 Locus: chr17:59760627	None*	None*	1
IIC	*CDK12 deletion* cyclin dependent kinase 12 Locus: chr17:37618286	None*	None*	1
IIC	*CHEK1 deletion* checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	*MSH6 p.(R248Qfs*7) c.743_744delGA* mutS homolog 6 Allele Frequency: 21.90% Locus: chr2:48025864 Transcript: NM_000179.3	None*	None*	1
IIC	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	1
IIC	*RAD50 deletion* RAD50 double strand break repair protein Locus: chr5:131892978	None*	None*	1
IIC	*RAD51C deletion* RAD51 paralog C Locus: chr17:56769933	None*	None*	1
IIC	*RAD51D deletion* RAD51 paralog D Locus: chr17:33427950	None*	None*	1

*** Public data sources included in relevant therapies: FDA**1, NCCN, **EMA**2, 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

*AXIN2 deletion, CUL4A deletion, KMT2A deletion, KMT2D p.(A328Rfs*6) c.982delG, KMT2D p.(E2723*) c.8167G>T, PARP3 deletion, SDHD deletion, CASP8 deletion, PDCD1 deletion, DOCK3 deletion, ERAP1 deletion, ADAMTS2 deletion, HLA-A deletion, HLA-A p.(L180*) c.539T>A, HLA-B deletion, NOTCH4 deletion, TAP2 deletion, TAP1 deletion, DAXX deletion, CDKN1A deletion, HDAC2 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, TPP2 deletion, CBFB deletion, CDH1 deletion, ZFHX3 deletion, GPS2 deletion, NCOR1 deletion, SPOP deletion, RNF43 deletion, PPM1D deletion, YES1 amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MSH6	p.(R248Qfs*7)	c.743_744delGA	.	chr2:48025864	21.90%	NM_000179.3	frameshift Deletion

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	47.51%	NM_001242758.1	nonsense
KMT2D	p.(E2723*)	c.8167G>T	.	chr12:49433280	29.28%	NM_003482.4	nonsense
KMT2D	p.(A328Rfs*6)	c.982delG	.	chr12:49446827	35.44%	NM_003482.4	frameshift Deletion
NGF	p.(Y6C)	c.17A>G	.	chr1:115829400	2.75%	NM_002506.3	missense
HCN1	p.(K24N)	c.72G>T	.	chr5:45696124	36.79%	NM_021072.4	missense
TAP1	p.(V617G)	c.1850T>G	.	chr6:32815343	38.19%	NM_000593.6	missense
ARID1B	p.(Q892H)	c.2676G>C	.	chr6:157454217	38.25%	NM_001371656.1	missense
PTPRD	p.(A722G)	c.2165C>G	.	chr9:8499804	50.25%	NM_002839.4	missense
POLE	p.(R1382C)	c.4144C>T	.	chr12:133225520	48.87%	NM_006231.4	missense
RB1	p.(?)	c.608-1G>A	.	chr13:48934152	37.87%	NM_000321.3	unknown
LIPC	p.(A214S)	c.640G>T	.	chr15:58838006	29.41%	NM_000236.3	missense
NOTCH3	p.(P898L)	c.2693C>T	.	chr19:15292486	29.38%	NM_000435.3	missense
STAG2	p.(?)	c.2026-1_2026delinsTT	.	chrX:123199725	55.75%	NM_001042749.2	unknown

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CASP8	chr2:202122934	0.91	0.7
BARD1	chr2:215593375	1	0.78
BARD1	chr2:215593375	1	0.78
PDCD1	chr2:242793161	0.88	0.69
DOCK3	chr3:51101879	0.77	0.66
PARP3	chr3:51976651	0.93	0.7
ERAP1	chr5:96112128	0.79	0.66
RAD50	chr5:131892978	0.91	0.7
ADAMTS2	chr5:178549645	0.93	0.7
HLA-A	chr6:29910229	0.36	0.54
HLA-B	chr6:31322252	0.88	0.69
NOTCH4	chr6:32163187	0.8	0.67
TAP2	chr6:32796585	0.82	0.67
TAP1	chr6:32814849	0.71	0.64
DAXX	chr6:33286486	0.79	0.66
CDKN1A	chr6:36645655	0.89	0.69
HDAC2	chr6:114262171	0.88	0.68

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ARID5B	chr10:63661463	0.93	0.7
PTEN	chr10:89623659	0.86	0.68
CYP2C9	chr10:96698378	0.88	0.69
SUFU	chr10:104263903	0.89	0.69
ATM	chr11:108098341	1	0.73
ATM	chr11:108098341	1	0.73
SDHD	chr11:111957573	0.66	0.62
KMT2A	chr11:118307146	0.84	0.67
CHEK1	chr11:125496639	1	0.69
CHEK1	chr11:125496639	1	0.69
BRCA2	chr13:32890491	1	0.74
BRCA2	chr13:32890491	1	0.74
TPP2	chr13:103249399	0.89	0.69
CUL4A	chr13:113863977	0.93	0.7
RAD51B	chr14:68290164	2	0.97
CBFB	chr16:67063242	0.75	0.65
CDH1	chr16:68771249	0.88	0.68
ZFHX3	chr16:72820995	0.88	0.69
GPS2	chr17:7216071	0.86	0.68
NCOR1	chr17:15935586	0.91	0.7
RAD51D	chr17:33427950	1	0.7
RAD51D	chr17:33427950	1	0.7
CDK12	chr17:37618286	1	0.69
CDK12	chr17:37618286	1	0.69
BRCA1	chr17:41197602	1	0.76
BRCA1	chr17:41197602	1	0.76
SPOP	chr17:47677716	0.88	0.68
RNF43	chr17:56432226	0.84	0.68
RAD51C	chr17:56769933	1	0.8
RAD51C	chr17:56769933	1	0.8
PPM1D	chr17:58677747	0.89	0.69
BRIP1	chr17:59760627	1	0.73
BRIP1	chr17:59760627	1	0.73
AXIN2	chr17:63526027	0.82	0.67

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
YES1	chr18:724481	5.66	2.02
MYCN	chr2:16082167	0.88	0.68
NFE2L2	chr2:178095457	0.79	0.66
PDGFRB	chr5:149497160	0.7	0.63
FGFR4	chr5:176517731	0.88	0.68
FLT4	chr5:180030092	0.89	0.69
CCND3	chr6:41903600	0.86	0.68
FYN	chr6:111982890	0.84	0.68
ESR1	chr6:152163831	0.91	0.69
RET	chr10:43609070	0.93	0.7
EMSY	chr11:76157926	0.86	0.68
YAP1	chr11:101981594	0.88	0.69
RARA	chr17:38487425	0.77	0.66
STAT3	chr17:40467740	0.8	0.67
RPS6KB1	chr17:57970507	0.84	0.67
SOX9	chr17:70117435	0.68	0.63
H3-3B	chr17:73772413	0.86	0.68

Biomarker Descriptions

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[2,3]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[3]. ARID5B is known to be essential for the development of hematopoietic cells[3]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[3].

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma[4,5]. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for ARID5B aberrations.

CUL4A deletion

cullin 4A

Background: The CUL4A gene encodes cullin 4A, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4b, CUL5, CUL7, and Parc[1,6]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[7]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[7,8]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[6]. CUL4A is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the

Biomarker Descriptions (continued)

substrate recognition component of the CRL4 complex[8]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4A in oncogenesis[7,8].

Alterations and prevalence: Somatic mutations in CUL4A are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma[4,5]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[4,5]. Amplification of CUL4A is observed in 4% of sarcoma and uterine carcinosarcoma, 3% of colorectal adenocarcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[4,5]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for CUL4A aberrations.

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,9]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[10,11]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[10,11,12]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[9,10,11,12]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[10]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[10].

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[4,5]. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma[4,5]. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CYP2C9.

DAXX deletion

death domain associated protein

Background: DAXX encodes the death domain associated protein, a transcription co-repressor known to repress the transcriptional potential of several sumoylated transcription factors[1]. DAXX mediates apoptosis through the death receptor pathway where it interacts and supports a multitude of cellular processes, which include gene regulation, transcriptional mediation through interaction with DNA-binding transcription factors, histones, and chromatin-associated proteins[13]. DAXX is proposed to function as a tumor suppressor due to its potential role in DNA damage repair(DDR) and through facilitating the inhibition of target genes by promoting H3K9 trimethylation[14,15].

Alterations and prevalence: Somatic mutations in DAXX are predominantly missense and truncating and occur in 5% of uterine corpus endometrial carcinoma, 3% skin cutaneous melanoma, adrenocortical carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of colorectal adenocarcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and glioblastoma multiforme[5]. DAXX mutations have also been observed to be enriched in pancreatic neuroendocrine tumors (Pan-NETs) with one study reporting mutations in 25% of 68 cases[16].

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

BRCA1 deletion

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[17,18]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[17,18]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for

Biomarker Descriptions (continued)

breast and ovarian cancer and in men for breast and prostate cancer[19,20,21]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[19,22].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[23,24,25,26,27,28,29,30]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[4,5].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[31]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[32,33]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[34] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[35] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[36] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[37] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[38] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[39]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[40]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[42], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

SDHD deletion

succinate dehydrogenase complex subunit D

Background: The SDHD gene encodes succinate dehydrogenase complex subunit D of the succinate dehydrogenase (SDH) enzyme complex[1,43]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[44,45]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[44,45]. SDHD, along with SDHC, anchors SDHA and SDHB to the inner mitochondrial membrane and provides a binding site for ubiquinone[43]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[43,44,45]. Inherited pathogenic mutations in SDHD have been associated with paragangliomas and gastrointestinal stromal tumors[1,43,46].

Alterations and prevalence: Somatic mutations in SDHD are observed in 1% of mesothelioma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, and lung adenocarcinoma[4,5]. Biallelic loss of SDHD is observed in 3% of testicular germ cell tumors, skin cutaneous melanoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and uterine carcinosarcoma[4,5].

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

TPP2 deletion

tripeptidyl peptidase 2

Background: The TPP2 gene encodes the tripeptidyl peptidase 2[1]. TPP2 is a serine peptidase that becomes activated upon homopolymer complex formation[47]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[47]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[47].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in TPP2 are observed in 8% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 4% of bladder urothelial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL), kidney renal papillary cell carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[4,5]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[4,5].

Potential relevance: Currently, no therapies are approved for TPP2 aberrations.

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[48]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[48,49]. PARP enzymes are involved in several DNA repair pathways[48,49]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[50,51]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[50].

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma[4,5]. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[52,53]. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[34] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[35] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[36] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[37] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes the lysine methyltransferase 2A protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily. KMT2A influences epigenetic regulation by means of its methyltransferase activity, which regulates a variety of cellular functions including neurogenesis, hematopoiesis, and osteogenesis[54]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[55]. Such translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[55]. Loss of methyltransferase activity along with partner gene gain of function contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[55,56,57,58].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[55,59,60]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[55]. In infant acute leukemic cases, KMT2A rearrangement is reported in up to 70% of those diagnosed with either AML or ALL[55,61,62]. Mutations in KMT2A are also reported in diverse solid tumors including 10-20% of melanoma, stomach, bladder, and uterine cancers and around 5% of lung and head and neck cancers[4]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations which result in KMT2A truncation and loss of methyltransferase activity[4,63].

Biomarker Descriptions (continued)

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[60,64]. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML[65,66,67]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[68]. KMT2A fusion is also associated with poor risk in ALL[69]. In 2024, the FDA approved the oral menin inhibitor, revumenib[70], for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also grant fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[71].

KMT2D p.(A328Rfs*6) c.982delG, KMT2D p.(E2723*) c.8167G>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[72]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[72]. 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[72].

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.

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[73]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[74]. 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[75,76,77]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[78].

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.

SPOP deletion

speckle type BTB/POZ protein

Background: The SPOP gene encodes the speckle type BTB/POZ protein[1]. SPOP is an E3 ligase substrate adaptor, with specificity for cullin3-RING ubiquitin ligase (CRL3), which recruits substrates for ubiquitination[79]. Substrates recruited by SPOP include proteins involved in epigenetic modification, hormone signaling effectors, and cascade effectors, such as androgen receptor (AR), estrogen receptor (ER), CCNE1, MYC, and PTEN[79]. Mutations in SPOP meprin and TRAF-C homology (MATH) domains have been implicated to have loss of function as well as gain of function roles that are cancer-type dependent and are based on SPOP's specificity for its various substrates[79,80,81,82]. In prostate cancer, mutations in the SPOP substrate-binding cleft of the MATH domain, involving residues F133, F102, W131 and Y87, lead to increased levels of AR. In endometrial cancer, mutations in the SPOP substrate-binding face of the MATH domain, involving residues M117, E47, R121 and E50, lead to decreased levels of estrogen and progesterone receptors[79,80,81,82]. Moreover, improved overall survival has been observed from hormonal therapies in patients with SPOP mutated prostate cancer[82].

Alterations and prevalence: Somatic mutations in SPOP are observed in 11% of prostate adenocarcinoma, 10% of uterine corpus endometrial carcinoma, 7% of uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma[4,5]. Amplification of SPOP is observed in 6% of breast invasive carcinoma, 5% of mesothelioma, and 2% of esophageal adenocarcinoma and pancreatic adenocarcinoma[4,5].

Biomarker Descriptions (continued)

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

MSH6 p.(R248Qfs*7) c.743_744delGA

mutS homolog 6

Background: The MSH6 gene encodes the mutS homolog 6 protein[1]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[83]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[83]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication. Mutations in MSH2 result in the degradation of MSH6[84]. MSH6, along with MLH1, MSH2, and PMS2 form the core components of the MMR pathway[83]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[85,86,87]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[85,88]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[86,88,89,90]. Specifically, MSH6 mutations are associated with increased risk of ovarian and pancreatic cancer[91,92,93,94].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[4,5].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[95]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[96,97].

HLA-A deletion, HLA-A p.(L180*) c.539T>A

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[73]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[74]. 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[75,76,77]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[78].

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.

ATM deletion

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[98]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[99]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[99,100]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[101]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[102,103]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[104].

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[36] in

Biomarker Descriptions (continued)

combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[102,105,106]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[107]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs[108]. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)[109]. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)[110]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing[111]. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity[112,113]. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[102,103].

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers[4].

Potential relevance: The PARP inhibitor, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation[114]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51D deletion

RAD51 paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[109]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[110]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[111]. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[102,103]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[115].

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer[4].

Potential relevance: The PARP inhibitor, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors[102]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA[116]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[117]. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[102,103]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[118]. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer[118,119]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[116,120].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma[4,5].

Potential relevance: The PARP inhibitor, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy[102,106]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene[1,121]. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage[1,121,122,123]. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction[1,122,124,125]. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[125,126]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[124]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[127]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[127,128].

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma[4,5]. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

AXIN2 deletion

axin 2

Background: The AXIN2 gene encodes the axis inhibition protein 2, a cytoplasmic protein that contains a regulation of G-protein signaling (RGS) domain and a disheveled and axin (DIX) domain, which are responsible for a variety of protein-protein interactions and signaling regulation[1,129,130,131]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[132,133]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[133]. AXIN2 has been observed to be involved the regulation of the cell cycle through its involvement in WNT signaling and has been suggested to promote mitochondrial-associated apoptosis[134,135]. Loss of AXIN2 expression has been observed to contribute to the development of gastric cancer[136].

Alterations and prevalence: Somatic mutations of AXIN2 are observed in 7% of uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma and skin cutaneous melanoma[4,5]. Biallelic deletion of AXIN2 is observed in 4% of diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for AXIN2 aberrations.

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,137,138]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[138,139]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[140,141,142,143,144]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[140,143,145,146].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6%

Biomarker Descriptions (continued)

of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[4,5]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

TAP1 deletion

transporter 1, ATP binding cassette subfamily B member

Background: The TAP1 gene encodes the transporter 1, ATP binding cassette subfamily B member protein[1]. Along with TAP2 TAP1 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP-controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[147,148]. TAP1 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression and survival[149,150,151].

Alterations and prevalence: Somatic mutations in TAP1 are predominantly missense or truncating and have been observed in 6% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma and thymoma[4,5]. Biallelic deletion of TAP1 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)[4,5].

Potential relevance: Currently, no therapies are approved for TAP1 aberrations.

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[152]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[153,154]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[155]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[156]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[157].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[4,5]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[154,158,159,160,161]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[4,5].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[162,163]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[164] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

TAP2 deletion

transporter 2, ATP binding cassette subfamily B member

Background: The TAP2 gene encodes the transporter 2, ATP binding cassette subfamily B member protein[1]. Along with TAP1, TAP2 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[147,148]. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression[151,165].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in TAP2 are predominantly missense or truncating and have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and stomach adenocarcinoma, and 2% of lung adenocarcinoma[4,5]. Biallelic deletion of TAP2 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)[4,5].

Potential relevance: Currently, no therapies are approved for TAP2 aberrations.

YES1 amplification

YES proto-oncogene 1, Src family tyrosine kinase

Background: YES1 encodes the YES proto-oncogene 1 and is part of the SRC family kinases (SFKs) which includes SRC, LCK, LYN, BLK, HCK, FYN, FGR, and YRK[1,166,167]. SFKs are membrane-associated, non-receptor tyrosine kinases that are involved in several cellular functions such as growth, survival, and differentiation[166,167,168]. YES1 alterations have been identified in several cancer types and are associated with tumor progression[166,169,170,171,172].

Alterations and prevalence: Somatic mutations in YES1 are observed in 5% of uterine corpus endometrial carcinoma and 2% diffuse large B-cell lymphoma, esophageal adenocarcinoma, skin cutaneous melanoma, and uterine carcinosarcoma[4,5]. Amplification of YES1 is observed in 5% of esophageal adenocarcinoma, 4% of bladder urothelial carcinoma, uterine carcinosarcoma, 3% of head and neck squamous cell carcinoma, lung squamous cell carcinoma, 2% of sarcoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous cell carcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and kidney chromophobe[4,5]. Biallelic loss of YES1 is observed in 2% diffuse large B-cell lymphoma and testicular germ cell tumors[4,5].

Potential relevance: Currently, no therapies are approved for YES1 aberrations. YES1 amplification and overexpression is associated with resistance to EGFR, HER2, and ALK inhibitors[169,170,172].

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[1]. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CFB) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis[173,174,175]. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation[174,175]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[175]

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma[4]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[4]. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with bone barrow eosinophilia (M4Eo) subtype[176]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[176].

Potential relevance: Currently, no therapies are approved for CBFB aberrations. In AML, CBFB translocations, including inv(16) and t(16;16) which result in CBFB::MYH11 fusion, are associated with favorable prognosis and define a distinct molecular subtype of AML according to the World Health Organization (WHO)[60,64,177].

CASP8 deletion

caspase 8

Background: CASP8 encodes caspase 8, a member of the cysteine-aspartic acid protease (caspase) family consisting of inflammatory caspases and apoptotic caspases. Apoptotic caspases consist of initiator and effector caspases[1,178,179]. CASP8 functions as an initiator caspase and following external stimulation of death receptors, undergoes processing and activation leading to CASP8 mediated cleavage of downstream targets[180]. CASP8 propagates the extrinsic apoptotic pathway by direct cleavage of effector caspases such as CASP3 and activates the intrinsic apoptotic pathway by cleaving BID, a pro-apoptotic proximal substrate of CASP8, resulting in an amplification of the death-inducing signal[180,181]. Certain cancer types have decreased expression or inactivation of CASP8, which results in poor prognosis and metastasis[182,183].

Alterations and prevalence: Somatic mutations in CASP8 are observed in 11% head and neck squamous cell carcinoma, 10% uterine corpus endometrial carcinoma, 5% stomach adenocarcinoma, 4% cervical squamous cell carcinoma, colorectal adenocarcinoma, and

Biomarker Descriptions (continued)

bladder urothelial carcinoma, 3% skin cutaneous melanoma, and 2% diffuse large B-cell lymphoma, lung squamous cell carcinoma, uterine carcinosarcoma, and breast invasive carcinoma[4,5]. Biallelic loss of CASP8 is observed in 2% bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CASP8 aberrations.

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[184]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[185,186]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[187]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and is observed almost exclusively in children less than 3 years of age[188].

Alterations and prevalence: Somatic mutations are observed in 4% endometrial carcinoma, 2% esophageal adenocarcinoma, and stomach adenocarcinoma[5]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[5].

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

NCOR1 deletion

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)[1,189,190]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[189,190,191,192]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[190]. 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[190,193].

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 are 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].

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

NOTCH4 deletion

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[194]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[195,196]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[197,198,199,200].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[4].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for NOTCH4 aberrations.

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein[1]. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[201,202]. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules[201,203]. ERAP1 has also been shown to be involved in the shedding of cytokine receptors (including TNFR1, IL6-Ra, and type II IL-II receptor) and is observed to be secreted by macrophages, which is believed to enhance phagocytosis[201,204,205]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[201,206].

Alterations and prevalence: Somatic mutations in ERAP1 are observed in 7% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ERAP1 aberrations.

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[207]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[207]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[207,208]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[207]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[207]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[207,209].

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[4,5]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[210]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[211]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[212]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[213].

PPM1D deletion

protein phosphatase, Mg2+/Mn2+ dependent 1D

Background: The PPM1D gene encodes the protein phosphatase, Mg2+/Mn2+ dependent 1D, which is a member of the PP2C family of Ser/Thr protein phosphatases[1]. Upon cellular stress, p53-induced PPM1D dephosphorylates and downregulates target CHK1 and P53, which are involved in DNA repair pathways and cell cycle checkpoints[214,215]. PPM1D function leads to the inhibition of apoptosis, cancer cell proliferation, migration, and invasion[214,215]. Mutations of PPM1D are associated with a predisposition to breast and ovarian cancer[214].

Alterations and prevalence: Somatic mutations in PPM1D are predominantly truncating or missense and are observed in 6% of uterine corpus endometrial carcinoma, 2% of stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[4,5]. Amplification of PPM1D is observed in 8% of breast invasive carcinoma, 5% of mesothelioma, 4% of liver hepatocellular carcinoma, and 3% of bladder urothelial carcinoma and stomach adenocarcinoma[4,5]. Biallelic deletion of PPM1D is observed in 2% of ovarian serous cystadenocarcinoma and less than 1% of cervical squamous cell carcinoma, lung squamous cell carcinoma, glioblastoma multiforme, brain lower grade glioma, uterine corpus endometrial carcinoma, and colorectal adenocarcinoma[4,5].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for PPM1D aberrations.

CDKN1A deletion

cyclin dependent kinase inhibitor 1A

Background: The CDKN1A gene encodes the cyclin-dependent kinase inhibitor 1A protein, also known as p21 or WAF1[1,216]. CDKN1A belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1B (also known as KIP/p27) and CDKN2C (also known as KIP2/p57)[216,217]. Through inhibition of cyclin dependent kinases, including CDK1 and CDK2, CDKN1A impacts several biological processes, including cell cycle arrest, differentiation, gene transcription, apoptosis, and DNA repair[218]. CDKN1A is also capable of binding to proliferating cell nuclear antigen (PCNA) and inhibiting PCNA-dependent DNA polymerase activity[218]. Deregulation of CDKN1A, including loss of expression, is observed in several tumor types, supporting a tumor suppressor role for CDKN1A[218].

Alterations and prevalence: Somatic mutations in CDKN1A are observed in 10% of bladder urothelial carcinoma, 3% of kidney chromophobe, and 2% of skin cutaneous melanoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[4,5]. Biallelic deletion of CDKN1A is observed in 2% of kidney chromophobe and 1% of sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for CDKN1A aberrations.

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[219]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[219,220]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[221,222,223].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[4,5]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[4,5,224]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[224].

Potential relevance: Currently, no therapies are approved for GPS2 aberrations.

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases[225,226]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[226,227]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[227,228]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[227,228]. RAD50 contains long coiled-coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response[227,229]. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[102,103]. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer[230].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[4,5]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[231].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[232]. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression[232]. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype[233].

Biomarker Descriptions (continued)

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2[1]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[234]. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)[235,236]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[235]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[235,237].

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases[4,238]. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases[4,238].

Potential relevance: The PARP inhibitor, olaparib[34] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

PDCD1 deletion

programmed cell death 1

Background: The PDCD1 gene encodes programmed cell death 1, also known as PD-1 or CD279[1]. PDCD1 is a type I transmembrane inhibitory receptor and member of the CD28/CTLA-4 family, which is part of the immunoglobulin superfamily[239]. PDCD1 is an immune checkpoint molecule that acts as a gatekeeper of immune responses through a balance of signaling suppression, which is critical in the facilitation of self and non-self cell recognition[240]. PDCD1 is expressed in a variety of hematopoietic cells, immune cells, tumor cells, and tumor specific T-cells[239,241]. The two main immunoregulatory ligands of PDCD1 are CD274 (PD-L1) and PDCD1LG2 (PD-L2), which are type I transmembrane proteins expressed in many cells including antigen presenting cells and tumor cells[239]. PDCD1 and CD274 act as co-inhibitors and regulate immune tolerance of central and peripheral T-cells and reduce the proliferation of CD8+ T-cells by inhibitor signals[239,241].

Alterations and prevalence: Somatic mutations in PDCD1 are observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of uterine carcinosarcoma[4,5]. Deletions in PDCD1 are observed in 8% of sarcoma, 5% of brain lower grade glioma, 3% of cervical squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, and uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for PDCD1 aberrations. Immune checkpoint inhibitor therapy uses immunotherapy to block receptor-ligand interactions and enhance immunity activity against tumor cells[242]. Although not approved for specific PDCD1 aberrations, approved checkpoint inhibitors targeting PDCD1 include the monoclonal antibodies pembrolizumab, nivolumab, and cemiplimab[239].

RNF43 deletion

ring finger protein 43

Background: The RNF43 gene encodes the ring finger protein 43[1]. RNF43 is a transmembrane E3 ubiquitin ligase and a negative regulator of the Wnt signaling pathway[243,244]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[243]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[243,244].

Alterations and prevalence: Somatic mutations in RNF43 are observed in 14% endometrial carcinoma, 8% gastroesophageal junction cancer and colorectal adenocarcinoma, and 6% pancreatic adenocarcinoma[4,5]. Somatic frameshift mutations in RNF43 including R117fs and G659fs are frequently observed in colorectal and endometrial cancers with microsatellite instability[243,245,246].

Potential relevance: Currently, no therapies are approved for RNF43 aberrations.

Biomarker Descriptions (continued)

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[247,248,249]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[103,247,248,249,250]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[103,249]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[250]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[250].

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]. 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[34] 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[36] 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[103,250]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[41], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDH1 deletion

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,251]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[252]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[253,254]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[255].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[4,5,256,257]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[4,5]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[17,18]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer[19] and in men for breast and prostate cancer[20,21]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer[258].테스트 입니다.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer[23,24,25,26,27,29,259]. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers[4,5].

Biomarker Descriptions (continued)

Potential clinical relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[31]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[32,33]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Rucaparib[] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with two or more chemotherapies. Talazoparib[] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Due to efficacy in both gBRCAm and non-gBRCAm patients, Niraparib (2017) is another PARPi approved for maintenance of epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of BRCA status[260]. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[39]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[40].

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[261]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,262,263]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[264,265]. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3[263].

Alterations and prevalence: Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe[4,5]. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for DOCK3 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,

Genes Assayed (continued)

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

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

BRCA2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	○	✖	✖	● (II)
niraparib	✖	○	✖	✖	✖

* 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

BRCA2 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
rucaparib	✖	○	✖	✖	✖
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

ATM deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	● (II)
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
senaparib, IMP-9064	✖	✖	✖	✖	● (I/II)

BRCA1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	● (II)
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

BARD1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

BRIP1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

CDK12 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

CHEK1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

MSH6 p.(R248Qfs*7) c.743_744delGA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ipilimumab + nivolumab	✖	✖	✖	✖	● (II)

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, gedatolisib	✖	✖	✖	✖	● (I)

RAD50 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

RAD51C deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

RAD51D deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

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

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 (6.0.2 data version 2025.04(004)). 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 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. 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.

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