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Patient Name: 조동학
Gender: M
Sample ID: N25-27

Primary Tumor Site: lung
Collection Date: 2025.05.15

Sample Cancer Type: Lung Cancer

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Report Highlights

19 Relevant Biomarkers
6 Therapies Available
20 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	***1.89 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	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	4
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	8

*** 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	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	*BRCA1 deletion* BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	2
IIC	*LATS1 deletion* large tumor suppressor kinase 1 Locus: chr6:149982844	None*	None*	2
IIC	*LATS2 deletion* large tumor suppressor kinase 2 Locus: chr13:21548922	None*	None*	2
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	2
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	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	*FANCA deletion* Fanconi anemia complementation group A Locus: chr16:89804984	None*	None*	1
IIC	*FANCG deletion* Fanconi anemia complementation group G Locus: chr9:35074046	None*	None*	1
IIC	*FBXW7 deletion* F-box and WD repeat domain containing 7 Locus: chr4:153243999	None*	None*	1
IIC	*RAD51C deletion* RAD51 paralog C Locus: chr17:56769933	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	*RAD51D deletion* RAD51 paralog D Locus: chr17:33427950	None*	None*	1
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	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

*ABRAXAS1 deletion, APC deletion, ARID1B deletion, ARID2 deletion, AXIN2 deletion, CUL4A deletion, MAP2K4 deletion, MSH3 deletion, Microsatellite stable, NF1 deletion, PARP4 deletion, PIK3R1 deletion, PPP2R2A deletion, RAD54L deletion, RPA1 deletion, TP53 deletion, TP53 p.(A74Vfs*75) c.220_221insT, TET2 deletion, INPP4B deletion, FAT1 deletion, MAP3K1 deletion, ERAP2 deletion, PRDM1 deletion, HDAC2 deletion, TNFAIP3 deletion, MAP3K4 deletion, ARID5B deletion, KMT2D deletion, TPP2 deletion, CDH1 deletion, ZFHX3 deletion, NCOR1 deletion, RNF43 deletion, DSC1 deletion, SMAD2 deletion, RUNX1 deletion, EP300 deletion, ZRSR2 deletion, BCOR deletion, USP9X deletion, DDX3X deletion, KDM5C deletion, AMER1 deletion, ZMYM3 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TP53	p.(A74Vfs*75)	c.220_221insT	.	chr17:7579466	55.09%	NM_000546.6	frameshift Insertion
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	49.77%	NM_002439.5	nonframeshift Insertion
TNFAIP3	p.(R632T)	c.1895G>C	.	chr6:138200477	2.60%	NM_001270507.2	missense
PMS2	p.(Q93R)	c.278A>G	.	chr7:6043396	10.00%	NM_000535.7	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
RAD54L	chr1:46714017	1	0.84
ABRAXAS1	chr4:84383635	0.93	0.61
TET2	chr4:106155068	1.07	0.67
INPP4B	chr4:142949914	1.07	0.67
FBXW7	chr4:153243999	1.1	0.67
FAT1	chr4:187509708	1.07	0.66
MAP3K1	chr5:56111388	1.06	0.66

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
PIK3R1	chr5:67522468	1.15	0.69
MSH3	chr5:79950540	1.11	0.68
ERAP2	chr5:96219500	0.24	0.37
APC	chr5:112043374	1.15	0.7
PRDM1	chr6:106534408	1.06	0.66
HDAC2	chr6:114262171	0.9	0.61
TNFAIP3	chr6:138192315	1.08	0.67
LATS1	chr6:149982844	1.14	0.69
ARID1B	chr6:157099057	0.97	0.63
MAP3K4	chr6:161412931	1.07	0.67
PPP2R2A	chr8:26149298	1.04	0.66
MTAP	chr9:21802646	0.13	0.33
CDKN2A	chr9:21968178	0	0.26
CDKN2B	chr9:22005728	0.03	0.29
FANCG	chr9:35074046	1.08	0.67
ARID5B	chr10:63661463	1.1	0.68
ARID2	chr12:46123536	1.06	0.66
KMT2D	chr12:49415529	0.89	0.6
LATS2	chr13:21548922	0.99	0.63
PARP4	chr13:25000551	0.96	0.62
BRCA2	chr13:32890491	1	0.66
RB1	chr13:48877953	0.97	0.63
TPP2	chr13:103249399	1	0.64
CUL4A	chr13:113863977	0.97	0.63
CDH1	chr16:68771249	1.01	0.64
ZFHX3	chr16:72820995	0.9	0.61
FANCA	chr16:89804984	0.93	0.61
RPA1	chr17:1733385	1.03	0.65
TP53	chr17:7572848	1.08	0.67
MAP2K4	chr17:11924164	1.17	0.7
NCOR1	chr17:15935586	1.06	0.66
NF1	chr17:29422233	1.1	0.67
RAD51D	chr17:33427950	1	0.67
CDK12	chr17:37618286	1	0.68

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
BRCA1	chr17:41197602	1	0.72
RNF43	chr17:56432226	0.97	0.63
RAD51C	chr17:56769933	1	0.74
BRIP1	chr17:59760627	1	0.71
AXIN2	chr17:63526027	1.14	0.69
DSC1	chr18:28710424	0.67	0.52
SMAD2	chr18:45368152	1.15	0.69
SMAD4	chr18:48573387	0.9	0.61
RUNX1	chr21:36164357	0.97	0.63
SMARCB1	chr22:24129273	0.93	0.61
CHEK2	chr22:29083868	1	0.7
NF2	chr22:29999923	0.96	0.63
EP300	chr22:41489001	1.08	0.67
ZRSR2	chrX:15808582	0.53	0.66
BCOR	chrX:39911340	0.5	0.64
USP9X	chrX:40982869	0.5	0.64
DDX3X	chrX:41193501	0.54	0.67
KDM5C	chrX:53221892	0.54	0.67
AMER1	chrX:63409727	0.53	0.66
ZMYM3	chrX:70460753	0.53	0.66
PDGFRA	chr4:55131078	1.13	0.69
KIT	chr4:55589693	1.1	0.67
FYN	chr6:111982890	0.83	0.58
ESR1	chr6:152163831	0.99	0.63
FGFR1	chr8:38271452	0.81	0.57
STAT6	chr12:57490294	0.79	0.56
CDK4	chr12:58142242	0.86	0.59
FGF9	chr13:22245989	0.74	0.54
CD276	chr15:73991923	0.97	0.63
SETBP1	chr18:42281265	0.86	0.59

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 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.

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[9,10]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[11]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[9].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[9,10,12,13]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[4].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[9]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[15].

Biomarker Descriptions (continued)

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-lined protein[1]. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases[16]. DUBs are responsible for protein deubiquitination, thereby counter-regulating post-transcriptional ubiquitin modification of proteins within the cell[16,17]. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X[17]. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its subtrates[17]. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair[17].

Alterations and prevalence: Somatic mutations are observed in 16% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of cholangiocarcinoma, 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma[4,5]. Biallelic deletions are observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, 2% of mesothelioma, uterine carcinosarcoma, and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for USP9X aberrations.

MSH3 deletion

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[1]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[18,19]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[18,19]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[20].

Alterations and prevalence: Somatic mutations in MSH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, and 3% of skin cutaneous melanoma[4,5]. Biallelic deletion of MSH3 are observed in 3% of ovarian serous cystadenocarcinoma and 2% of prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MSH3 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[21,22]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[21,22]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[23,24,25]. 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%[23,26].

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[27,28,29,30,31,32,33,34]. 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)[35]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[36,37]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[38] (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[38] is approved

Biomarker Descriptions (continued)

(2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[39] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[40] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[40] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[41] (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[42] 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[43]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[44]. 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[14], 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[45], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

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[46]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[46]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[46].

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.

FANCA deletion

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[47,48]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[47]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[49,50]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[51,52]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[53,54]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[48,54,55,56,57].

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma[4]. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer[4].

Potential relevance: The PARP inhibitor, talazoparib[40] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[58,59]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[57].

Biomarker Descriptions (continued)

AMER1 deletion

APC membrane recruitment protein 1

Background: The AMER1 gene encodes APC membrane recruitment protein 1[1]. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway[1,60]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[61,62]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[62]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[63]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[60].

Alterations and prevalence: Somatic mutations of AMER1 are observed in 13% of colorectal adenocarcinoma,10% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 4% of stomach adenocarcinoma, and uterine carcinosarcoma, 3% of lung squamous cell carcinoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, and 2% of diffuse large B-cell lymphoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, and breast invasive carcinoma[4,5]. Biallelic deletion of AMER1 is observed in 2% of esophageal adenocarcinoma, diffuse large b-cell lymphoma, uterine carcinosarcoma, lung squamous cell carcinoma, and pancreatic adenocarcinoma, and 1% of stomach adenocarcinoma, sarcoma, liver hepatocellular carcinoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for AMER1 aberrations.

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)[64].

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[4,5]. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively[65]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[4,5].

Potential relevance: Currently, no therapies are approved for ZMYM3 aberrations.

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[66,67]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[68]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[66,67,69]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[70].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[5]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[5]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[71,72,73].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

SMARCB1 deletion

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1

Background: The SMARCB1 gene encodes SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 protein[1]. SMARCB1, also known as SNF5 or INI1, acts as a tumor suppressor protein[1]. SMARCB1 is a core member of ATP-

Biomarker Descriptions (continued)

dependent, multisubunit SWI/SNF chromatin-remodeling complex, along with SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1, and SMARCA2/BRM[74]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[74,75]. Independent of its functions in chromatin remodeling, SMARC1B inhibits MYC activation, consequently, loss of function in SMARCB1 enhances the activity of MYC[76]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[77,78].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[75]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[4,5]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[76].

Potential relevance: Currently, no therapies are approved for SMARCB1 aberrations. Mutations in SMARCB1 and SMARCB1 deletions are considered diagnostic markers of epithelioid sarcoma[79].

ARID2 deletion

AT-rich interaction domain 2

Background: The ARID2 gene encodes the AT-rich interaction domain 2 protein[1]. ARID2, also known as BAF200, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID5B[80]. ARID2 is an essential member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[80,81]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[74,81]. ARID2 may alter the expression of IFN responsive genes, which suppress cell proliferation[80]. Loss of function mutations in ARID2 may promote cell proliferation, suggesting a tumor suppressor role of ARID2[80].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[75]. Somatic mutations in ARID2 are observed in 17% of skin cutaneous melanoma, 11% of uterine corpus endometrial carcinoma, 8% of bladder urothelial carcinoma and stomach adenocarcinoma, 7% of colorectal adenocarcinoma, and 5% of liver hepatocellular carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[4,5]. ARID2 biallelic deletions are observed in 2% of mesothelioma[4,5].

Potential relevance: Currently, no therapies are approved for ARID2 aberrations.

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[82]. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)[83]. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)[84]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing[85]. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity[86,87]. 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[51,88].

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[38] 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[40] 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[89]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], 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)[83]. RAD51D associates with other RAD51 paralogs to form

Biomarker Descriptions (continued)

RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[84]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[85]. 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[51,88]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[90].

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[38] 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[88]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit[1]. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36[91,92]. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks[91]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[91]. Together with the rest of the BRCA1-A complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer[91,93].

Alterations and prevalence: Somatic mutations in ABRAXAS1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, and 1% of stomach adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ABRAXAS1 aberrations.

RAD54L deletion

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B[94]. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair[94,95,96]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[94,97]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[98]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[88].

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[38] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], 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[99]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[100]. 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[51,88]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[101]. 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[101,102]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[99,103].

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[38] 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[88,104]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

SMAD2 deletion

SMAD family member 2

Background: The SMAD2 gene encodes the SMAD family member 2, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes[1,105,106]. SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class while SMAD4 belongs to the common mediator SMAD (co-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[105,106]. As part of the R-SMAD class, SMAD2 functions by mediating signal transmission in the transforming growth factor beta (TGF-β) signaling pathway, a pathway critical in cell growth, differentiation, and tumor development[106]. Following activation of type I TGF-β receptors, SMAD2 and SMAD3 are activated via phosphorylation and form a complex with SMAD4, leading to nuclear translocation and activation or repression of target genes[107,108]. Deregulation of SMAD2, including mutation and loss of expression, has been observed in cancer leading to disruption of SMAD2/3/4 complex formation and tumorigenesis, supporting a tumor suppressor role for SMAD2[108,109].

Alterations and prevalence: Somatic mutations in SMAD2 are observed in 5% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma, 3% of skin cutaneous melanoma, and 2% of stomach adenocarcinoma and lung adenocarcinoma[4,5]. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent[4,5,108]. Two recurrent hotspot mutations R321 and P305 occur in the mad homology 2 (MH2) domain leading to the disruption of the heterotrimeric SMAD2/SMAD3-SMAD4 complex[4,5,110]. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for SMAD2 aberrations.

NF2 deletion

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells. NF2 is structurally and functionally related to the Ezrin, Radixin, Moesin (ERM) family which is known to control plasma membrane function, thereby influencing cell shape, adhesion, and growth[111,112,113]. NF2 regulates several cellular pathways including the RAS/RAF/MEK/ERK, PI3K/AKT, and Hippo-YAP pathways, thus impacting cell motility, adhesion, invasion, proliferation, and apoptosis[111,112,113,114]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[112,113,115]. Specifically, deleterious germline mutations or deletion of NF2 leading to loss of heterozygosity (LOH) is causal of neurofibromatosis type 2, a tumor prone disorder characterized by early age onset of multiple Schwannomas and meningiomas[112,113,115].

Alterations and prevalence: Somatic mutations in NF2 are predominantly misssense or truncating and are observed in about 23% of mesothelioma, 5% of cholangiocarcinoma and uterine cancer, and about 3% of papillary renal cell carcinoma (pRCC), bladder, and cervical cancers[4]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[4].

Potential relevance: Currently, no therapies are approved for NF2 aberrations. However, the FDA granted Fast Track designation (2022) to the novel TEAD inhibitor, IK-930, for unresectable NF2-deficient malignant pleural mesothelioma (MPM)[116].

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[1,117,118,119]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[61,62]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[62]. 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[120,121]. Loss of AXIN2 expression has been observed to contribute to the development of gastric cancer[122].

Biomarker Descriptions (continued)

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.

FBXW7 deletion

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[123]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[123,124,125,126,127,128,129].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[4,5,130,131,132].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[133], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[130]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[129].

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[134]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[135,136]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[137]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[138]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[138]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[139,140,141,142,143]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[136]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[135,136,140,144].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[135,136,145,146]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[145,146].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[147] (2014) and nivolumab[148] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[147] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[147]. Dostarlimab[149] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[141,150]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[151] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[141,152,153]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[153]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[154,155]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[154,155].

Biomarker Descriptions (continued)

APC deletion

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[156]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[157,158]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[156,159]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[160].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[4,5,161]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[162,163].

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

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1[1]. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation[164,165,166]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[167]. PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression[166]. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1[167].

Alterations and prevalence: Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma[4,5]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[167]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for PRDM1 aberrations.

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[168]. All RUNX proteins share several conserved regions with similar functionality including a highly conserved N-terminal ‘runt’ domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[169]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[170,171]. RUNX1 is frequently mutated in various hematological malignancies[171]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[172,173]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[171].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[174]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 20-25% of childhood ALL[175,176]. This translocation is also observed in adult ALL at a lower frequency (2%)[176]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[177]. The RUNX1::RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[171,177]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[171]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[4,171,178,179].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[178,180]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1 in AML and t(12;21)(q34;q11)/

Biomarker Descriptions (continued)

ETV6::RUNX1 in ALL, are associated with favorable risk[181,182]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[179,181,183].

DSC1 deletion

desmocollin 1

Background: The DSC1 gene encodes desmocollin 1, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC2 and DSC3[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[184]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[185]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC1 in tumorigenesis[184,186,187,188].

Alterations and prevalence: Somatic mutations in DSC1 are observed in 17% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, and 3% of lung adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DSC1 aberrations.

ZRSR2 deletion

zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3’ intron splice site[189]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[189,190]. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes[189,191].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[5,179].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[178,179,181].

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes the cyclin-dependent kinase inhibitor 2A protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[192,193,194]. CDKN2A codes for two alternate transcript variants namely p16 and p14ARF, both of which exhibit differential tumor suppressor function[195]. Specifically, the CDKN2A/p16 transcript functions as an inhibitor of cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript variant stabilizes the tumor suppressor protein p53 to prevent its degradation[1,195,196]. CDK2NA aberrations commonly co-occur with CDKN2B. Loss of CDKN2A/p16 demonstrates downstream inactivation of Rb and p53 pathways leading to uncontrolled cell proliferation[197]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[198,199].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations. Copy number loss of CDKN2A is observed in 63% of esophageal cancer, 54% of glioblastoma, 45% of pleural mesothelioma, 31% of bladder urothelial carcinoma, and 29% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma[4,5]. Additionally, CDKN2A mutations have been observed in 19% of pancreatic adenocarcinoma and 6% of bladder urothelial carcinoma cases[4,5].

Potential relevance: CDKN2A loss can be useful in the diagnosis of mesothelioma and mutations are used as an ancillary diagnostic marker of malignant peripheral nerve sheath tumors[79,200,201]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[202,203,204]. Alternatively, CDK2NA expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[205]. CDKN2A (p16) expression is also associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[206,207,208,209,210].

Biomarker Descriptions (continued)

FANCG deletion

Fanconi anemia complementation group G

Background: The FANCG gene encodes the FA complementation group G protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[47,48]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[47]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[49,50]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[51,52]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[53,54].

Alterations and prevalence: Somatic mutations in FANCG are observed in 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[4,5].

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

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes the cyclin-dependent kinase inhibitor 2B protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[192,193,194]. CDK2NB is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,211,212].

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 56% of esophageal squamous cell carcinoma, 54% of glioblastoma, 42% of pleural mesothelioma, 31% of bladder urothelial carcinoma, 28% of head and neck squamous cell carcinoma, and 27% of pancreatic adenocarcinoma[5].

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[213,214,215]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[51,213,214,215,216]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[51,215]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[216]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[216].

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[38] 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[40] 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[51,216]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

EP300 deletion

E1A binding protein p300

Background: The EP300 gene encodes the E1A binding protein p300[1]. EP300 is a member of the KAT3 family of lysine acetyl transferases, which, along with CREBBP (also known as CBP), interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[217,218]. EP300 functions as a transcriptional coactivator and has been observed to activate members of the E2F transcription factor family, thereby regulating expression of genes required for cell cycle G1/S phase transition[219,220]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[219]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[221].

Alterations and prevalence: Somatic mutations in EP300 are observed in 15% of bladder urothelial carcinoma, 14% of uterine corpus endometrial carcinoma, 12% of cervical squamous cell carcinoma, 8% of skin cutaneous melanoma, 7% of head and neck squamous cell carcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and colorectal adenocarcinoma[4,5]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[222].

Potential relevance: Currently, no therapies are approved for EP300 aberrations.

PIK3R1 deletion

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[223]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[223]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[223]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[224,225]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[224,225,226,227]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[228]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[223].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[4]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[4].

Potential relevance: Currently, no therapies are approved for PIK3R1 aberrations.

SMAD4 deletion

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[105,106]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[106,229,230]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[105,106]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[105]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[5,230,231]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[4,5,161].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[106,230,232,233,234]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[235,236]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[236]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[237].

Biomarker Descriptions (continued)

TNFAIP3 deletion

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3[1]. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity[238]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[238,239]. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions[238]. TNFAIP3 deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[238,240].

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma[4,5]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[4,5,238].

Potential relevance: Currently, no therapies are approved for TNFAIP3 aberrations.

NF1 deletion

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[241]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[241,242]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[241]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[179,241,243].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[241]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[241,244]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[179,241].

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)[79].

FAT1 deletion

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,245]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[245]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[245]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[245]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[245].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[4,5]. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma[4,5]. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma[4,5].

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

Biomarker Descriptions (continued)

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[246]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[247,248]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[249]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[246,247,248]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[179]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[247,250]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[251]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[251,252]

LATS1 deletion

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1[1]. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members[253,254]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[255]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[255]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[256].

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma[4,5]. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma[4,5].

Potential relevance: Currently, no therapies are approved for LATS1 aberrations.

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[257,258]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[258].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[258,259]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

Biomarker Descriptions (continued)

KMT2D deletion

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[260]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[260]. 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[260].

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.

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[261]. Activation of MAPK proteins occurs through a kinase signaling cascade[261,262,263]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[261,262,263]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[261,262,263]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[264].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[4,5]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[4,5]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[265,266].

Potential relevance: Currently, no therapies are approved for MA2PK4 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[1,267,268]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[268,269]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[270,271,272,273,274]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[270,273,275,276].

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% 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.

Biomarker Descriptions (continued)

DDX3X deletion

DEAD-box helicase 3, X-linked

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II[1,277]. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)[277,278,279,280]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[277]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[281,282,283,284,285,286,287,288]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[281].

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma[4,5]. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DDX3X aberrations.

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2[1]. LATS2 is a serine/threonine protein kinase and, along with LATS1, is a member of the AGC kinase family comprised of more than 60 members[253,254]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[255]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[255]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[256].

Alterations and prevalence: Somatic mutations in LATS2 are observed in 9% of mesothelioma, 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% stomach adenocarcinoma, and 3% of colorectal adenocarcinoma[4,5]. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma[4,5].

Potential relevance: Currently, no therapies are approved for LATS2 aberrations.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[289]. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)[290,291,292]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[293,294,295].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[4,5]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[38] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[40] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[14], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein[1]. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3[296]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-

Biomarker Descriptions (continued)

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[296,297]. PARP enzymes are involved in several DNA repair pathways[296,297]. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins[298].

Alterations and prevalence: Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma[4,5]. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)[4,5].

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (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[299,300]. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[38] (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[38] 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[39] (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[40] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[41] (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.

BCOR deletion

BCL6 corepressor

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) corepressor protein which potentiates transcriptional repression by BCL6[301,302]. BCOR also associates with class I and II histone deacetylases (HDACs) suggesting an alternate mechanism for BCOR mediated transcriptional repression independent of BCL6[302]. Genetic alterations in BCOR result in protein dysfunction which suggests BCOR functions as a tumor suppressor gene[303,304,305].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[4,179,306,307]. Higher mutational frequencies are reported in some solid tumors, including up to 15% of uterine cancer and 5-10% of colorectal cancer, stomach cancer, cholangiocarcinoma, and melanoma. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[308,309,310]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[311,312]. In clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, one study described the presence of BCOR ITDs in more than 90% of cases[308].

Potential relevance: BCOR rearrangement, including inv(X)(p11.4p11.22) resulting in BCOR::CCNB3 fusion, is diagnostic of sarcoma with BCOR genetic alterations, a subset of undifferentiated round cell sarcomas[79,313]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[79]. Somatic mutation in BCOR is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR) and is associated with poor prognosis in AML and MDS[178,179,180,181,306]. In FLT3-ITD negative AML patients under 65 with intermediate cytogenetic prognosis, mutations in BCOR confer inferior overall survival (OS) as well as relapse free survival (RFS) compared to those without BCOR abnormalities (OS= 13.6% vs. 55%; RFS= 14.3% vs. 44.5%)[307].

KDM5C deletion

lysine demethylase 5C

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C[1,314]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[315]. KDM5C removes methylation of di- and trimethylated histone H3 lysine 4 (H3K4) and is involved in the repression of transcription in response to DNA damage[314,315]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[316].

Alterations and prevalence: Somatic mutations in KDM5C are observed in 9% of uterine corpus endometrial carcinoma, 5% of kidney renal clear cell carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, 4% of lung adenocarcinoma and uterine

Biomarker Descriptions (continued)

carcinosarcoma[4,5]. Biallelic loss of KDM5C is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for KDM5C 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)[1,317,318]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[317,318,319,320]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[318]. 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[318,321].

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.

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[322]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[322]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[322].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[4,5]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for RPA1 aberrations.

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[1]. Activation of MAPK proteins occurs through a kinase signaling cascade[261,262,263]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[261,262,263]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[261,262,263]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[323]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[323]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[323].

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[4,5]. MAP3K1

Biomarker Descriptions (continued)

mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[323]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K1 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)[324]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[324]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[324,325]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[324]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[324]. 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[324,326].

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[327]. 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[328]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[329]. 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[330].

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[331,332]. 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[331,333]. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic[331].

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma[4,5]. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ERAP2 aberrations.

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4[1]. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10[261]. Activation of MAPK proteins occurs through a kinase signaling cascade[261,262,263]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[261,262,263]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[261,262,263]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[334].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K4 aberrations.

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[335,336]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[335]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[335,336].

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[335,337,338].

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

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)[1,339]. 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[340]. 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[341,342]. 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[343].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[4,5,344,345]. 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.

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[1]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[1,346]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[74,346].The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[74]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[74,75]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[346].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[75]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[4,5].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases[347,348].

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[21,22]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer[23] and in men for breast and prostate cancer[24,25]. 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[349].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[27,28,29,30,31,33,350]. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers[4,5].

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)[35]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[36,37]. 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[351]. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[43]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[44].

TP53 deletion, TP53 p.(A74Vfs*75) c.220_221insT

tumor protein p53

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[352]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[353,354].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[4,5,355,356,357,358]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[4,5]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[359,360,361,362].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[363]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[364] and breakthrough designation[365] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[366,367]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[178,179,181,182,251,368]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell

Biomarker Descriptions (continued)

transplant[369]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[370].

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,371]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[372]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[373,374].

Alterations and prevalence: Somatic mutations in INPP4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, 3% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma, and 2% of cervical squamous cell carcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma[4,5]. Biallelic loss of INPP4B is observed in 2% of bladder urothelial carcinoma, uterine carcinosarcoma, and brain lower grade glioma[4,5]. Amplification of INPP4B is observed in 3% of cholangiocarcinoma and esophageal adenocarcinoma, and 2% of sarcoma, stomach adenocarcinoma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for INPP4B aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-03-19. For the most up-to-date information, search www.fda.gov.

NF2 deletion

IK-930

Cancer type: Mesothelioma **Variant class:** NF2 deletion

Supporting Statement:

The FDA has granted Fast Track designation for IK-930, a novel TEAD inhibitor targeting the Hippo signaling pathway, for unresectable NF2-deficient malignant pleural mesothelioma (MPM).

Reference:

https://ir.ikenaoncology.com//news-releases/news-release-details/ikena-oncology-receives-fda-fast-track-designation-novel-tead

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed (continued)

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	✖	○	✖	✖	✖
rucaparib	✖	○	✖	✖	✖
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

SMARCB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
pazopanib	✖	✖	✖	○	✖
sunitinib	✖	✖	✖	○	✖
nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (II)
atezolizumab, tiragolumab	✖	✖	✖	✖	● (I/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

SMARCB1 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tazemetostat, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
MRTX1719	✖	✖	✖	✖	● (I/II)
TNG-462	✖	✖	✖	✖	● (I/II)
AMG 193, pembrolizumab	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)

BRCA1 deletion

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

LATS1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BPI-460372	✖	✖	✖	✖	● (I)
IAG-933	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

LATS2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BPI-460372	✖	✖	✖	✖	● (I)
IAG-933	✖	✖	✖	✖	● (I)

NF2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BPI-460372	✖	✖	✖	✖	● (I)
IAG-933	✖	✖	✖	✖	● (I)

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)

CDKN2B deletion

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

CHEK2 deletion

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

FANCA 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

FANCG deletion

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

FBXW7 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/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)

RB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/II)

SMAD4 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***60.38%***
BRCA1	***CNV, CN:1.0***
BRCA1	***LOH, 17q21.31(41197602-41276231)x1***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***
BRIP1	***CNV, CN:1.0***
BRIP1	***LOH, 17q23.2(59760627-59938976)x1***
CDK12	***CNV, CN:1.0***
CDK12	***LOH, 17q12(37618286-37687611)x1***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130729)x1***
RAD51C	***CNV, CN:1.0***
RAD51C	***LOH, 17q22(56769933-56811619)x1***
RAD51D	***CNV, CN:1.0***
RAD51D	***LOH, 17q12(33427950-33446720)x1***
RAD54L	***CNV, CN:1.0***
RAD54L	***LOH, 1p34.1(46714017-46743978)x1***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.0.2 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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