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Patient Name: 길미애
Gender: F
Sample ID: N25-324

Primary Tumor Site: tubo-ovary
Collection Date: 20240403

Sample Cancer Type: Ovarian Cancer

Report Highlights

7 Relevant Biomarkers
3 Therapies Available
22 Clinical Trials

Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
BRCA1	***BRCA1 deletion***	NTRK2	None detected
BRCA2	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***3.8 Mut/Mb measured***
Genomic Instability	***GIM 8 (Low)***

HRD Status: ***HR Proficient (HRD-)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	2
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	14
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	4

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA1 deletion* BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	1
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	None*	None*	1
IIC	*TP53 deletion* tumor protein p53 Locus: chr17:7572848	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

*ARID1B deletion, ATRX deletion, BLM deletion, CDK12 deletion, CHEK2 deletion, CUL4B deletion, ERCC2 deletion, FANCC deletion, FANCE deletion, FANCF deletion, FANCG deletion, FANCI deletion, LATS1 deletion, MAP2K4 deletion, Microsatellite stable, NBN deletion, PMS2 deletion, POLD1 deletion, RAD51 deletion, RAD51D deletion, RPA1 deletion, TP53 p.(I251Sfs*94) c.750delC, TSC1 deletion, HLA-A deletion, HLA-B deletion, NOTCH4 deletion, TAP2 deletion, TAP1 deletion, DAXX deletion, CDKN1A deletion, PRDM1 deletion, HDAC2 deletion, TNFAIP3 deletion, MAP3K4 deletion, JAK2 deletion, PTCH1 deletion, PPP6C deletion, NOTCH1 deletion, MGA deletion, PDIA3 deletion, B2M deletion, GPS2 deletion, NCOR1 deletion, DSC3 deletion, DSC1 deletion, SMAD2 deletion, PRKACA amplification, CIC deletion, ARHGAP35 deletion, EP300 deletion, ZRSR2 deletion, BCOR deletion, USP9X deletion, DDX3X deletion, KDM6A deletion, RBM10 deletion, KDM5C deletion, SMC1A deletion, AMER1 deletion, ZMYM3 deletion, STAG2 deletion, PHF6 deletion, Tumor Mutational Burden, Genomic Instability (Low)*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TP53	p.(I251Sfs*94)	c.750delC	.	chr17:7577530	98.69%	NM_000546.6	frameshift Deletion
TATDN2	p.(P254T)	c.760C>A	.	chr3:10302166	31.50%	NM_014760.4	missense
MAML3	p.(Q489Tfs*29)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	21.33%	NM_018717.5	frameshift Block Substitution

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGCAACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	78.67%	NM_018717.5	frameshift Block Substitution
MSH3	p.(P63_P64insAAAAAPAAP)	c.189_190insGCAGCGGCCGCAGCGCCCGCAGCGCCC	.	chr5:79950735	7.43%	NM_002439.5	nonframeshift Insertion
HLA-B	p.(C125S)	c.373T>A	.	chr6:31324190	21.98%	NM_005514.8	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	0.96	0.53
MTAP	chr9:21802646	0.99	0.55
CDKN2A	chr9:21968178	0.82	0.47
BRCA1	chr17:41197602	1.06	0.57
NF2	chr22:29999923	0.97	0.54
SMAD4	chr18:48573387	0.92	0.51
TP53	chr17:7572848	0.93	0.52
ARID1B	chr6:157099057	0.91	0.51
ATRX	chrX:76763769	1.11	0.6
BLM	chr15:91290599	0.97	0.54
CDK12	chr17:37618286	0.94	0.52
CHEK2	chr22:29083868	0.92	0.51
CUL4B	chrX:119660593	1.11	0.6
ERCC2	chr19:45854865	0.94	0.52
FANCC	chr9:97863909	0.93	0.52
FANCE	chr6:35420188	0.98	0.54
FANCF	chr11:22646196	1.13	0.61
FANCG	chr9:35074046	0.91	0.51
FANCI	chr15:89790860	0.97	0.54
LATS1	chr6:149982844	0.88	0.49
MAP2K4	chr17:11924164	1.08	0.58
NBN	chr8:90947783	0.83	0.47

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
PMS2	chr7:6012922	0.99	0.54
POLD1	chr19:50902079	1	0.55
RAD51	chr15:40990871	0.99	0.55
RAD51D	chr17:33427950	0.96	0.53
RPA1	chr17:1733385	0.99	0.54
TSC1	chr9:135771600	0.93	0.52
HLA-A	chr6:29910229	1.04	0.57
HLA-B	chr6:31322252	0.41	0.29
NOTCH4	chr6:32163187	0.9	0.51
TAP2	chr6:32796585	0.81	0.47
TAP1	chr6:32814849	0.87	0.49
DAXX	chr6:33286486	0.93	0.52
CDKN1A	chr6:36645655	0.87	0.49
PRDM1	chr6:106534408	0.83	0.48
HDAC2	chr6:114262171	0.89	0.5
TNFAIP3	chr6:138192315	0.91	0.51
MAP3K4	chr6:161412931	0.9	0.51
JAK2	chr9:5021954	0.98	0.54
PTCH1	chr9:98209140	0.93	0.52
PPP6C	chr9:127911878	0.89	0.5
NOTCH1	chr9:139390441	1.02	0.56
MGA	chr15:41961065	1.04	0.57
PDIA3	chr15:44038719	1.06	0.58
B2M	chr15:45003690	1.18	0.63
GPS2	chr17:7216071	0.91	0.51
NCOR1	chr17:15935586	0.87	0.49
DSC3	chr18:28574139	0.93	0.52
DSC1	chr18:28710424	0.98	0.54
SMAD2	chr18:45368152	0.91	0.51
PRKACA	chr19:14204349	6.72	3.13
CIC	chr19:42775916	0.84	0.48
ARHGAP35	chr19:47421913	0.92	0.51
EP300	chr22:41489001	0.9	0.5
ZRSR2	chrX:15808582	1.18	0.63

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
BCOR	chrX:39911340	1	0.55
USP9X	chrX:40982869	1.04	0.57
DDX3X	chrX:41193501	1.06	0.58
KDM6A	chrX:44732715	1.08	0.59
RBM10	chrX:47006798	1.2	0.64
KDM5C	chrX:53221892	1.02	0.56
SMC1A	chrX:53406966	0.99	0.55
AMER1	chrX:63409727	0.97	0.53
ZMYM3	chrX:70460753	1.04	0.57
STAG2	chrX:123156472	1.08	0.58
PHF6	chrX:133511628	1.09	0.59
TPMT	chr6:18130879	1	0.55
DDR1	chr6:30852922	0.86	0.48
PIM1	chr6:37138341	1.18	0.63
CCND3	chr6:41903600	0.83	0.47
FYN	chr6:111982890	0.81	0.46
ROS1	chr6:117622071	0.97	0.54
CARD11	chr7:2949684	1.02	0.56
RAC1	chr7:6426823	0.97	0.54
RUNX1T1	chr8:92982878	0.84	0.48
FAM135B	chr8:139144776	0.86	0.48
CD274	chr9:5456050	0.9	0.51
PDCD1LG2	chr9:5522530	0.99	0.54
NTRK2	chr9:87549097	0.93	0.52
ABL1	chr9:133738250	0.83	0.47
HRAS	chr11:532637	1.16	0.62
WT1	chr11:32410528	5.93	2.77
USP8	chr15:50731245	0.96	0.53
MAP2K1	chr15:66727348	0.97	0.53
CD276	chr15:73991923	0.79	0.46
NTRK3	chr15:88420191	0.93	0.52
IDH2	chr15:90628015	0.96	0.53
IGF1R	chr15:99192814	0.97	0.53
ERBB2	chr17:37863255	1.04	0.57

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RARA	chr17:38487425	1.07	0.58
STAT5B	chr17:40354722	1.01	0.55
STAT3	chr17:40467740	0.91	0.51
YES1	chr18:724481	0.89	0.5
SETBP1	chr18:42281265	0.92	0.52
BCL2	chr18:60795830	1	0.55
MAP2K7	chr19:7968792	8.6	3.97
KEAP1	chr19:10597314	9.29	4.28
SMARCA4	chr19:11094814	8.99	4.14
RNASEH2A	chr19:12917452	6.47	3.01
NOTCH3	chr19:15271451	6.67	3.1
JAK3	chr19:17937461	6.71	3.12
AKT2	chr19:40739751	1.02	0.56
AXL	chr19:41725295	0.82	0.47
BCL2L12	chr19:50169053	1	0.55
PPP2R1A	chr19:52693246	0.87	0.49
AURKC	chr19:57742416	0.9	0.51
MAPK1	chr22:22123473	1.06	0.58
EIF1AX	chrX:20148599	1.11	0.6
ARAF	chrX:47422311	1.01	0.55
AR	chrX:66766015	1.21	0.64

Biomarker Descriptions

SMARCB1 deletion

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

Background: The SMARCB1 gene encodes SWI/SNF related BAF chromatin remodeling complex subunit B1[1]. SMARCB1, also known as SNF5 or INI1, is a core member of the ATP-dependent, multi-subunit SWI/SNF chromatin-remodeling complex, along with SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1, and SMARCA2/BRM[100]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[100,101]. Independent of its functions in chromatin remodeling, SMARCB1 acts as a tumor suppressor and inhibits MYC activation, so loss of function in SMARCB1 enhances MYC activity[102]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[103,104].

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[101]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[102]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Alterations in SMARCB1 are also observed in pediatric cancers[5,6]. Somatic mutations in SMARCB1 are observed in 10% of pediatric rhabdoid tumors, 6% of non-Hodgkin lymphoma, 4% of embryonal tumors, and less than 1% of bone cancer (3 in 327

Biomarker Descriptions (continued)

cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and Ewing sarcoma (1 in 354 cases)[5,6]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5,6].

Potential relevance: Currently, no therapies are approved for SMARCB1 aberrations. Mutations and deletions of SMARCB1 are considered diagnostic markers of epithelioid sarcoma and SMARCB1-deficient renal medullary carcinoma[105,106].

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[281,282]. 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[282].

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[282,283]. 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[5,6]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[5,6].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[221]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[222,223,224]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[225]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,225,226]. CDKN2A aberrations commonly co-occur with CDKN2B[221]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[227]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[228,229].

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[230]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[5,6]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[5,6]. Alterations in CDKN2A are also observed in pediatric cancers[6]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[6]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[6].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[106,231,232]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[233]. 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[234,235,236]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[237].

Biomarker Descriptions (continued)

CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[238,239,240,241].

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[53,54]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[53,54]. 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[55,56,57]. 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%[55,58].

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[59,60,61,62,63,64,65,66]. 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[5,6].

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)[67]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[68,69]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[70] (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[70] 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[71] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[43] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[43] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[72] (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[73] 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[74]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[75]. 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[76], 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.

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[143,144,145]. 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[143,144,145,146]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[144,145,147]. 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[144,145,147].

Biomarker Descriptions (continued)

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[5]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[5].

Potential relevance: Currently, no therapies are approved for NF2 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[137,138]. 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[138,255,256]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[137,138]

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[137]. 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[6,256,257]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[5,6,258].

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[138,256,259,260,261]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[262,263]. 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)[263]. 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[264].

TP53 deletion, TP53 p.(I251Sfs*94) c.750delC

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[381]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[382]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[383,384].

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%)[5,6,312,385,386,387]. 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[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[388,389,390,391]. Alterations in TP53 are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[5,6]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[392] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[393,394]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[190]. 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)[23,26,197,198,395]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[396]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[397].

Biomarker Descriptions (continued)

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[1,371]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[100,371].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[100]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[100,101]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[371].

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[101]. 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[5,6]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[5,6].

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[372,373].

ATRX deletion

ATRX, chromatin remodeler

Background: The ATRX gene encodes the ATRX chromatin remodeler and ATPase/helicase domain protein, which belongs to SWI/SNF family of chromatin remodeling proteins[1]. The SWI/SNF proteins are a group of DNA translocases that use ATP hydrolysis to remodel chromatin structure and maintain genomic integrity by controlling transcriptional regulation, DNA repair, and chromosome stability through the regulation of telomere length[181,182,183,184]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[185,186,187].

Alterations and prevalence: Somatic mutations of ATRX are observed in 38% of brain lower grade glioma, 15% of uterine corpus endometrial carcinoma, 14% of sarcoma, 9% of glioblastoma multiforme and skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of lung adenocarcinoma, stomach adenocarcinoma, and cervical squamous cell carcinoma, 5% of bladder urothelial carcinoma and lung squamous cell carcinoma, 4% of adrenocortical carcinoma, head and neck squamous cell carcinoma and uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, pheochromocytoma and paraganglioma, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma and kidney chromophobe[5,6]. Biallelic deletion of ATRX is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma[5,6]. Although alterations of ATRX in pediatric populations are rare, somatic mutations are observed in 6% of gliomas, 4% of bone cancer, 3% of soft tissue sarcoma, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (3 in 332 cases), and leukemia (2 in 354 cases)[6]. Biallelic deletion of ATRX is observed in 1% of peripheral nervous system tumors (1 in 91 cases) in and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for ATRX aberrations. Loss of ATRX protein expression correlates with the presence of ATRX mutations[188,189]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[190,191].

BLM deletion

Bloom syndrome RecQ like helicase

Background: The BLM gene encodes the BLM RecQ like helicase, a protein responsible for the unwinding of various DNA substrates[1]. During homologous recombination repair (HRR), BLM forms a complex with TOP3A, RMI1, and RMI2, which facilitates the separation of repaired/template DNA and Holliday junction resolution[130,131]. BLM also functions as an endonuclease in end resection during HRR and is capable of displacing RAD51 from DNA strand breaks, thereby preventing further recombination in the end stages of HRR[130,132]. Germline BLM mutations result in Bloom Syndrome, a recessive genetic disorder that is classified by chromosomal breakage and causes a predisposition for gastrointestinal cancer, bladder cancer, skin cancer, B-cell and T-cell immunodeficiencies[133].

Alterations and prevalence: Somatic mutations in BLM are observed in 7% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma and colorectal adenocarcinoma, 3% of stomach adenocarcinoma, skin cutaneous melanoma, and cholangiocarcinoma[5,6].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for BLM aberrations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[245,246,247]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[40,245,246,247,248]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[40,247]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[248]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[248].

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[1,5]. 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[1,5].

Potential relevance: The PARP inhibitor, olaparib[70] 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[43] 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[40,248]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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[315]. 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)[316,317,318]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[319,320,321].

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[5,6]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[70] 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[43] 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[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CUL4B deletion

cullin 4B

Background: The CUL4B gene encodes cullin 4B, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4a, CUL5, CUL7, and Parc[1,2]. CUL4B belongs to the CUL4 subfamily which also includes CUL4A[3]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[3,4]. 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)[2]. CUL4B 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[4]. 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 CUL4B in oncogenesis[3,4].

Alterations and prevalence: Somatic mutations in CUL4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 2% of bladder urothelial carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, uterine

Biomarker Descriptions (continued)

carcinosarcoma, brain lower grade glioma, and lung squamous cell carcinoma[5,6]. Amplification of CUL4B is observed in 2% of diffuse large B-cell lymphoma[5,6]. Biallelic loss of CUL4B is observed in 1% sarcoma and testicular germ cell tumors[5,6].

Potential relevance: Currently, no therapies are approved for CUL4B aberrations.

ERCC2 deletion

ERCC excision repair 2, TFIIH core complex helicase subunit

Background: The ERCC2 gene encodes ERCC excision repair 2, TFIIH core complex helicase subunit, also known as XPD[1]. ERCC2 is a protein involved in the nucleotide excision repair (NER) pathway responsible for repairing bulky DNA lesions caused by UV radiation, environmental mutagens, chemical agents, and cyclopurines generated by reactive oxygen species[296]. ERCC2 functions as a helicase along with ERCC3/XPB in the TFIIH core complex[296]. During repair of bulky lesions by NER, the TFIIH core complex binds to the lesion, followed by DNA damage verification by ERCC2, which is essential for NER[296]. Following lesion binding and verification, ERCC2 unwinds DNA in the 5'-3' direction[296]. Mutations in ERCC2 lead to stalled RNA polymerase, resulting in persistent block of transcription[296]. Germline ERCC2 mutations can lead to hereditary disorders including: Cockayne syndrome, characterized by skin cancer susceptibility and neurodegerneration; xeroderma pigmentosum (XP), characterized by neurodegeneration and developmental defects; and trichothiodystrophy (TTD), characterized by brittle hair due to sulfur deficiency as well as other developmental defects[296,297].

Alterations and prevalence: Somatic mutations in ERCC2 are predominantly missense and occur in 9% of bladder urothelial carcinoma, 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of lung squamous cell carcinoma[5,6]. The missense mutation, N238S, is observed to be recurrent in bladder urothelial carcinoma and is predicted to result in ERCC2 loss of function[5,6,298]. Biallelic loss of ERCC2 is observed in 2% of brain lower grade glioma and diffuse large B-cell lymphoma, as well as 1% of sarcoma and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ERCC2 aberrations. In one study, ERCC2 mutations correlated with enhanced response to cisplatin based chemotherapy compared to wild-type ERCC2 in patients with muscle-invasive urothelial carcinoma[299].

FANCC deletion

Fanconi anemia complementation group C

Background: The FANCC gene encodes the FA complementation group C protein, a member of the Fanconi anemia (FA) family, which also includes FANCA, FANCB, 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[77,78]. 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[77]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[79,80]. Loss of function mutations in the FA family and HRR pathway, including FANCC, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[40,81]. 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[82,83].

Alterations and prevalence: Somatic mutations in FANCC are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, 2% of colorectal adenocarcinoma, stomach adenocarcinoma and uterine carcinosarcoma, and 1% of bladder urothelial carcinoma and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for FANCC aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCC are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[216].

FANCE deletion

Fanconi anemia complementation group E

Background: The FANCE gene encodes the FA complementation group E protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, 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[77,78]. 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[77]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[79,80]. Loss of function mutations

Biomarker Descriptions (continued)

in the FA family and HRR pathway, including FANCE, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[40,81]. 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[82,83].

Alterations and prevalence: Somatic mutations in FANCE are observed in 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL), skin cutaneous melanoma, and uterine carcinosarcoma[5,6].

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

FANCF deletion

Fanconi anemia complementation group F

Background: The FANCF gene encodes the FA complementation group F protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, 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[77,78]. 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[77]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[79,80]. Loss of function mutations in the FA family and HRR pathway, including FANCF, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[40,81]. 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[82,83].

Alterations and prevalence: Somatic mutations in FANCF are observed in 2% of uterine corpus endometrial carcinoma, and 1% of lung squamous cell carcinoma, adrenocortical carcinoma, and bladder urothelial carcinoma[5,6].

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

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[77,78]. 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[77]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[79,80]. 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[40,81]. 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[82,83].

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[5,6].

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

FANCI deletion

Fanconi anemia complementation group I

Background: The FANCI gene encodes the FA complementation group I protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, 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[77,78]. 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[77]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[79,80]. Loss of function mutations in the FA family and HRR pathway, including FANCI, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[40,81]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized

Biomarker Descriptions (continued)

by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[82,83]. Specifically, germline FANCI mutations have been reported in some solid tumors including sporadic sarcomas[84].

Alterations and prevalence: Somatic mutations in FANCI are observed in 4-8% of melanoma and uterine cancer and 2-4% of cervical, stomach, colorectal, and bladder cancer[5].

Potential relevance: Currently, no therapies are approved for FANCI aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCI are shown to confer enhanced sensitivity in vitro to DNA damaging agents including cisplatin[85]. Additionally, in one study, FANCI amplification was associated with increased sensitivity to cisplatin in triple negative breast cancer (TNBC) exhibiting copy number gain in 33% of cisplatin sensitive patients vs. 0% of those exhibiting cisplatin resistance[86]. In the same study, FANCI overexpression was associated with carboplatin sensitivity in ovarian cancer[86].

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[277,278]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[279]. 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[279]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[280].

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[5,6]. 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[5,6].

Potential relevance: Currently, no therapies are approved for LATS1 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[290]. Activation of MAPK proteins occurs through a kinase signaling cascade[290,291,292]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[290,291,292]. 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[290,291,292]. 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[293].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[5,6]. 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[5,6]. 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[294,295].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[148]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[111,113]. 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[112]. 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[149]. 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)[149]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[114,150,151,152,153]. 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[113].

Biomarker Descriptions (continued)

LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[111,113,114,115].

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[111,113,154,155]. 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[154,155].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[116] (2014) and nivolumab[117] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[116] 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[116]. Dostarlimab[156] (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[151,157]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[118] (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[151,158,159]. 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[159]. 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[160,161]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[160,161].

NBN deletion

nibrin

Background: The NBN gene encodes nibrin, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) protein complex, which is necessary for the maintenance of genomic stability[34,35]. The MRN complex is involved in repair of double-stranded breaks (DSB) by homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[36,37,38]. Specifically, NBN contains a nuclear localization signaling motif responsible for translocation of the MRN complex into the nucleus and contributes to DNA repair by mediating protein-protein interactions at the site of DNA damage[34]. NBN is a tumor suppressor gene. Loss of function mutations in NBN are implicated in the BRCAness phenotype, which is characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[39,40]. Germline mutations in NBN are associated with Nijmegen breakage syndrome, an autosomal recessive disorder resulting in microcephaly at birth, immunodeficiency, radiosensitivity, and cancer predisposition[41,42].

Alterations and prevalence: Somatic mutations in NBN are observed in 7-8% of uterine cancer and 2-4% of melanoma, colorectal, esophageal, bladder and stomach cancers[5].

Potential relevance: The PARP inhibitor, talazoparib[43] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Loss of function mutations in one or more HRR genes, including NBN, may confer sensitivity to platinum agents and PARP inhibitors[39,40,44]. NBN overexpression has been shown to be associated with poor prognosis in uveal melanoma, head and neck cancer, and ovarian cancer[45,46,47,48].

PMS2 deletion

PMS1 homolog 2, mismatch repair system component

Background: The PMS2 gene encodes the PMS1 homolog 2 protein[1]. PMS2 is a tumor suppressor gene that heterodimerizes with MLH1 to form the MutLα complex[107]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process[1]. Mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[108]. PMS2, along with MLH1, MSH6, and MSH2, form the core components of the MMR pathway[107,108]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[107]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[109]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[110,111,112]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[110,113]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[111,113,114,115].

Alterations and prevalence: Somatic mutations in PMS2 are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, and 4% of adrenocortical carcinoma[5,6]. Iterations in PMS2 are observed in pediatric cancers[5,6]. Somatic mutations are observed in 3% of soft tissue sarcoma, 2% of B-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)[5,6].

Biomarker Descriptions (continued)

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[116]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[117,118]. PMS2 mutations are consistent with high grade in pediatric diffuse gliomas[119,120].

POLD1 deletion

DNA polymerase delta 1, catalytic subunit

Background: The POLD1 gene encodes the DNA polymerase delta 1, catalytic subunit protein[1]. POLD1 is one of four subunits that make up the DNA polymerase delta (Polδ) enzyme along with POLD2, POLD3, and POLD4[322,323]. Specifically, POLD1 is responsible for the polymerase and 3'-5' exonuclease activity of Polδ in the synthesis of DNA during DNA replication and repair observed in homologous recombination repair (HRR), mismatch repair (MMR), and nucleotide excision repair (NER)[107,296,322,323]. Independent of Polδ, POLD1 associates with γ-tubulin ring complexes to control cytoplasmic microtubule growth[322]. Germline mutations in POLD1 are associated with polymerase proofreading-associated polyposis, which confers predisposition to colorectal adenomas and carcinomas[324,325,326,327,328].

Alterations and prevalence: Somatic mutations in POLD1 are observed in 8% of uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for POLD1 aberrations.

RAD51 deletion

RAD51 recombinase

Background: The RAD51 gene encodes the RAD51 recombinase protein and is a member of the RAD51 protein family that also includes RAD51B (RAD51L1), RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[126]. RAD51 interacts with many DNA repair and cell cycle genes, including BRCA1, BRCA2, p53, and ATM[134]. RAD51 is expressed in proliferating cells in the S or S/G2 phases of the cell cycle and mediates DNA strand invasion and homologous pairing between DNA duplexes[135,136]. RAD51 is a tumor suppressor gene. Loss of function mutations in RAD51 can lead to deficiencies in DSB repair and are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[39,40,135].

Alterations and prevalence: Somatic mutations in RAD51 have been described in breast and prostate cancers[134].

Potential relevance: Currently, no therapies are approved for RAD51 aberrations.

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)[126]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[127]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[128]. 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[39,40]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[129].

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer[5].

Potential relevance: The PARP inhibitor, olaparib[70] 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[39]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

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)[352]. 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)[352]. 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[352].

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[5,6]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[5,6].

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

TSC1 deletion

tuberous sclerosis 1

Background: The TSC1 gene encodes the hamartin protein. TSC1 and TSC2 (also known as tuberin) form a complex through their respective coiled-coil domains[87]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[88]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[87,89]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[87].

Alterations and prevalence: Somatic mutations are observed in up to 8.5% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, and up to 6% of skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for TSC1 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[284]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[285]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[286,287,288]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[289].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of HLA-A is observed in 4% of DLBCL[5,6].

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[284]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[285]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino

Biomarker Descriptions (continued)

acids, to the immune system to distinguish self from non-self[286,287,288]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[289].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[5,6]. Biallelic loss of HLA-B is observed in 5% of DLBCL[5,6].

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

NOTCH4 deletion

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[204]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[205,206]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[207,208,209,210].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[5].

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

TAP2 deletion

transporter 2, ATP binding cassette subfamily B member

Background: The TAP2 gene encodes the transporter 2, ATP binding cassette subfamily B member protein[1]. Along with TAP1, TAP2 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[166,167]. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression[170,171].

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

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

TAP1 deletion

transporter 1, ATP binding cassette subfamily B member

Background: The TAP1 gene encodes the transporter 1, ATP binding cassette subfamily B member protein[1]. Along with TAP2 TAP1 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP-controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[166,167]. TAP1 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression and survival[168,169,170].

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

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

Biomarker Descriptions (continued)

DAXX deletion

death domain associated protein

Background: DAXX encodes the death domain associated protein, a transcription co-repressor known to repress the transcriptional potential of several sumoylated transcription factors[1]. DAXX mediates apoptosis through the death receptor pathway where it interacts and supports a multitude of cellular processes, which include gene regulation, transcriptional mediation through interaction with DNA-binding transcription factors, histones, and chromatin-associated proteins[28]. DAXX is proposed to function as a tumor suppressor due to its potential role in DNA damage repair(DDR) and through facilitating the inhibition of target genes by promoting H3K9 trimethylation[29,30].

Alterations and prevalence: Somatic mutations in DAXX are predominantly missense and truncating and occur in 5% of uterine corpus endometrial carcinoma, 3% skin cutaneous melanoma, adrenocortical carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of colorectal adenocarcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and glioblastoma multiforme[6]. DAXX mutations have also been observed to be enriched in pancreatic neuroendocrine tumors (Pan-NETs) with one study reporting mutations in 25% of 68 cases[31].

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

CDKN1A deletion

cyclin dependent kinase inhibitor 1A

Background: The CDKN1A gene encodes the cyclin-dependent kinase inhibitor 1A protein, also known as p21 or WAF1[1,242]. CDKN1A belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1B (also known as KIP/p27) and CDKN2C (also known as KIP2/p57)[242,243]. Through inhibition of cyclin dependent kinases, including CDK1 and CDK2, CDKN1A impacts several biological processes, including cell cycle arrest, differentiation, gene transcription, apoptosis, and DNA repair[244]. CDKN1A is also capable of binding to proliferating cell nuclear antigen (PCNA) and inhibiting PCNA-dependent DNA polymerase activity[244]. Deregulation of CDKN1A, including loss of expression, is observed in several tumor types, supporting a tumor suppressor role for CDKN1A[244].

Alterations and prevalence: Somatic mutations in CDKN1A are observed in 10% of bladder urothelial carcinoma, 3% of kidney chromophobe, and 2% of skin cutaneous melanoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[5,6]. Biallelic deletion of CDKN1A is observed in 2% of kidney chromophobe and 1% of sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for CDKN1A 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[162,163,164]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[165]. 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[164]. 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[165].

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[5,6]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[165]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[5,6].

Potential relevance: Currently, no therapies are approved for PRDM1 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)[353]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[353]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[353,354]. HDAC2 negatively regulates

Biomarker Descriptions (continued)

antigen presentation by inhibiting CIITA, which regulates MHC class II genes[353]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[353]. 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[353,355].

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[5,6]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[5,6].

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[356]. 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[357]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[358]. 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[359].

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[265]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[265,266]. 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[265]. TNFAIP3 deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[265,267].

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[5,6]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[5,6,265].

Potential relevance: Currently, no therapies are approved for TNFAIP3 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[290]. Activation of MAPK proteins occurs through a kinase signaling cascade[290,291,292]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[290,291,292]. 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[290,291,292]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[360].

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[5,6]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[5,6].

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

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,7]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[7]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[8]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine

Biomarker Descriptions (continued)

receptor and interferon-alpha/beta/gamma signaling[8,9,10]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[11,12].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[13,14]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[15,16]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[17,18]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[19,20,21,22]. JAK2 fusions are infrequently observed in solid tumors[5]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[5]. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[5,6]. Alterations in JAK2 are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[5,6]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[5,6]. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5,6].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)[23,24]. Ruxolitinib[25] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[26]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[27]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[19,20,21,22].

PTCH1 deletion

patched 1

Background: The PTCH1 gene encodes the patched 1 protein, a transmembrane protein that along with PTCH2, belongs to the patched gene family[1]. PTCH1 is involved in the Hedgehog (Hh) signaling pathway that plays a significant role in embryonic development, cell proliferation, and cell differentiation[378,379]. PTCH1 is a tumor suppressor gene that inhibits the transmembrane receptor Smoothened (SMO) and prevents downstream Hh signaling pathway activation[378,379]. The Hh pathway is activated when one of the Hh ligands including Sonic hedgehog (SHh), Indian hedgehog (IHh), or Desert Hedgehog (DHh) bind to PTCH1 and disrupt SMO inhibition[379]. Inactivating mutations in PTCH1 lead to ligand-independent signaling of Hh, as PTCH1 no longer prevents SMO activity[379]. Germline mutations in PTCH1 are associated with basal cell nevus syndrome (BCNS) or Gorlin Syndrome with a predisposition to non-cancerous and cancerous tumors including basal cell carcinoma[379,380].

Alterations and prevalence: Inactivating mutations in PTCH1 are observed in 85% of sporadic basal cell carcinomas[380]. Somatic mutations in PTCH1 are also observed in 11% of uterine corpus endometrial carcinoma and 4-5% of stomach adenocarcinoma, skin cutaneous melanoma, cholangiocarcinoma, esophagus adenocarcinoma, colorectal adenocarcinoma, and mesothelioma[5,6].

Potential relevance: Currently, no therapies are approved for PTCH1 aberrations.

PPP6C deletion

protein phosphatase 6 catalytic subunit

Background: PPP6C encodes protein phosphatase 6 catalytic subunit and is a member of the serine/threonine protein phosphatase family[1,268]. As the catalytic subunit of the heterotrimeric phosphoprotein phosphatase 6 (PP6) holoenzyme, PPP6C is involved in diverse processes such as cell cycle regulation, DNA damage response, autophagy, miRNA processing, inflammatory signaling, and lymphocyte development[268,269]. Loss of PPP6C results in hyperphosphorylation of Aurora A kinase, which results in defects in mitotic spindle assembly and subsequent genomic instability[269]. Overexpression of PPP6C has been observed to result in decreased colony formation of human endometrial carcinoma cells in vitro, supporting a possible tumor suppressor role for PPP6C[270].

Alterations and prevalence: Somatic mutations in PPP6C are observed in 7% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma[5,6]. Biallelic loss of PPP6C is observed in 1% of thyroid carcinoma, pancreatic adenocarcinoma, and skin cutaneous melanoma[5,6]. Amplification of PPP6C is observed in 2% kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for PPP6C aberrations.

Biomarker Descriptions (continued)

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[204]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[205,206]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[207,208,209,210].

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers[5,6,312]. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia[313,314].

Potential relevance: Currently, no therapies are approved for NOTCH1 aberrations.

MGA deletion

MGA, MAX dimerization protein

Background: The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily[1,374]. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT[375]. MGA is capable of heterodimerization with the MAX bHLHZ transcription factor, which results in DNA recognition and transcriptional regulation of target genes involved in cell growth and proliferation[374]. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation[376]. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair[377].

Alterations and prevalence: Somatic mutations in MGA are predominantly missense or truncating and are observed in 16% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 8% of stomach adenocarcinoma and lung adenocarcinoma, and 6% of colorectal adenocarcinoma and bladder urothelial carcinoma[5,6]. MGA biallelic deletion is observed in 6% of diffuse large B-cell lymphoma (DLBCL), 3% of mesothelioma, and 2% of ovarian serous cystadenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for MGA aberrations. However, MGA mutation has been observed to be enriched in non-small cell lung cancer (NSCLC) patients with higher objective response rates to immune checkpoint inhibitor (ICI) therapy[377].

PDIA3 deletion

protein disulfide isomerase family A member 3

Background: The PDIA3 gene encodes the protein disulfide isomerase family A member 3[1]. PDIA3 is a member of the protein disulfide isomerase (PDI) gene family, and acts as an enzymatic chaperone for reconstructing misfolded proteins[49]. PDIA3 has also been identified as being involved EGFR regulation, mTOR signaling, and associated with the major histocompatibility complex (MHC) protein loading complex (PLC)[50]. Deregulation of PDIA3, including both overexpression and loss, has been observed in several cancer types, suggesting that PDIA3 may exhibit differing roles depending on the tumor type[50,51,52].

Alterations and prevalence: Somatic mutations in PDIA3 are observed in 5% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, skin cutaneous melanoma, and 1% of stomach adenocarcinoma, bladder urothelial carcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, and glioblastoma multiforme[5,6]. Deletions in PDIA3 are observed in 6% of diffuse large B-cell lymphoma 5% of mesothelioma, and 2% of lung adenocarcinoma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for PDIA3 aberrations. Overexpression of PDIA3 in hepatocellular carcinoma and colon cancer is associated with advanced disease and poor prognosis[49]. Conversely, PDIA3 loss is correlated with aggressive disease and poor survival in gastric cancer and head and neck cancer[51,52].

Biomarker Descriptions (continued)

B2M deletion

beta-2-microglobulin

Background: The B2M gene encodes the beta-2-microglobulin protein[1]. B2M is an extracellular component of the major histocompatibility class (MHC) class I and is important for proper folding and transport of MHC class I to the cell surface of nucleated cells[367]. MHC class I molecules are located on the cell surface and present antigens from within the cell for recognition by cytotoxic T cells[284]. Peptide antigen presentation by MHC class I requires B2M, and mutation or loss of B2M prevents presentation and results in escape from immune recognition[368]. In cancer, mutations or loss of B2M allows for immune evasion by tumor cells, thereby preventing their destruction and supporting a tumor suppressor role for B2M[368].

Alterations and prevalence: Somatic mutations in B2M are observed in 22% of diffuse large B-cell lymphoma (DLBCL), 5% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of cervical squamous cell carcinoma and skin cutaneous melanoma[5,6]. Biallelic loss of B2M is observed in 8% of DLBCL 5% of mesothelioma, and 2% of lung adenocarcinoma and skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for B2M aberrations. Loss of B2M has been implicated in resistance to immunotherapy in melanoma[368,369]. However, B2M mutations in microsatellite instability-high colorectal carcinomas show response to immune checkpoint inhibitors[370].

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[361]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[361,362]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[363,364,365].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[5,6]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[5,6]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[5,6,366]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[366].

Potential relevance: Currently, no therapies are approved for GPS2 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)[1,347,348]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[347,348,349,350]. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[348]. 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[348,351].

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[5,6]. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[5,6]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[5,6]. Alterations in NCOR1 are also observed in pediatric cancer[6]. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[6]. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)[6].

Biomarker Descriptions (continued)

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

DSC3 deletion

desmocollin 3

Background: The DSC3 gene encodes desmocollin 3, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC1 and DSC2[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[172]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[173]. 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 DSC3 in tumorigenesis[172,174,175,176].

Alterations and prevalence: Somatic mutations in DSC3 are observed in 19% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, and 3% of bladder urothelial carcinoma[5,6]. Biallelic deletion of DSC3 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for DSC3 aberrations.

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[172]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[173]. 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[172,174,175,176].

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[5,6]. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[5,6].

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

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[1,137,138]. 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[137,138]. 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[138]. 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[139,140]. 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[140,141].

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[5,6]. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent[5,6,140]. 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[5,6,142]. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma[5,6].

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

PRKACA amplification

protein kinase cAMP-activated catalytic subunit alpha

Background: The PRKACA gene encodes the protein kinase cAMP-activated catalytic subunit alpha (C-alpha) of protein kinase A (PKA), an inactive tetrameric holoenzyme with two regulatory (R) subunits and two catalytic (C) subunits (namely PRKACA and PRKACB)[1]. PKA is a cAMP-dependent protein kinase involved in the phosphorylation of several downstream targets and an essential regulator of

Biomarker Descriptions (continued)

several cell signaling pathways including differentiation, proliferation, and apoptosis[1,121,122]. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins[1,121]. Aberrations in PRKACA are oncogenic, as they are predicted to abolish the interaction with R subunits leading to cAMP-independent activation of PKA[123]. Germline amplification and somatic mutation of PRKACA are associated with the development and pathogenesis of benign adrenal tumors leading to Cushing syndrome, which is characterized by overproduction of cortisol resulting in metabolic abnormalities[123,124].

Alterations and prevalence: Somatic mutations in PRKACA are predominantly missense and occur in about 2-3% of melanoma, diffuse large B-cell lymphoma, and uterine cancer[5,6]. PRKACA fusions have also been observed in 2% of liver cancer[5,6]. Specifically, PRKACA fusion with DNAJB1 has been observed to be recurrent in fibrolamellar hepatocellular carcinoma, which results in the retention of a functional PRKACA catalytic domain and increased protein levels[121,125]. PRKACA amplification is observed in about 11% of ovarian cancer and 2-3% of adrenocortical carcinoma, sarcoma, and uterine cancer[121,125].

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

CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,329]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,329]. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5[329]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[329].

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[5,6]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[5,6]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[329,330].

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma[106,331].

ARHGAP35 deletion

Rho GTPase activating protein 35

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription[1]. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell membrane[211,212]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[213,214].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[5,6]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[215]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for ARHGAP35 aberrations.

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[249,250]. 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[251,252]. Along with transcriptional

Biomarker Descriptions (continued)

coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[251]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[253].

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[5,6]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[254].

Potential relevance: Currently, no therapies are approved for EP300 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[200]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[200,201]. 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[200,202].

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[6,197].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[197,198,203].

BCOR deletion

BCL6 corepressor

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) co-repressor protein, which potentiates transcriptional repression by BCL6[332,333]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism for BCOR-mediated transcriptional repression independent of BCL6[333]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[334,335,336].

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)[5,197,337,338]. 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[5,6]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[339,340,341]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[342,343]. Alterations in BCOR are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 13% of soft tissue sarcoma, 4% of glioma, 3% of retinoblastoma, 2% of bone cancer, 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and less than 1% of embryonal tumors (3 in 332 cases), leukemia (2 in 311 cases), and Wilms tumor (2 in 710 cases)[5,6]. Other alterations have been reported in clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, with one study reporting the presence of BCOR ITDs in more than 90% of cases[339].

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[106,331]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[106]. 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[24,197,198,203,337]. 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%)[338]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[344,345].

Biomarker Descriptions (continued)

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-linked protein[1]. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases[32]. DUBs catalyze the removal of ubiquitin from target proteins, thereby counter-regulating post-translational ubiquitin modifications within the cell[32,33]. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X[33]. 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 substrates[33]. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair[33].

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, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma[5,6]. Biallelic deletion in USP9X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma, uterine carcinosarcoma, and lung squamous cell carcinoma[5,6]. Alterations in USP9X are also observed in the pediatric population[6]. Somatic mutations are observed in 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (1 in 311 cases)[6]. Biallelic deletion in USP9X is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

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

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[1,300]. 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)[300,301,302,303]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[300]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[304,305,306,307,308,309,310,311]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[304].

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[5,6]. 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[5,6].

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

KDM6A deletion

lysine demethylase 6A

Background: The KDM6A gene encodes the lysine demethylase 6A protein[1]. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C[217]. Methylation of histone lysine and arginine residues functions to regulate transcription and the DNA damage response, specifically in the recruitment of DNA repair proteins and transcriptional repression[218]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[217,219]. KDM6A also interacts with various transcription factors as well as KMT2C, KMT2D, and CBP/p300 chromatin-modifying enzymes, and the SWI/SNF chromatin-remodeling complex to facilitate transcriptional regulation[217]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[217]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[217,220].

Alterations and prevalence: Somatic mutations in KDM6A are observed in 26% of bladder urothelial carcinoma, 7% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, cervical squamous cell carcinoma, and head and neck squamous cell carcinoma[5,6]. Biallelic loss of KDM6A is observed in 8% of esophageal adenocarcinoma, 4% of lung squamous cell carcinoma, 3% of head and neck squamous cell carcinoma, bladder urothelial carcinoma, and pancreatic adenocarcinoma[5,6].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for KDM6A aberrations. Pre-clinical data suggest that KDM6A loss of function or inactivating mutations may respond to EZH2 inhibitors[220].

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,177]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[177,178]. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression[177]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[179,180].

Alterations and prevalence: Somatic mutations in RBM10 are observed in 7% of lung adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma, 3% of colorectal adenocarcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6]. Amplification of RBM10 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6].

Potential relevance: Currently, no therapies are approved for RBM10 aberrations.

KDM5C deletion

lysine demethylase 5C

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C[1,219]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[218]. 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[218,219]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[346].

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 carcinosarcoma[5,6]. Biallelic loss of KDM5C is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KDM5C aberrations.

SMC1A deletion

structural maintenance of chromosomes 1A

Background: SMC1A encodes the structural maintenance of chromosomes 1A and belongs to structural maintenance of chromosomes (SMCs) family, which consists of SMC1A, SMC1B, SMC2, SMC3, SMC4, SMC5, and SMC6[1,90,91]. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis[90,92]. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization[90]. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition[91,93].

Alterations and prevalence: Somatic mutations in SMC1A are observed in 11% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma and acute myeloid leukemia, 4% of colorectal adenocarcinoma and bladder urothelial carcinoma, 3% cervical squamous cell carcinoma and glioblastoma multiforme, 2% diffuse large B-Cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma and lung adenocarcinoma[5,6]. Amplification of SMC1A is found in 4% of diffuse large B-Cell lymphoma, 3% of sarcoma, and 2% of ovarian serous cystadenocarcinoma, adrenocortical carcinoma, and uterine carcinosarcoma[5,6]. Biallelic loss of SMC1A is found in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for SMC1A aberrations.

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[1,94]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[95,96]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[96]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[97]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[94].

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[5,6]. 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[5,6].

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)[98].

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[5,6]. 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[99]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[5,6].

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

STAG2 deletion

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[192,193]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[194,195]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[194,196].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants[197]. Somatic mutations in STAG2 are observed in 14% of bladder cancer, 10% of uterine cancer, 5% of glioblastoma multiforme, 4% of lung adenocarcinoma and skin cutaneous melanoma, 3% of acute myeloid leukemia, stomach adenocarcinoma, kidney renal papillary cell carcinoma, and lung squamous cell carcinoma, and 2% of cholangiocarcinoma, diffuse large B-cell lymphoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, uterine carcinosarcoma, breast invasive carcinoma, and esophageal adenocarcinoma[6]. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia[6]. Alterations in STAG2 are also observed in pediatric cancers[6]. Somatic mutations in STAG2 are observed in 10% of bone cancer (34 in 327 cases), 5% of soft tissue sarcoma (2 in 38 cases), 2% of embryonal tumors (5 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases) and peripheral nervous system cancers (1 in 1158 cases)[6]. Structural variants in STAG2 are observed in 2% of leukemia (1 in 64 cases) and less than 1% of bone cancer (1 in 150 cases)[6]. Biallelic deletion of STAG2 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of leukemia (1 in 250 cases)[6].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and acute myeloid leukemia[197,198]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[199].

Biomarker Descriptions (continued)

PHF6 deletion

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[271,272].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[271,273,274,275]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[273,275]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[273]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[271,273].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[276].

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

SMARCB1 deletion

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
CTS-3497	✖	✖	✖	✖	● (I/II)
IDE397	✖	✖	✖	✖	● (I/II)
MRTX-1719	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (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

MTAP deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TNG-462, pembrolizumab	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)
GH-56	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
HSK-41959	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)

BRCA1 deletion

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

NF2 deletion

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

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.

Relevant Therapy Summary (continued)

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

TP53 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
A2A-252	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
BRCA1	***CNV, CN:1.06***
CDK12	***CNV, CN:0.94***
CHEK2	***CNV, CN:0.92***
RAD51D	***CNV, CN:0.96***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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