

Patient Name: 김영준
Gender: Male
Sample ID: N26-44

Primary Tumor Site: soft tissue
Collection Date: 2024.12.03

Sample Cancer Type: Soft Tissue Sarcoma

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Relevant Soft Tissue Sarcoma Findings

Gene	Finding	Gene	Finding
ALK	None detected	MYOD1	None detected
APC	None detected	NF1	NF1 deletion
BCOR	BCOR deletion	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
CDK4	None detected	NTRK3	None detected
CDKN2A	CDKN2A deletion	RET	None detected
CIC	None detected	ROS1	None detected
CTNNB1	None detected	SMARCB1	SMARCB1 deletion
FOXO1	None detected	STAT6	None detected
GLI1	None detected	YAP1	None detected
MDM2	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	0.95 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	SMARCB1 deletion SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273 Diagnostic significance: Epithelioid Sarcoma	None*	cabozantinib pazopanib sunitinib	3
IIC	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib ^{II+} olaparib ^{II+} rucaparib ^{II+}	2

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Line of therapy: I: First-line therapy, II+: Other line of therapy

Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>CDKN2A deletion</i> cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	6
IIC	<i>ATM deletion</i> ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	<i>CDKN2B deletion</i> cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	3
IIC	<i>ARID1A deletion</i> AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	2
IIC	<i>BRCA1 deletion</i> BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	2
IIC	<i>PTEN deletion</i> phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	2
IIC	<i>RB1 deletion</i> RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	2
IIC	<i>ATRX deletion</i> ATRX, chromatin remodeler Locus: chrX:76763769	None*	None*	1
IIC	<i>CDK12 deletion</i> cyclin dependent kinase 12 Locus: chr17:37618286	None*	None*	1
IIC	<i>CHEK1 deletion</i> checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	<i>CHEK2 deletion</i> checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	<i>FANCA deletion</i> Fanconi anemia complementation group A Locus: chr16:89804984	None*	None*	1
IIC	<i>FANCF deletion</i> Fanconi anemia complementation group F Locus: chr11:22646196	None*	None*	1

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Line of therapy: I: First-line therapy, II+: Other line of therapy

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>FANCG</i> deletion Fanconi anemia complementation group G Locus: chr9:35074046	None*	None*	1
IIC	<i>NF2</i> deletion neurofibromin 2 Locus: chr22:29999923	None*	None*	1
IIC	<i>PALB2</i> deletion partner and localizer of BRCA2 Locus: chr16:23614759	None*	None*	1
IIC	<i>RAD51D</i> deletion RAD51 paralog D Locus: chr17:33427950	None*	None*	1
IIC	<i>SMAD4</i> deletion SMAD family member 4 Locus: chr18:48573387	None*	None*	1
IIC	<i>TSC2</i> deletion tuberous sclerosis 2 Locus: chr16:2098579	None*	None*	1

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Line of therapy: I: First-line therapy, II+: Other line of therapy

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

AXIN1 deletion, *CDKN2C* deletion, *CREBBP* deletion, *CUL4B* deletion, *ERCC4* deletion, *JAK1* deletion, *KMT2A* deletion, *LATS2* deletion, *MAP2K4* deletion, *MRE11* deletion, *MUTYH* deletion, *Microsatellite stable*, *NF1* deletion, *PARP4* deletion, *POLD1* deletion, *RAD54L* deletion, *RNASEH2A* deletion, *RNASEH2B* deletion, *RPA1* deletion, *SDHB* deletion, *SLX4* deletion, *TCF7L2* deletion, *TP53* deletion, *TNFRSF14* deletion, *ERRFI1* deletion, *ENO1* deletion, *PGD* deletion, *SPEN* deletion, *EPHA2* deletion, *FUBP1* deletion, *NOTCH2* deletion, *UGT1A1* p.(G71R) c.211G>A, *ERAP1* deletion, *ADAMTS2* deletion, *NOTCH1* deletion, *MAPK8* deletion, *ARID5B* deletion, *CYP2C9* deletion, *SUFU* deletion, *MEN1* deletion, *SDHD* deletion, *CBFB* deletion, *CTCF* deletion, *CDH1* deletion, *NQO1* p.(P187S) c.559C>T, *ZFH3* deletion, *GPS2* deletion, *NCOR1* deletion, *DSC3* deletion, *DSC1* deletion, *SMAD2* deletion, *NOTCH3* 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*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	48.20%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	3.90%	NM_000903.3	missense
HLA-A	p.([D85G;Q86E])	c.254_256delACCinsG CG	.	chr6:29910714	1.92%	NM_001242758.1	missense, missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NF1	p.(?)	c.61-29_76delAACGTG . TTTTTTTTTCTTTTTT TTTCAGCTTCCAATAA AAACAG	.	chr17:29482971	95.11%	NM_001042492.3	unknown
SETBP1	p.(M432T)	c.1295T>C	.	chr18:42530600	3.87%	NM_015559.3	missense
PLCG1	p.(G11C)	c.31G>T	.	chr20:39766312	51.33%	NM_002660.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	1.05	0.55
BRCA2	chr13:32890491	1	0.53
CDKN2A	chr9:21968178	1.32	0.67
ATM	chr11:108098341	1	0.53
CDKN2B	chr9:22005728	1.14	0.59
ARID1A	chr1:27022875	1.08	0.57
BRCA1	chr17:41197602	1	0.79
PTEN	chr10:89623659	1.03	0.54
RB1	chr13:48877953	0.98	0.51
ATRX	chrX:76763769	0.51	0.53
CDK12	chr17:37618286	1	0.76
CHEK1	chr11:125496639	1	0.56
CHEK2	chr22:29083868	1	0.57
FANCA	chr16:89804984	1	0.53
FANCF	chr11:22646196	1.19	0.61
FANCG	chr9:35074046	1.17	0.6
NF2	chr22:29999923	0.98	0.51
PALB2	chr16:23614759	1	0.53
RAD51D	chr17:33427950	1	0.31
SMAD4	chr18:48573387	0.97	0.51
TSC2	chr16:2098579	0.99	0.52
AXIN1	chr16:338145	1.06	0.56
CDKN2C	chr1:51434849	1.07	0.56
CREBBP	chr16:3777679	0.97	0.51
CUL4B	chrX:119660593	0.54	0.56
ERCC4	chr16:14013959	1.03	0.54

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
JAK1	chr1:65300225	1.06	0.55
KMT2A	chr11:118307146	1.02	0.54
LATS2	chr13:21548922	0.96	0.51
MAP2K4	chr17:11924164	1.07	0.56
MRE11	chr11:94153270	1.04	0.54
MUTYH	chr1:45794962	1.01	0.53
NF1	chr17:29422233	0.92	0.48
PARP4	chr13:25000551	0.95	0.5
POLD1	chr19:50902079	1.12	0.58
RAD54L	chr1:46714017	1	0.56
RNASEH2A	chr19:12917452	1.13	0.58
RNASEH2B	chr13:51484145	0.97	0.51
RPA1	chr17:1733385	1.03	0.54
SDHB	chr1:17345303	1.03	0.54
SLX4	chr16:3632292	1.02	0.53
TCF7L2	chr10:114710485	1.06	0.56
TP53	chr17:7572848	1.13	0.58
TNFRSF14	chr1:2488070	1.13	0.59
ERRFI1	chr1:8073246	0.94	0.49
ENO1	chr1:8921399	1.04	0.55
PGD	chr1:10459132	0.97	0.51
SPEN	chr1:16174516	1.03	0.54
EPHA2	chr1:16451707	1.12	0.58
FUBP1	chr1:78414385	1.01	0.53
NOTCH2	chr1:120457903	1	0.53
ERAP1	chr5:96112128	1.34	0.69
ADAMTS2	chr5:178549645	1.34	0.69
NOTCH1	chr9:139390441	1	0.53
MAPK8	chr10:49609682	0.91	0.48
ARID5B	chr10:63661463	0.88	0.47
CYP2C9	chr10:96698378	0.89	0.47
SUFU	chr10:104263903	1.01	0.53
MEN1	chr11:64571785	1.07	0.56
SDHD	chr11:111957573	0.96	0.51

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CBFB	chr16:67063242	1.03	0.54
CTCF	chr16:67644720	1.02	0.54
CDH1	chr16:68771249	1.02	0.53
ZFHX3	chr16:72820995	0.99	0.52
GPS2	chr17:7216071	1.08	0.57
NCOR1	chr17:15935586	1.01	0.53
DSC3	chr18:28574139	0.97	0.51
DSC1	chr18:28710424	0.91	0.48
SMAD2	chr18:45368152	1.05	0.55
NOTCH3	chr19:15271451	1.14	0.59
ARHGAP35	chr19:47421913	0.94	0.49
EP300	chr22:41489001	1.04	0.55
ZRSR2	chrX:15808582	0.53	0.55
BCOR	chrX:39911340	0.52	0.54
USP9X	chrX:40982869	0.52	0.54
DDX3X	chrX:41193501	0.47	0.5
KDM6A	chrX:44732715	0.52	0.54
RBM10	chrX:47006798	0.54	0.56
KDM5C	chrX:53221892	0.55	0.57
SMC1A	chrX:53406966	0.52	0.54
AMER1	chrX:63409727	0.51	0.53
ZMYM3	chrX:70460753	0.53	0.55
STAG2	chrX:123156472	0.54	0.56
PHF6	chrX:133511628	0.51	0.53
MYCL	chr1:40362966	1	0.53
MPL	chr1:43803495	1.14	0.59
MAGOH	chr1:53692690	1.07	0.56
NRAS	chr1:115251152	1.04	0.55
CTNND2	chr5:10988230	1.33	0.68
PRDM9	chr5:23509577	1.27	0.66
NTRK2	chr9:87549097	1.05	0.55
RET	chr10:43609070	0.99	0.52
FGFR2	chr10:123239426	1.06	0.55
HRAS	chr11:532637	1.16	0.6

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RNASEH2C	chr11:65487230	1.19	0.62
CCND1	chr11:69455949	1.04	0.55
FGF19	chr11:69513948	1.01	0.53
FGF4	chr11:69588019	0.92	0.48
FGF3	chr11:69625020	1.17	0.6
EMSY	chr11:76157926	0.87	0.47
YAP1	chr11:101981594	0.94	0.5
CBL	chr11:119103202	1.02	0.53
FGF9	chr13:22245989	0.99	0.52
FLT3	chr13:28578185	1.07	0.56
SOCS1	chr16:11348676	0.96	0.51
YES1	chr18:724481	0.99	0.52
SETBP1	chr18:42281265	0.92	0.48
BCL2	chr18:60795830	1.08	0.56
PRKACA	chr19:14204349	1.26	0.65
ZNF429	chr19:21688488	0.99	0.52
CCNE1	chr19:30303647	1.09	0.57
BCL2L12	chr19:50169053	1.14	0.59
PPP2R1A	chr19:52693246	1.06	0.56
AURKC	chr19:57742416	1.01	0.53
MAPK1	chr22:22123473	1.15	0.6
EIF1AX	chrX:20148599	0.56	0.58
ARAF	chrX:47422311	0.57	0.59
AR	chrX:66766015	0.49	0.52

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 B1¹. 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/BRM⁹⁶. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{96,97}. 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 activity¹³⁷. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis^{138,139}.

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 tumors⁹⁷. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors¹³⁷.

Biomarker Descriptions (continued)

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 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^{140,141}.

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{43,44}. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{43,44}. 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^{45,46,47}. 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%^{45,48}.

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^{49,50,51,52,53,54,55,56}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, 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)⁵⁷. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{58,59}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁶⁰ (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, olaparib⁶⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib⁶¹ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib²⁵ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib²⁵ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA2. Niraparib⁶² (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 acetate⁶³ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib⁶⁴ received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁶⁵. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁶⁶. 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, pidnarulex⁶⁷, 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.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)²⁶⁵. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{266,267,268}. CDKN2A encodes two alternative transcript variants, namely p16

Biomarker Descriptions (continued)

and p14ARF, both of which exhibit differential tumor suppressor functions²⁶⁹. 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^{1,269,270}. CDKN2A aberrations commonly co-occur with CDKN2B²⁶⁵. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation²⁷¹. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{272,273}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations²⁷⁴. 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 cancers⁶. 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 tumors⁶. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)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^{141,275,276}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma²⁷⁷. 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^{278,279,280}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme²⁸¹. 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^{282,283,284,285}.

ATM deletion

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)¹⁴⁵. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair¹⁴⁶. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB^{146,147}. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins¹⁴⁸. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss^{15,16}. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability¹⁴⁹.

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer^{5,6}.

Potential relevance: The PARP inhibitor, olaparib⁶⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib²⁵ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors^{15,150,151}. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib¹⁵². However, gene-level analyses from the phase III PROfound trial indicate that ATM-mutated tumors do not experience meaningful radiographic progression-free survival (rPFS) or overall survival (OS) benefit from olaparib, and that the observed survival advantage in the broader HRR-altered population is largely driven by BRCA1/2 alterations rather than ATM^{153,154}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression^{1,265}. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)²⁶⁵. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{266,267,268}. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A²⁶⁵. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma^{1,296,297}.

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

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma²⁷⁷.

ARID1A deletion

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein¹. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes ARID1B^{1,95}. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex^{95,96}. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B⁹⁶. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{96,97}. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription⁹⁵. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function⁹⁵.

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 tumors⁹⁷. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations⁹⁵. Somatic mutations in ARID1A have been identified in several cancers including 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma^{5,6,96}. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response⁹⁸. Biallelic deletion of ARID1A is observed in 3% of cholangiocarcinoma and stomach adenocarcinoma, and 2% of pheochromocytoma and paraganglioma^{5,6}. Alterations in ARID1A are also observed in pediatric cancers⁶. Somatic mutations in ARID1A are observed in 12% of non-Hodgkin lymphoma (2 in 17 cases), 8% of Hodgkin lymphoma (5 in 61 cases), 5% of T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of embryonal tumors (5 in 332 cases), 1% of glioma (4 in 297 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and peripheral nervous system tumors (2 in 1158 cases)⁶. Biallelic deletion of ARID1A is observed in 2% of peripheral nervous system cancers (2 in 91 cases), 1% of leukemia (3 in 250 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)⁶.

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800⁹⁹, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulumimostat¹⁰⁰, dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

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

Biomarker Descriptions (continued)

and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{43,44}. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{43,44}. 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^{45,46,47}. 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%^{45,48}.

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^{49,50,51,52,53,54,55,56}. 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)⁵⁷. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{58,59}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁶⁰ (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, olaparib⁶⁰ 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. Rucaparib⁶¹ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib²⁵ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib²⁵ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA1. Niraparib⁶² (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 acetate⁶³ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib⁶⁴ received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁶⁵. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁶⁶. 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, pidnarulex⁶⁷, 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.

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities⁴⁰⁴. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT^{405,406}. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency⁴⁰⁷. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation⁴⁰⁸. PTEN germline mutations are also associated with inherited cancer risk in several cancer types⁴⁰⁹.

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are observed in several cancers including 65% of uterine cancer, 34% of uterine corpus endometrial carcinoma, 20% of uterine carcinosarcoma, 11% of lung squamous cell carcinoma, and 5-10% of skin cutaneous melanoma, kidney chromophobe, stomach adenocarcinoma, stomach squamous cell carcinoma, and cervical squamous cell carcinoma^{5,6}. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN^{406,410,411,412,413}. PTEN gene deletion is observed in several cancers including 17% of prostate adenocarcinoma, 10% of lung squamous cell carcinoma and glioblastoma multiforme, 7% of skin cutaneous melanoma, 6% of diffuse large B-cell lymphoma, sarcoma, and 1-5% of breast invasive carcinoma, melanoma, sarcoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, and uterine corpus endometrial carcinoma^{5,6}. Alterations in PTEN are also observed in pediatric cancers⁶. Somatic mutations in PTEN are observed in 10% of T-lymphoblastic leukemia/lymphoma (4 in 41 cases), 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of glioma (7 in 297 cases), and 1% of bone cancer (4 in 327 cases) and embryonal tumors (4 in 332 cases)⁶. Biallelic

Biomarker Descriptions (continued)

deletion of PTEN is observed in 6% of glioma (1 in 16 cases), 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (10 in 250 cases), and less than 1% of embryonal tumors (5 in 731 cases)⁶. Structural alterations in PTEN are observed in less than 1% of bone cancer (1 in 150 cases)⁶.

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors^{414,415}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib⁴¹⁶ in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer¹²⁹. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation^{129,130}. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase¹³¹. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation^{129,130,132}. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma¹³³.

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in 20% of bladder urothelial carcinoma, 13% of uterine corpus endometrial carcinoma, and 10% of sarcoma and glioblastoma multiforme^{5,6}. Biallelic loss of RB1 is also observed in several cancers including 15% of sarcoma, 10% of prostate adenocarcinoma, 9% of uterine carcinosarcoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma, 5% of liver hepatocellular carcinoma and adrenocortical carcinoma, and 4% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma^{5,6}. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)^{134,135,136}. Alterations in RB1 are also observed in pediatric cancers⁶. Somatic mutations in RB1 are observed in 52% of retinoblastoma (16 in 31 cases), 3% of bone cancer (10 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (2 in 311 cases)⁶. Biallelic deletion of RB1 is observed in 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (28 in 731 cases), 3% of leukemia (7 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)⁶. Structural variants in RB1 are observed in 3% of bone cancer (5 in 150 cases)⁶.

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

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 proteins¹. 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^{168,169,170,222}. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair^{223,224,225}.

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^{226,227}. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)^{228,229}.

Biomarker Descriptions (continued)

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability^{307,308,309}. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes^{16,307,308,309,310}. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype^{16,309}. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors³¹⁰. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene³¹⁰.

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, olaparib⁶⁰ 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, talazoparib²⁵ 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^{16,310}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2¹. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest³⁰². CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)^{303,304}. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR³⁰³. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication^{303,305}.

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases^{5,306}. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases^{5,306}.

Potential relevance: The PARP inhibitor, olaparib⁶⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, 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, a cell cycle checkpoint regulator¹. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis³⁸⁸. 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)^{304,389,390}. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer^{391,392,393}. Reduced expression of CHEK2 is associated with several cancers including breast cancer, colorectal cancer, and prostate cancer, supporting its role as a tumor suppressor³⁹².

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations³⁹⁴. Somatic mutations in CHEK2 are observed in 7% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, and 2% of diffuse large B-cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, lung adenocarcinoma, colorectal adenocarcinoma, and kidney chromophobe^{5,6}. Deletion of CHEK2 is observed in 3% of adrenocortical carcinoma and thymoma, and 2% of bladder urothelial carcinoma^{5,6}. Alterations in CHEK2 are also observed in pediatric cancers⁶. Somatic mutations in CHEK2 are observed in less than 1% of bone cancer (2 in 327 cases), B-lymphoblastic leukemia/lymphoma (1

Biomarker Descriptions (continued)

in 252 cases), glioma (1 in 297 cases), and peripheral nervous system cancers (1 in 1158 cancers)⁶. Deletion of CHEK2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)⁶.

Potential relevance: The PARP inhibitor, olaparib⁶⁰ (2020) is approved for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including CHEK2. Additionally, talazoparib²⁵(2023) in combination with enzalutamide is approved for mCRPC with mutations in HRR genes, including CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FANCA deletion

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI (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) complex⁷⁷. 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 FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{16,81}. 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}. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors^{78,83,84,85,86}.

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma⁵. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer⁵.

Potential relevance: The PARP inhibitor, talazoparib²⁵ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib^{87,88}. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)⁸⁶.

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, FANCI (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) complex⁷⁷. 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^{16,81}. 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, FANCI (BRIP1), FANCL, FANCM and FANCN (PALB2)¹. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage

Biomarker Descriptions (continued)

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) complex⁷⁷. 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^{16,81}. 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.

NF2 deletion

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein¹. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells¹⁷⁹. 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^{180,181,182}. 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^{180,181,182,183}. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development^{179,181,182}. 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^{179,181,182}.

Alterations and prevalence: Somatic mutations in NF2 are predominantly missense or truncating and are observed in about 23% of mesothelioma, 6% of cholangiocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma (pRCC), bladder urothelial carcinoma, and cervical squamous cell carcinoma, and 2% of colorectal adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, and liver hepatocellular carcinoma^{5,6}. Biallelic loss of NF2 is observed in 8% of mesothelioma and 2% of thymoma^{5,6}. Structural variants in NF2 are observed in 3% of cholangiocarcinoma and 2% of mesothelioma^{5,6}. Alterations in NF2 are also observed in pediatric cancers⁶. Somatic mutations in NF2 are observed in less than 1% of bone cancer (2 in 327 cases) and glioma (1 in 297 cases)⁶. Biallelic deletion of NF2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)⁶.

Potential relevance: Currently, no therapies are approved for NF2 aberrations.

PALB2 deletion

partner and localizer of BRCA2

Background: The PALB2 gene encodes the partner and localizer of BRCA2 protein that binds to and promotes intranuclear localization of the breast cancer 2 early onset (BRCA2) protein¹⁵⁹. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA) complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, and FANCM. FA genes are tumor suppressors that play a role in interstrand cross-link (ICL) DNA repair through homologous recombination repair (HRR) of double-strand breaks (DSB) and nucleotide excision repair (NER)⁷⁷. Loss of function mutations of genes in the FA family and HRR pathway, including PALB2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{16,81}. 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}. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric malignancies^{160,161}. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer^{160,162}.

Alterations and prevalence: Somatic alterations in PALB2 include missense or truncating mutations and are observed in 2-6% of melanoma, uterine, bladder, breast, lung, stomach and colorectal cancers⁵.

Potential relevance: The PARP inhibitor, olaparib⁶⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes PALB2. Additionally, talazoparib²⁵ in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes PALB2. In a phase II trial of patients with metastatic, castration-resistant prostate cancer, one patient exhibiting a somatic PALB2 frameshift mutation exhibited durable response to olaparib for 39 weeks^{152,163}. However, olaparib resistance was observed following 9-months of treatment due to the emergence of a secondary deletion which restored the PALB2 reading frame, a resistance mechanism similar to that observed in PARPi treated BRCA mutated patients^{66,163}. Follow-up genomic studies have further shown that although PALB2-mutated cancers

Biomarker Descriptions (continued)

can respond to PARP inhibition, they frequently develop resistance through similar PALB2 reversion events^{164,165,166}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Rucaparib is recommended as a maintenance therapy for germline or somatic PALB2 mutations in metastatic pancreatic cancer¹⁶⁷.

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)¹⁵⁵. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex¹⁵⁶. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP¹⁵⁷. 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^{15,16}. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer¹⁵⁸.

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer⁵.

Potential relevance: The PARP inhibitor, olaparib⁶⁰ 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 inhibitors¹⁵. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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^{173,174}. 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^{174,318,319}. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC^{173,174}.

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)¹⁷³. 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^{6,319,320}. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers^{5,6,321}.

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^{174,319,322,323,324}. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy^{325,326}. 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)³²⁶. 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 tumors³²⁷.

TSC2 deletion

tuberous sclerosis 2

Background: The TSC2 gene encodes the tuberlin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains²⁶². The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis²⁶³. 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)²⁶³. GTP-bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1)²⁶³. TSC1 and TSC2 are tumor suppressor genes and loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway^{262,264}. 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 organs²⁶².

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in TSC2 are observed in 9% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma, 3% of stomach adenocarcinoma, liver hepatocellular carcinoma, lung squamous cell carcinoma, colorectal cancer, kidney chromophobe, cholangiocarcinoma, and esophageal adenocarcinoma, and 2% of sarcoma, bladder urothelial carcinoma, kidney renal papillary cell carcinoma, and lung adenocarcinoma^{5,6}. Alterations in CRLF1 are also observed in pediatric cancers⁶. Somatic mutations in TSC2 are observed in 5% of Hodgkin lymphoma (3 in 61 cases), 2% of bone cancer (7 in 327 cases), 1% of embryonal tumors (4 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (1 in 297 cases), and leukemia (1 in 311 cases)⁶. Biallelic deletion of TSC2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)⁶.

Potential relevance: Currently, no therapies are approved for TSC2 aberrations.

AXIN1 deletion

axin 1

Background: The AXIN1 gene encodes the axis inhibition protein 1, a cytoplasmic protein that contains a regulation of G-protein signaling (RGS) domain and a disheveled and axin (DIX) domain, which are responsible for a variety of protein-protein interactions and signaling regulation^{1,184,185,186}. AXIN1 functions as a negative regulator of the WNT signaling pathway through facilitating β -catenin degradation^{1,187,188,189}. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis^{124,125}. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types¹²⁵. AXIN1 has also been observed to function in complex with DAXX, HIPK2, and TP53 to regulate cell growth, apoptosis, and cellular development¹⁹⁰.

Alterations and prevalence: Somatic mutations of AXIN1 are observed in 7% of liver hepatocellular carcinoma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma and colorectal adenocarcinoma, and 2% of head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, and glioblastoma multiforme^{5,6}. Biallelic deletion of AXIN1 is observed in 4% of diffuse large B-cell lymphoma and uterine carcinosarcoma, 3% of esophageal adenocarcinoma, and 2% of bladder urothelial carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for AXIN1 aberrations.

CDKN2C deletion

cyclin dependent kinase inhibitor 2C

Background: CDKN2C encodes the cyclin-dependent kinase inhibitor 2C protein, a cell cycle regulator that controls G1/S progression¹. CDKN2C, also known as p18/INK4C, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which includes CDKN2A (p16/INK4A), CDKN2B (p15/INK4B), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{266,267,268}. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer²⁹⁸.

Alterations and prevalence: Somatic mutations in CDKN2C are observed in 2% of uterine corpus endometrial carcinoma and glioblastoma. Biallelic deletion of CDKN2C is observed in 3% of glioblastoma and 2% of pheochromocytoma, paraganglioma, brain lower grade glioma, kidney chromophobe, and sarcoma^{5,6}. Deletion of chromosome 1p32, where CDKN2C resides, is observed to be recurrent in multiple myeloma with variable frequency (7%-20%), depending on the study^{299,300,301}.

Potential relevance: Currently, no therapies are approved for CDKN2C aberrations.

CREBBP deletion

CREB binding protein

Background: The CREBBP gene encodes the CREB binding protein (also known as CBP), a highly conserved and ubiquitously expressed tumor suppressor. CREBBP is a member of the KAT3 family of lysine acetyl transferases, which, along with EP300, interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6^{29,30}. CREBBP functions as a global transcriptional coactivator through the modification of lysines on nuclear proteins²⁹. CREBBP binds to cAMP-response element binding protein (CREB) and is known to play a role in embryonic development, growth, and chromatin remodeling²⁹. Upon disruption of normal CREBBP functions through genomic alterations, cells become susceptible to defects in differentiation and malignant transformation³¹. Inherited CREBBP mutations and deletions result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors³².

Alterations and prevalence: Mutations in CREBBP are observed in up to 12% of bladder urothelial carcinoma, uterine corpus endometrial carcinoma, and skin cutaneous melanoma, and in 5-10% of stomach adenocarcinoma, lung squamous cell carcinoma, and cervical squamous cell carcinoma^{5,6}. CREBBP is frequently mutated in 15-17% of small cell lung cancer (SCLC)³³. Inactivating

Biomarker Descriptions (continued)

mutations and deletions of CREBBP account for over 70% of all B-cell non-Hodgkin lymphoma diagnoses including 60% of follicular lymphoma and 30% of diffuse large-B-cell lymphoma (DLBCL)²⁹. Alterations in CREBBP are also found in pediatric cancers⁶. Somatic mutation of CREBBP is observed in 6% of Non-Hodgkin lymphoma (1 in 17 cases), 5% of B-lymphoblastic leukemia/lymphoma (13 in 252 cases), Hodgkin lymphoma (3 in 61 cases), and T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 2% of glioma (6 in 297 cases), embryonal tumor (6 in 332 cases), and bone cancer (5 in 327 cases), and less than 1% of leukemia (2 in 354 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancer (1 in 1158 cases)⁶. Biallelic deletion of CREBBP is observed in 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)⁶. The rare t(11;16)(q23;p13) translocation fuses CREBBP with the partner gene KMT2A/MLL, in 0.2% secondary AML and 0.1% myelodysplastic syndrome (MDS)^{34,35,36}. Elevated expression of CBP was detected in lung cancer cells and tumor tissue as compared to normal lung cells in one study³⁷.

Potential relevance: Translocation of t(8;16)(p11.2;p13.3) resulting in the KAT6A::CREBBP fusion is associated with poor/adverse risk in AML^{38,39,40}. A mutation in CREBBP is a diagnostic marker of diffuse large B-cell lymphoma⁴¹. SCLC patients with CREBBP-positive tumors demonstrate lower overall survival (OS) and disease-free survival (DFS) compared to those with CREBBP-negative tumors⁴².

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 CUL4A³. 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 complex⁴. 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 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.

ERCC4 deletion

ERCC excision repair 4, endonuclease catalytic subunit

Background: The ERCC4 gene encodes ERCC excision repair 4, endonuclease catalytic subunit, also known as XPF¹. The ERCC4-ERCC1 heterodimer is a structure-specific endonuclease which creates the 5' incision at sites of DNA damage during nucleotide excision repair (NER), while ERCC5 creates the 3' incision⁴²⁰. Together with ERCC5, the ERCC4-ERCC1 heterodimer is involved in the removal of damaged DNA, leading to ATR activation and DNA damage repair⁴²⁰. Germline mutations in ERCC4 are associated with Xeroderma Pigmentosum (XP) complementation group F, a multisystem degenerative disorder that results in photo-sensitivity and a predisposition to skin cancer⁴⁹².

Alterations and prevalence: Somatic mutations in ERCC4 are observed in 8% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, 2% of colorectal adenocarcinoma, lung adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for ERCC4 aberrations.

JAK1 deletion

Janus kinase 1

Background: The JAK1 gene encodes Janus kinase 1, a non-receptor protein tyrosine kinase (PTK)^{1,509}. JAK1 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2⁵¹⁰. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain⁵¹⁰. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling^{510,511,512}. Since JAK1 mediates interferon-γ regulated tumor surveillance, inactivation of JAK1 is believed to inhibit the presentation of tumor antigens and contribute to immune evasion^{512,513,514}.

Biomarker Descriptions (continued)

Alterations and prevalence: Activating missense mutations in JAK1 that result in constitutive signal transduction are observed in both pediatric and adult T-cell lymphoblastic leukemia^{515,516,517}. The recurrent somatic mutation V658F observed in JAK1 is homologous to the V617F mutation in JAK2 and is a known driver mutation in myeloproliferative disease⁵¹⁶. Recurrent activating mutations in JAK1 are infrequently observed in solid cancers, although two variants, S703I and S729C, were reported in hepatocellular carcinomas^{518,519,520}. In addition, V658F and R724H were infrequently observed in diverse cancer types^{5,6}. Truncating mutations in JAK1, resulting from dispersed or recurrent frameshift mutations, are common in solid cancers and particularly enriched in uterine cancers^{5,6,512}. Recurrent truncating mutations in JAK1 are also associated with high tumor mutation burden (TMB) and microsatellite instability (MSI)^{513,514}. JAK1 alterations are rare in pediatric cancers^{5,6}. Somatic mutations are observed in 12% of T-lymphoblastic leukemia/lymphoma, 2% of B-lymphoblastic leukemia/lymphoma (4 in 252 cases), and less than 1% of bone cancer (3 in 327 cases) and glioma (1 in 297 cases)^{5,6}. JAK1 is amplified in less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)^{5,6}.

Potential relevance: Currently, no therapies are approved for JAK1 aberrations. However, ruxolitinib⁵²¹ is a JAK1/2 inhibitor that is FDA approved (2011) for primary myelofibrosis and polycythemia vera. Other JAK inhibitors, including tofacitinib (2012) and baricitinib (2018), are approved for rheumatoid arthritis. JAK1 mutations and fusions confer poor risk in B-cell ALL¹¹⁷. Clinical cases associated with high TMB but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2⁵²².

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes lysine methyltransferase 2A, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase^{1,101}. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily¹⁰¹. KMT2A influences the epigenetic regulation of several cellular functions, including neurogenesis, hematopoiesis, and osteogenesis¹⁰². Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes, including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)¹⁰³. These translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity¹⁰³. Loss of methyltransferase activity, along with gain-of-function partner gene activation, contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells^{103,104,105,106}.

Alterations and prevalence: KMT2A fusions are observed in 3-10% of adult AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)^{5,6,103,107}. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias¹⁰³. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations, which result in KMT2A truncation and loss of methyltransferase activity^{5,108}. KMT2A alterations are also observed in pediatric cancers^{5,6}. In infant acute leukemic cases, KMT2A rearrangement is reported in more than 70% of pediatric patients diagnosed with either AML or ALL and is observed in 5% of T-lymphoblastic leukemia/lymphoma^{5,6,103,109,110}.

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion^{111,112}. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML^{113,114,115}. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities¹¹⁶. KMT2A fusion is also associated with poor risk in adult and pediatric ALL^{117,118,119}. Translocations in KMT2A are recognized by the World Health Organization (WHO) as a molecular subtype of B-lymphoblastic leukemia/lymphoma with KMT2A-rearrangement¹²⁰. In 2024, the FDA approved the oral menin inhibitor, revumenib¹²¹, for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also granted fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements¹²².

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2¹. LATS2 is a serine/threonine protein kinase and, along with LATS1, is a member of the AGC kinase family comprised of more than 60 members^{378,379}. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ³⁸⁰. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes³⁸⁰. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1³⁸¹.

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in LATS2 are observed in 9% of mesothelioma, 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% stomach adenocarcinoma, and 3% of colorectal adenocarcinoma^{5,6}. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma^{5,6}.

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

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4¹. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6³²⁸. Activation of MAPK proteins occurs through a kinase signaling cascade^{328,329,331}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{328,329,331}. 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^{328,329,331}. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4³⁵³.

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^{354,355}.

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

MRE11 deletion

MRE11 homolog, double strand break repair nuclease

Background: The MRE11 gene encodes the meiotic recombination 11 protein, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) complex, which is necessary for the maintenance of genomic stability¹¹. The MRN complex is involved in the repair of double-stranded breaks (DSB) through two mechanisms namely homologous recombination repair (HRR) and non-homologous end joining (NHEJ)^{12,13,14}. Dimerization of MRE11 is required for DNA binding of the MRN complex, and it acts as a 3'-5' exonuclease and ssDNA endonuclease upon binding DNA¹¹. MRE11 is a tumor suppressor gene and loss of function mutations are implicated in the BRCAness phenotype, characterized by a defect in the HRR pathway mimicking BRCA1 or BRCA2 loss^{15,16}. Germline mutations in MRE11 have been identified as candidate susceptibility aberrations in colorectal cancer and a hallmark of ataxia-telangiectasia-like disorder (ALTD), a heritable disease resulting in progressive cerebellar degeneration and cancer predisposition^{17,18,19,20}.

Alterations and prevalence: Somatic mutations in MRE11 are observed in 6-7% of uterine cancer as well as 2-3% of lung adenocarcinoma and melanoma⁵. Mutations in the T11 polypyrimidine tract of MRE11 intron 5 are associated with aberrant splicing and reduced MRE11 protein expression. The presence of MRE11 splice variants is frequently observed in mismatch repair deficient (dMMR)/microsatellite instability (MSI-H) colorectal and endometrial cancers^{21,22,23,24}.

Potential relevance: The PARP inhibitor, talazoparib²⁵ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors^{15,16}. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro^{26,27,28}.

MUTYH deletion

mutY DNA glycosylase

Background: The MUTYH gene encodes the mutY DNA glycosylase protein¹. DNA glycosylases are structurally specific enzymes that function in base excision repair (BER) by removing damaged or incorrect bases in DNA⁶⁸. MUTYH functions by removing adenine residues that have been misincorporated opposite of 8-oxoG (7,8-dihydro-8-oxoguanine) and FapyG (2,6-diamino-4-hydroxy-5-formamidopyrimidine)⁶⁸. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer^{69,70}.

Alterations and prevalence: Somatic mutations in MUTYH are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 2% of lung squamous cell carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma^{5,6}. Biallelic deletions in MUTYH are observed in 2% of pheochromocytoma and paraganglioma^{5,6}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for MUTYH 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 genome¹⁹¹. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{192,193}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2¹⁹⁴. 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 D17S250¹⁹⁵. 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)¹⁹⁵. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{196,197,198,199,200}. 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 genes¹⁹³. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{192,193,197,201}.

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^{192,193,202,203}. 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^{202,203}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab²⁰⁴ (2014) and nivolumab²⁰⁵ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab²⁰⁴ 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 indication²⁰⁴. Dostarlimab²⁰⁶ (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^{198,207}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab²⁰⁸ (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^{198,209,210}. 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 patients²¹⁰. 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^{211,212}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{211,212}.

NF1 deletion

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family³³⁶. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state^{336,337}. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival³³⁶. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)^{240,336,338}.

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements³³⁶. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis^{336,339}. Somatic mutations in NF1 are observed in several cancer types including 17% of skin cutaneous melanoma, 14% of uterine corpus endometrial carcinoma, and 12% of glioblastoma multiforme, lung adenocarcinoma, and lung squamous cell carcinoma^{5,6}. Structural variants in NF1 are observed in 3% of cholangiocarcinoma^{5,6}. Biallelic deletion of NF1 is observed in 6% of ovarian serous cystadenocarcinoma, 4% of sarcoma, and 2% of uterine corpus endometrial carcinoma, pheochromocytoma and paraganglioma, lung squamous cell carcinoma, adrenocortical carcinoma, glioblastoma multiforme, uterine carcinosarcoma, and acute myeloid leukemia^{5,6}. Alterations in NF1 are also observed in pediatric cancers⁶. Somatic mutations in NF1 are observed in 8% of soft tissue sarcoma (3 in 38 cases), 4% of B-lymphoblastic leukemia/lymphoma (9 in 252 cases), 3% of Hodgkin lymphoma (2 in 61 cases), 2% of glioma (6 in 297 cases), 1% of bone cancer (4 in 327 cases) and leukemia (4 in 354 cases), and less than 1% of peripheral nervous system tumors (7 in 1158 cases), embryonal tumors (2 in 332 cases), and Wilms tumor (1 in 710 cases)⁶. Biallelic deletion of

Biomarker Descriptions (continued)

NF1 is observed in 2% of bone cancer (1 in 42 cases) and less than 1% of leukemia (2 in 250 cases), Wilms tumor (1 in 136 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)⁶.

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)¹⁴¹.

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein¹. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3³⁹⁹. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure^{399,400}. PARP enzymes are involved in several DNA repair pathways^{399,400}. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins⁴⁰¹.

Alterations and prevalence: Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma^{5,6}. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)^{5,6}.

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (HRR) deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death^{402,403}. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib⁶⁰ (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, olaparib⁶⁰ 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. Rucaparib⁶¹ (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib²⁵ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib⁶² (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.

POLD1 deletion

DNA polymerase delta 1, catalytic subunit

Background: The POLD1 gene encodes the DNA polymerase delta 1, catalytic subunit protein¹. POLD1 is one of four subunits that make up the DNA polymerase delta (Pol δ) enzyme along with POLD2, POLD3, and POLD4^{417,418}. Specifically, POLD1 is responsible for the polymerase and 3'-5' exonuclease activity of Pol δ in the synthesis of DNA during DNA replication and repair observed in homologous recombination repair (HRR), mismatch repair (MMR), and nucleotide excision repair (NER)^{417,418,419,420}. Independent of Pol δ , POLD1 associates with γ -tubulin ring complexes to control cytoplasmic microtubule growth⁴¹⁷. Germline mutations in POLD1 are associated with polymerase proofreading-associated polyposis, which confers predisposition to colorectal adenomas and carcinomas^{421,422,423,424,425}.

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.

RAD54L deletion

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B¹⁶⁸. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair^{168,169,170}. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases^{168,171}. RAD54L specifically appears to stabilize the association of RAD51 DNA

Biomarker Descriptions (continued)

strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination¹⁷². RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss¹⁵.

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer^{5,6}.

Potential relevance: The PARP inhibitor, olaparib⁶⁰ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RNASEH2A deletion

ribonuclease H2 subunit A

Background: The RNASEH2A gene encodes the ribonuclease H2 subunit A protein¹. RNASEH2A functions as the catalytic subunit of the RNase H2 holoenzyme along with the auxiliary RNASEH2B and RNASEH2C subunits^{447,448}. RNase H2 removes ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription⁴⁴⁷. Specifically, RNase H2 interacts with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)⁴⁴⁷. Although deregulation of RNASEH2A expression has been observed in multiple cancer types, its role in oncogenesis is unclear⁴⁴⁹.

Alterations and prevalence: Somatic mutations in RNASEH2A are observed in 2% of uterine corpus endometrial carcinoma, skin cutaneous melanoma, and kidney chromophobe^{5,6}.

Potential relevance: Currently, no therapies are approved for RNASEH2A aberrations.

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein¹. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A^{447,448}. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription⁴⁴⁷. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)⁴⁴⁷.

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma^{5,6}. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for RNASEH2B aberrations.

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1¹. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)⁴⁵⁵. 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)⁴⁵⁵. 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 repair⁴⁵⁵.

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.

Biomarker Descriptions (continued)

SDHB deletion

succinate dehydrogenase complex iron sulfur subunit B

Background: The SDHB gene encodes succinate dehydrogenase complex iron sulfur subunit B, a subunit of the succinate dehydrogenase (SDH) enzyme complex¹. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD^{72,73}. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain^{72,73}. SDHB iron clusters facilitate the transfer of electrons from FADH₂ to ubiquinone⁷⁵. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis^{72,73}. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors^{1,76}.

Alterations and prevalence: Somatic mutations in SDHB are observed in 1% cervical squamous cell carcinoma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, stomach adenocarcinoma, thymoma, lung squamous cell carcinoma, and kidney renal clear cell carcinoma^{5,6}. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma^{5,6}.

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

SLX4 deletion

SLX4 structure-specific endonuclease subunit

Background: The SLX4 gene encodes the SLX4 structure-specific endonuclease subunit¹. SLX4, also known as FANCP, is a tumor suppressor protein that functions as a scaffold for DNA repair endonucleases⁴⁷³. SLX4 functions in DNA repair mechanisms including double-strand break (DSB) repair and interstrand crosslink repair^{473,474,475}. Specifically, SLX4 localizes at DSB sites and recruits and interacts with other repair proteins such as ERCC1-XPF, MUS81-EME1, and SLX1^{473,474,475}. Germline SLX4 mutations are associated with Fanconi Anemia, a genetic condition characterized by genomic instability and congenital abnormalities, including bone marrow failure and cancer predisposition⁴⁷⁴.

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

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

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway^{1,382}. Through its interaction with β -catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC^{382,383,384}. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression³⁸². Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2³⁸².

Alterations and prevalence: Somatic mutations of TCF7L2 are observed in 11% colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma^{5,6}. Biallelic deletion of TCF7L2 is observed in 2% diffuse large B-cell lymphoma, brain lower grade glioma, and colorectal adenocarcinoma, and 1% of bladder urothelial carcinoma, mesothelioma, stomach adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and skin cutaneous melanoma^{5,6}.

Potential relevance: Currently, no therapies are approved for TCF7L2 aberrations.

TP53 deletion

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis⁴⁹³. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential⁴⁹⁴. Germline mutations in TP53 are

Biomarker Descriptions (continued)

the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{495,496}.

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%)^{5,6,385,497,498,499}. 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^{500,501,502,503}. 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, PC14586⁵⁰⁴ (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^{505,506}. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma²²⁸. 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)^{112,116,117,240,507}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁴¹. 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 system⁵⁰⁸.

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14¹. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines³¹¹. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death³¹¹. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160^{311,312}. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival³¹¹. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role³¹².

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma^{5,6}. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma⁴¹. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma^{313,314}.

ERRF1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRF1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein^{1,483}. As an early response gene, expression of ERRF1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF^{483,484}. ERRF1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation^{483,485}. As a tumor suppressor, ERRF1 induces apoptosis and inhibits proliferation and invasion^{483,486,487,488,489}. ERRF1 downregulation has been identified in several cancer types and loss of ERRF1 promotes proliferation and migration^{483,486,487,490,491}.

Alterations and prevalence: Somatic mutations in ERRF1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma^{5,6}. Biallelic loss of ERRF1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme^{5,6}.

Potential relevance: Currently, no therapies are approved for ERRF1 aberrations.

Biomarker Descriptions (continued)

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)^{1,395}. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis³⁹⁵. In addition to its role in glycolysis, ENO1 acts as a cell surface plasminogen receptor and is involved in cytoskeleton reorganization, stabilization of the mitochondrial membrane, and modulation of several oncogenic pathways, including PI3K/AKT, AMPK/mTOR and Wnt/ β -catenin^{395,396,397}. ENO1 has been found to be overexpressed in various cancers contributing to upregulation of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases^{395,396,398}. In contrast, MBP1 is known to repress c-MYC transcription under cellular stress and low glucose conditions, leading to suppression of cellular proliferation, migration, and invasion^{395,396}.

Alterations and prevalence: Somatic mutations in ENO1 are observed in 3% uterine corpus endometrial carcinoma and kidney chromophobe, and 2% of diffuse large B-cell lymphoma, skin cutaneous melanoma, and cervical squamous cell carcinoma^{5,6}. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma^{5,6}. Biallelic loss of ENO1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma, and 2% of pheochromocytoma and paraganglioma, liver hepatocellular carcinoma, and diffuse large B-cell lymphoma^{5,6}.

Potential relevance: Currently, no therapies are approved for ENO1 aberrations.

PGD deletion

phosphogluconate dehydrogenase

Background: The PGD gene encodes phosphogluconate dehydrogenase, an essential enzyme of the pentose phosphate pathway (PPP) that catalyzes oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and reduction of NADP⁺ to NADPH^{1,286}. PPP mediated generation of pentose phosphates and NADPH is essential for nucleic acid synthesis and fatty acid synthesis, respectively, making it a crucial metabolic pathway for cancer cell survival and proliferation^{287,288}. Although biallelic deletion appears to be more common than amplification across cancer types, post-translational modifications and overexpression of PGD in cancer have also been observed to result in elevated PPP activity, which is associated with cancer cell proliferation^{286,289}.

Alterations and prevalence: Somatic mutations in PGD have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, and bladder urothelial carcinoma^{5,6}. Biallelic loss of PGD has been observed in 4% of adrenocortical carcinoma, 3% of cholangiocarcinoma, and 2% of pheochromocytoma and paraganglioma and diffuse large B-cell lymphoma^{5,6}. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma^{5,6}.

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

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor¹. SPEN plays a role in chromosome X inactivation and regulation of transcription^{468,469,470}. As a transcriptional repressor, SPEN sequesters transcriptional activators and interacts with other repressors and chromatin remodeling complexes, such as histone deacetylases (HDACs) and the NuRD complex^{468,470}. In ER α -positive breast cancers, SPEN binds ER α in a ligand-independent manner and negatively regulates the transcription of ER α targets, acting as a tumor suppressor gene to regulate cell proliferation, tumor growth, and survival^{471,472}.

Alterations and prevalence: Somatic mutations in SPEN are observed in 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 10% of stomach adenocarcinoma, 7% of diffuse large B-cell lymphoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and lung adenocarcinoma, 4% of lung squamous cell carcinoma and ovarian serous cystadenocarcinoma, 3% of kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, breast invasive carcinoma, glioblastoma multiforme, and acute myeloid leukemia, and 2% of pancreatic adenocarcinoma, adrenocortical carcinoma, liver hepatocellular carcinoma, uterine carcinosarcoma, and esophageal adenocarcinoma^{5,6}. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma^{5,6}.

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

Biomarker Descriptions (continued)

EPHA2 deletion

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2¹. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins^{89,90}. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis⁹⁰. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins^{89,90}.

Alterations and prevalence: Somatic mutations in EPHA2 are observed in 11% of cholangiocarcinoma, 7% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and skin cutaneous melanoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for EPHA2 aberrations.

FUBP1 deletion

far upstream element binding protein 1

Background: The FUBP1 gene encodes the far upstream element binding protein 1, a DNA/RNA binding protein implicated in a variety of cellular functions^{1,257}. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of transcription, translation, and splicing²⁵⁷. FUBP1 activates the transcription of targets including the oncogene MYC which functions in cell cycle regulation, metabolism, and apoptosis²⁵⁷. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation²⁵⁷.

Alterations and prevalence: Somatic mutations in FUBP1 are observed in 9% of brain lower grade glioma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of colorectal adenocarcinoma^{5,6}. Mutations typically result in inactivation of FUBP1 through alteration of splicing sites, introduction of stop codons, or out-of-frame insertions or deletions²⁵⁷. Biallelic loss of FUBP1 is observed in 3% of pheochromocytoma and paraganglioma^{5,6}. Co-deletion of 1p and 19q is frequently observed in oligodendrogliomas, which results in the monoallelic loss of FUBP1 and CIC on 19q²⁵⁷.

Potential relevance: Currently, no therapies are approved for FUBP1 aberrations.

NOTCH2 deletion

notch 2

Background: The NOTCH2 gene encodes the notch receptor 2 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, 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 signaling²⁵⁰. 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^{251,252}. 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^{253,254,255,256}.

Alterations and prevalence: Somatic mutations observed in NOTCH2 are primarily missense or truncating and are found in about 11% of uterine cancer, 6% of melanoma and stomach cancer, as well as 3-5% diffuse large B-cell lymphoma (DLBCL), lung, colorectal, bladder, cervical, and head and neck cancers⁵.

Potential relevance: Currently, no therapies are approved for NOTCH2 aberrations.

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily^{1,346}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{346,347}. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance³⁴⁸. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active

Biomarker Descriptions (continued)

drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation^{348,349,350,351}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38³⁵².

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

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

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein¹. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway^{456,457}. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules^{456,458}. ERAP1 has also been shown to be involved in the shedding of cytokine receptors (including TNFR1, IL6-Ra, and type II IL-II receptor) and is observed to be secreted by macrophages, which is believed to enhance phagocytosis^{456,459,460}. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma^{456,461}.

Alterations and prevalence: Somatic mutations in ERAP1 are observed in 7% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma^{5,6}. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma^{5,6}.

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

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 signaling²⁵⁰. 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^{251,252}. 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^{253,254,255,256}.

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^{5,6,385}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{386,387}.

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

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1¹. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10^{328,329,330}. Activation of MAPK proteins occurs through a kinase signaling cascade^{328,329,331}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{328,329,331}. 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^{328,329,331}.

Alterations and prevalence: Somatic mutations in MAPK8 are observed in 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma^{5,6}. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma^{5,6}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for MAPK8 aberrations.

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein¹. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2^{7,8}. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes⁸. ARID5B is known to be essential for the development of hematopoietic cells⁸. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)⁸.

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

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

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins¹. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids^{1,332}. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents^{333,334}. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro^{333,334,335}. CYP2C9 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis^{332,333,334,335}. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors³³³. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease³³³.

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe^{5,6}. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma^{5,6}. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma^{5,6}.

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

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling¹. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation²³⁰. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling^{231,232}. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU²³³. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and are observed almost exclusively in children less than 3 years of age²³⁴.

Alterations and prevalence: Somatic mutations are observed in 4% uterine corpus endometrial carcinoma and 2% esophageal adenocarcinoma and stomach adenocarcinoma⁶. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma⁶. Alterations in SUFU are also observed in pediatric cancers⁶. Somatic mutations in SUFU are observed in 1% of embryonal tumors (4 in 332 cases) and less than 1% of glioma (2 in 297 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)⁶. Biallelic deletion of SUFU 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 SUFU aberrations.

Biomarker Descriptions (continued)

MEN1 deletion

menin 1

Background: The MEN1 gene encodes the menin 1 protein¹. MEN1 is a tumor suppressor that functions as a scaffold protein and is known to play a role in histone modification and epigenetic gene regulation through alteration of chromatin structure^{1,290}. MEN1 interacts with several proteins involved in transcription, signaling pathways, and cell division, including JUND, NF-κB, SMAD3, and estrogen receptor α^{290,291,292}. MEN1 also interacts with the lysine methyltransferase 2A gene, KMT2A (MLL1), and UBTf to influence HOX expression, whose dysregulation plays a critical role in leukemic transformation^{293,294}. Germline mutations in MEN1 result in multiple endocrine neoplasia type 1 (also referred to as MEN1), which is an inherited familial cancer syndrome that causes a predisposition to endocrine tumors, including pituitary, parathyroid, and pancreatic cancer^{291,292}.

Alterations and prevalence: Somatic mutations in MEN1 are observed in 8% of adrenocortical carcinoma, 5% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of uterine carcinosarcoma, pancreatic adenocarcinoma, and colorectal adenocarcinoma^{5,6}. Biallelic deletion of MEN1 is observed in 1% of adrenocortical carcinoma and esophageal adenocarcinoma^{5,6}. Alterations in MEN1 are also observed in pediatric cancers⁶. Somatic mutations in MEN1 are observed in 3% soft tissue sarcoma (1 in 38 cases) and less than 1% of bone cancer (3 in 327 cases), embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and leukemia (1 in 311 cases)⁶. Biallelic deletion of MEN1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases), leukemia (2 in 250 cases), and Wilms tumor (1 in 136 cases)⁶.

Potential relevance: Although not approved for specific MEN1 alterations, the menin inhibitor revumenib¹²¹ (2024) is approved for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older. However, somatic missense mutations in MEN1, including S155T, M327V, G331R, G331D, and T349M, are associated with acquired resistance to revumenib treatment in KMT2A-rearranged and NPM1-mutated acute leukemia²⁹⁵.

SDHD deletion

succinate dehydrogenase complex subunit D

Background: The SDHD gene encodes succinate dehydrogenase complex subunit D of the succinate dehydrogenase (SDH) enzyme complex^{1,71}. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD^{72,73}. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain^{72,73}. SDHD, along with SDHC, anchors SDHA and SDHB to the inner mitochondrial membrane and provides a binding site for ubiquinone⁷¹. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis^{71,72,73}. Inherited pathogenic mutations in SDHD have been associated with paragangliomas and gastrointestinal stromal tumors^{1,71,74}.

Alterations and prevalence: Somatic mutations in SDHD are observed in 1% of mesothelioma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, and lung adenocarcinoma^{5,6}. Biallelic loss of SDHD is observed in 3% of testicular germ cell tumors, skin cutaneous melanoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and uterine carcinosarcoma^{5,6}.

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

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family¹. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CBF) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis^{426,427,428}. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation^{427,428}. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB⁴²⁸.

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma⁵. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma⁵. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with

Biomarker Descriptions (continued)

bone marrow eosinophilia (M4Eo) subtype⁴²⁹. Translocations often result in CBFβ::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused⁴²⁹.

Potential relevance: Currently, no therapies are approved for CBFβ aberrations. In AML, CBFβ translocations, including inv(16) and t(16;16) which result in CBFβ::MYH11 fusion, are associated with favorable prognosis and define a distinct molecular subtype of AML according to the World Health Organization (WHO)^{111,112,430}.

CTCF deletion

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family¹. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression¹⁴². Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression^{142,143,144}. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis¹⁴².

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma^{5,6}.

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

CDH1 deletion

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)^{1,476}. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells¹. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments⁴⁷⁷. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis^{478,479}. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer⁴⁸⁰.

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function^{5,6,481,482}. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocellular carcinomas^{5,6}. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma^{5,6}.

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

ZFH3 deletion

zinc finger homeobox 3

Background: ZFH3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains^{1,356,357}. Functionally, ZFH3 is found to be necessary for neuronal and myogenic differentiation^{357,358}. ZFH3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth^{359,360,361,362,363}. In addition, ZFH3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFH3^{359,362,364,365}.

Alterations and prevalence: Somatic mutations in ZFH3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid

Biomarker Descriptions (continued)

leukemia^{5,6}. Biallelic loss of ZFH3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma^{5,6}.

Potential relevance: Currently, no therapies are approved for ZFH3 aberrations.

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2¹. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling⁴⁶². GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development^{462,463}. 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^{464,465,466}.

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^{5,6,467}. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma⁴⁶⁷.

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)^{1,450,451}. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability^{450,451,452,453}. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models⁴⁵¹. 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^{451,454}.

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 cancer⁶. 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.

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 DSC2¹. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes²¹³. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion²¹⁴. 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^{213,215,216,217}.

Biomarker Descriptions (continued)

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 DSC3¹. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes²¹³. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion²¹⁴. 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^{213,215,216,217}.

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^{1,173,174}. 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^{173,174}. 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 development¹⁷⁴. 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^{175,176}. 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^{176,177}.

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^{5,6,176}. 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^{5,6,178}. 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.

NOTCH3 deletion

notch 3

Background: The NOTCH3 gene encodes the notch receptor 3 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, 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 signaling²⁵⁰. 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^{251,252}. 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^{253,254,255,256}.

Alterations and prevalence: Somatic mutations observed in NOTCH3 are primarily missense or truncating and are found in about 12% of melanoma and uterine cancer, as well as 3-6% of diffuse large B-cell lymphoma (DLBCL), adrenocortical carcinoma, esophageal, colorectal, cervical, squamous lung, bladder, and head and neck cancers⁵.

Potential relevance: Currently, no therapies are approved for NOTCH3 aberrations.

Biomarker Descriptions (continued)

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 transcription¹. 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^{245,246}. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis^{247,248}.

Alterations and prevalence: Somatic mutations of ARHGAP35 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 domain²⁴⁹. Amplification of ARHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma^{5,6}. Biallelic loss of ARHGAP35 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 p300¹. 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^{29,30}. 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^{315,316}. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex³¹⁵. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors³².

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 targets³¹⁷.

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 site²⁴². ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer^{242,243}. 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^{242,244}.

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^{6,240}.

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)^{111,112,240}.

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^{431,432}. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism

Biomarker Descriptions (continued)

for BCOR-mediated transcriptional repression independent of BCL6⁴³². Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene^{433,434,435}.

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)^{5,240,436,437}. 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^{438,439,440}. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)^{441,442}. 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 cases⁴³⁸.

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^{141,443}. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma¹⁴¹. 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^{111,112,240,430,436}. 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%)⁴³⁷. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas^{444,445}.

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-linked protein¹. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases⁹. DUBs catalyze the removal of ubiquitin from target proteins, thereby counter-regulating post-translational ubiquitin modifications within the cell^{9,10}. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X¹⁰. 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 substrates¹⁰. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair¹⁰.

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 population⁶. 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^{1,366}. 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)^{366,367,368,369}. In DEAD-box proteins, the DEAD domain interacts with β - and γ -phosphates of ATP through Mg²⁺ and is required for ATP hydrolysis³⁶⁶. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation^{370,371,372,373,374,375,376,377}. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance³⁷⁰.

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

Biomarker Descriptions (continued)

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 protein¹. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C²⁵⁸. 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 repression²⁵⁹. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)^{258,260}. 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 regulation²⁵⁸. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression²⁵⁸. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation^{258,261}.

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}.

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 inhibitors²⁶¹.

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family^{1,218}. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA^{218,219}. 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 expression²¹⁸. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10^{220,221}.

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^{1,260}. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response²⁵⁹. 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^{259,260}. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication⁴⁴⁶.

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}.

Biomarker Descriptions (continued)

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^{1,91,92}. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis^{91,93}. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization⁹¹. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition^{92,94}.

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.

AMER1 deletion

APC membrane recruitment protein 1

Background: The AMER1 gene encodes APC membrane recruitment protein 1¹. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway^{1,123}. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis^{124,125}. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types¹²⁵. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer¹²⁶. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest¹²³.

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 protein¹. 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)¹²⁷.

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, and 2% of thymoma, diffuse large B-cell lymphoma, head and neck squamous cell carcinoma, stomach adenocarcinoma, prostate adenocarcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, and breast invasive 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, respectively¹²⁸. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe^{5,6}. Alterations in ZMYM3 are also observed in pediatric cancers⁶. Somatic mutations in ZMYM3 are observed in 2% of embryonal tumors (8 in 332 cases), 1% of bone cancer (4 in 327 cases), and less than 1% of glioma (1 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)⁶.

Biomarker Descriptions (continued)

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^{235,236}. Components of the cohesin complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs^{237,238}. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer^{237,239}.

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants²⁴⁰. 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 adenocarcinoma⁶. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia⁶. Alterations in STAG2 are also observed in pediatric cancers⁶. 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^{112,240}. 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 tumors²⁴¹.

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^{340,341}.

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression^{340,342,343,344}. 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)^{342,344}. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6³⁴². PHF6 mutations are frequently observed in hematologic malignancies from male patients^{340,342}.

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy³⁴⁵.

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, CTNNA1, 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, MYO10, 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, PXDN, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC11B3, SMC1A, SMO,

Genes Assayed (continued)

Genes Assayed for the Detection of DNA Sequence Variants (continued)

SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, 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, CBF, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRF1, 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, PLAG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDN, 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, SLC1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBF, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRF1, 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, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ① In this cancer type and other cancer types ✕ No evidence

SMARCB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✕	✕	✕	○	✕
pazopanib	✕	✕	✕	○	✕
sunitinib	✕	✕	✕	○	✕
SHR-2554	✕	✕	✕	✕	● (II)
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✕	✕	✕	✕	● (II)
tazemetostat, nivolumab, ipilimumab	✕	✕	✕	✕	● (I/II)

BRCA2 deletion

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

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✕	✕	✕	✕	● (II)
palbociclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
AMG 193	✕	✕	✕	✕	● (I/II)
ABSK-131	✕	✕	✕	✕	● (I)
CID-078	✕	✕	✕	✕	● (I)

ATM deletion

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

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
CID-078	✕	✕	✕	✕	● (I)

ARID1A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✕	✕	✕	✕	● (II)
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✕	✕	✕	✕	● (II)

BRCA1 deletion

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

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
amquiliX	✕	✕	✕	✕	● (I/II)
palbociclib, gedatolisib	✕	✕	✕	✕	● (I)

RB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✕	✕	✕	✕	● (I/II)
CID-078	✕	✕	✕	✕	● (I)

ATRX deletion

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

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

Relevant Therapy Summary (continued)

In this cancer type
 In other cancer type
 In this cancer type and other cancer types
 ✕ No evidence

CDK12 deletion

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

CHEK1 deletion

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

CHEK2 deletion

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

FANCA deletion

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

FANCF deletion

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

FANCG deletion

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

NF2 deletion

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

PALB2 deletion

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

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

Relevant Therapy Summary (continued)

In this cancer type
 In other cancer type
 In this cancer type and other cancer types
 No evidence

RAD51D deletion

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

SMAD4 deletion

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

TSC2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nab-rapamycin (Abraxis), chemotherapy	✗	✗	✗	✗	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	47.65%
BRCA1	CNV, CN:1.0
BRCA1	LOH, 17q21.31(41197602-41276231)x1
BRCA2	CNV, CN:1.0
BRCA2	LOH, 13q13.1(32890491-32972932)x1
ATM	CNV, CN:1.0
ATM	LOH, 11q22.3(108098341-108236285)x1
CDK12	CNV, CN:1.0
CDK12	LOH, 17q12(37618286-37687611)x1
CHEK1	CNV, CN:1.0
CHEK1	LOH, 11q24.2(125496639-125525271)x1
CHEK2	CNV, CN:1.0
CHEK2	LOH, 22q12.1(29083868-29130729)x1
PALB2	CNV, CN:1.0
PALB2	LOH, 16p12.2(23614759-23652528)x1
RAD51D	CNV, CN:1.0
RAD51D	LOH, 17q12(33427950-33446720)x1
RAD54L	CNV, CN:1.0
RAD54L	LOH, 1p34.1(46714017-46743978)x1

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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