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Patient Name: 육동욱
Gender: M
Sample ID: N25-244

Primary Tumor Site: Lung
Collection Date: 2025.09.22.

Sample Cancer Type: Lung Cancer

Report Highlights

16 Relevant Biomarkers
3 Therapies Available
17 Clinical Trials

Relevant Lung Cancer Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	***8.53 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	10
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	*ARID1A deletion* AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	2

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA1 deletion* BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	2
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	*BARD1 deletion* BRCA1 associated RING domain 1 Locus: chr2:215593375	None*	None*	1
IIC	*BRIP1 deletion* BRCA1 interacting protein C-terminal helicase 1 Locus: chr17:59760627	None*	None*	1
IIC	*CDK12 deletion* cyclin dependent kinase 12 Locus: chr17:37618286	None*	None*	1
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	*FANCF deletion* Fanconi anemia complementation group F Locus: chr11:22646196	None*	None*	1
IIC	*FBXW7 deletion* F-box and WD repeat domain containing 7 Locus: chr4:153243999	None*	None*	1
IIC	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	1
IIC	*RAD50 deletion* RAD50 double strand break repair protein Locus: chr5:131892978	None*	None*	1
IIC	*RAD51C deletion* RAD51 paralog C Locus: chr17:56769933	None*	None*	1
IIC	*RAD51D deletion* RAD51 paralog D Locus: chr17:33427950	None*	None*	1

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

ABRAXAS1 deletion, APC deletion, BCL6 amplification, CDKN2C deletion, FANCE deletion, MLH1 deletion, MSH3 deletion, MUTYH deletion, Microsatellite stable, PARP2 deletion, PARP3 deletion, PIK3R1 deletion, PIK3R1 p.(Y73) c.219C>A, POLD1 deletion, RAD54L deletion, SDHB deletion, SETD2 deletion, TCF7L2 deletion, TP53 p.(G245V) c.734G>T, TP53 p.*

(V157F) c.469G>T, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, JAK1 deletion, FUBP1 deletion, DPYD deletion, CASP8 deletion, CUL3 deletion, PDCD1 deletion, TGFBR2 deletion, DOCK3 deletion, PBRM1 deletion, TET2 deletion, INPP4B deletion, SDHA deletion, CDH10 deletion, ADAMTS12 deletion, MAP3K1 deletion, RASA1 deletion, ERAP1 deletion, ERAP2 deletion, ADAMTS2 deletion, HLA-A deletion, HLA-B deletion, NOTCH4 deletion, TAP2 deletion, TAP1 deletion, DAXX deletion, CDKN1A deletion, JAK2 deletion, LARP4B deletion, GATA3 deletion, MAPK8 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, WT1 deletion, NQO1 p.(P187S) c.559C>T, RUNX1 deletion, ZRSR2 deletion, BCOR deletion, USP9X deletion, DDX3X deletion, KDM6A deletion, RBM10 deletion, KDM5C deletion, SMC1A deletion, AMER1 deletion, ZMYM3 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3R1	p.(Y73*)	c.219C>A	.	chr5:67522722	2.03%	NM_181523.3	nonsense
TP53	p.(G245V)	c.734G>T	COSM11196	chr17:7577547	50.15%	NM_000546.6	missense
TP53	p.(V157F)	c.469G>T	COSM10670	chr17:7578461	25.97%	NM_000546.6	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	46.24%	NM_000903.3	missense
ARID1A	p.(E119G)	c.356A>G	.	chr1:27023250	85.00%	NM_006015.6	missense
USP33	p.(D174N)	c.520G>A	.	chr1:78201768	65.64%	NM_015017.5	missense
OR2L13	p.(G305W)	c.913G>T	.	chr1:248263590	32.91%	NM_175911.3	missense
BARD1	p.(E655K)	c.1963G>A	.	chr2:215595173	64.26%	NM_000465.4	missense
RASA1	p.(?)	c.2603+1G>T	.	chr5:86675668	70.07%	NM_002890.3	unknown
HDAC9	p.(H584Q)	c.1752C>G	.	chr7:18767223	3.65%	NM_178425.3	missense
CDKN2A	p.(A85P)	c.253G>C	.	chr9:21971105	63.47%	NM_001195132.2	missense
WT1	p.(G183R)	c.547G>A	.	chr11:32456360	32.99%	NM_024426.6	missense
RB1	p.(?)	c.1215+3A>T	.	chr13:48947631	4.29%	NM_000321.3	unknown
AAGAB	p.(E137G)	c.410A>G	.	chr15:67528358	50.93%	NM_024666.5	missense
ERBB2	p.(V987E)	c.2960T>A	.	chr17:37882902	52.08%	NM_004448.4	missense
ZNF682	p.(R473Sfs*11)	c.1415_1416delAG	.	chr19:20116894	49.11%	NM_033196.3	frameshift Deletion

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.83
MTAP	chr9:21802646	0.99	0.58
CDKN2A	chr9:21968178	0.78	0.5
ARID1A	chr1:27022875	0.98	0.58
BRCA1	chr17:41197602	1	0.86
BAP1	chr3:52436290	0.96	0.57
BARD1	chr2:215593375	1	0.6
BRIP1	chr17:59760627	1	0.78

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CDK12	chr17:37618286	1	0.81
CHEK2	chr22:29083868	1	0.79
FANCF	chr11:22646196	0.95	0.57
FBXW7	chr4:153243999	0.9	0.55
PTEN	chr10:89623659	0.88	0.54
RAD50	chr5:131892978	0.98	0.58
RAD51C	chr17:56769933	1	0.9
RAD51D	chr17:33427950	1	0.82
ABRAXAS1	chr4:84383635	1.02	0.6
APC	chr5:112043374	1.01	0.59
BCL6	chr3:187440209	5.04	2.24
CDKN2C	chr1:51434849	0.95	0.57
FANCE	chr6:35420188	1.05	0.61
MLH1	chr3:37034957	1	0.59
MSH3	chr5:79950540	1.01	0.59
MUTYH	chr1:45794962	1.05	0.61
PARP2	chr14:20811781	1.04	0.61
PARP3	chr3:51976651	0.96	0.57
PIK3R1	chr5:67522468	0.99	0.58
POLD1	chr19:50902079	1.07	0.62
RAD54L	chr1:46714017	1	0.58
SDHB	chr1:17345303	1.09	0.62
SETD2	chr3:47058542	1.05	0.61
TCF7L2	chr10:114710485	1	0.59
TNFRSF14	chr1:2488070	1.11	0.64
ERRFI1	chr1:8073246	1.01	0.6
ENO1	chr1:8921399	1.02	0.6
PGD	chr1:10459132	1.01	0.59
SPEN	chr1:16174516	0.98	0.58
EPHA2	chr1:16451707	1.18	0.66
JAK1	chr1:65300225	1.01	0.6
FUBP1	chr1:78414385	0.99	0.58
DPYD	chr1:97544504	1.04	0.61
CASP8	chr2:202122934	0.91	0.56

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CUL3	chr2:225338933	1.07	0.62
PDCD1	chr2:242793161	1.07	0.62
TGFBR2	chr3:30648337	1.01	0.59
DOCK3	chr3:51101879	0.85	0.53
PBRM1	chr3:52582040	1.02	0.6
TET2	chr4:106155068	1.04	0.6
INPP4B	chr4:142949914	0.98	0.58
SDHA	chr5:218412	1.23	0.68
CDH10	chr5:24487706	1.06	0.62
ADAMTS12	chr5:33527235	1.2	0.67
MAP3K1	chr5:56111388	0.98	0.58
RASA1	chr5:86564256	0.91	0.56
ERAP1	chr5:96112128	1	0.59
ERAP2	chr5:96219500	0.33	0.31
ADAMTS2	chr5:178549645	0.85	0.53
HLA-A	chr6:29910229	0.6	0.42
HLA-B	chr6:31322252	0.32	0.31
NOTCH4	chr6:32163187	0.89	0.54
TAP2	chr6:32796585	0.72	0.47
TAP1	chr6:32814849	0.74	0.49
DAXX	chr6:33286486	0.95	0.57
CDKN1A	chr6:36645655	1.04	0.6
JAK2	chr9:5021954	1.06	0.61
LARP4B	chr10:858847	1	0.59
GATA3	chr10:8097519	0.8	0.51
MAPK8	chr10:49609682	0.98	0.58
ARID5B	chr10:63661463	0.85	0.53
CYP2C9	chr10:96698378	0.8	0.51
SUFU	chr10:104263903	0.93	0.56
WT1	chr11:32410528	1.07	0.62
RUNX1	chr21:36164357	1.04	0.61
ZRSR2	chrX:15808582	0.84	0.52
BCOR	chrX:39911340	0.8	0.51
USP9X	chrX:40982869	0.85	0.53

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
DDX3X	chrX:41193501	0.76	0.49
KDM6A	chrX:44732715	0.91	0.55
RBM10	chrX:47006798	0.87	0.53
KDM5C	chrX:53221892	0.85	0.53
SMC1A	chrX:53406966	0.83	0.52
AMER1	chrX:63409727	0.24	0.28
ZMYM3	chrX:70460753	0.29	0.3
MYCL	chr1:40362966	0.8	0.51
MAGOH	chr1:53692690	0.95	0.57
SF3B1	chr2:198256951	0.99	0.58
CTLA4	chr2:204732664	1.04	0.61
ERBB4	chr2:212248561	1	0.59
MITF	chr3:69788729	0.95	0.57
TP63	chr3:189456442	5.1	2.27
FGFR3	chr4:1801456	0.89	0.54
PDGFRA	chr4:55131078	1.05	0.61
KIT	chr4:55589693	1.16	0.66
KDR	chr4:55955541	0.88	0.54
CTNND2	chr5:10988230	0.88	0.54
PRDM9	chr5:23509577	0.77	0.49
PDGFRB	chr5:149497160	0.73	0.48
FGFR4	chr5:176517731	0.93	0.56
FLT4	chr5:180030092	1	0.59
DDR1	chr6:30852922	1.04	0.6
PXDNL	chr8:52233342	1.09	0.62
CD274	chr9:5456050	1.11	0.63
PDCD1LG2	chr9:5522530	1.07	0.62
FANCG	chr9:35074046	5.33	2.37
RET	chr10:43609070	0.98	0.58
FGFR2	chr10:123239426	0.99	0.58
HRAS	chr11:532637	0.83	0.52
BCL2L12	chr19:50169053	0.73	0.48
PPP2R1A	chr19:52693246	0.96	0.57
AURKC	chr19:57742416	0.79	0.5

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
U2AF1L5	chr21:44513260	0.99	0.58
EIF1AX	chrX:20148599	0.95	0.57
ARAF	chrX:47422311	0.77	0.5
AR	chrX:66766015	0.28	0.29
TAF1	chrX:70608133	0.06	0.21

Biomarker Descriptions

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[52,53]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[52,53]. 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[54,55,56]. 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%[54,57].

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[58,59,60,61,62,63,64,65]. 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[4,5].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[66]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[67,68]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[69] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[70] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[71] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib[72] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[73] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[74]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[75]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[77], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

Biomarker Descriptions (continued)

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[349,350]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[350].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[350,351]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[268]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[269,270,271]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[272]. 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[1,272,273]. CDKN2A aberrations commonly co-occur with CDKN2B[268]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[274]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[275,276].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[277]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[4,5]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[4,5]. Alterations in CDKN2A are also observed in pediatric cancers[5]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[5]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[5].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[278,279,280]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[281]. 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[282,283,284]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[285]. 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[286,287,288,289].

Biomarker Descriptions (continued)

ARID1A deletion

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,105]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[96,105]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[96]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[96,106]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[105]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[105].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[106]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[105]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[4,5,96]. 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 response[107].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[108], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[109], 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 and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[52,53]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[52,53]. 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[54,55,56]. 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%[54,57].

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[58,59,60,61,62,63,64,65]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[4,5].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[66]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[67,68]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[69] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[70] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[71] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[72] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[73] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[74]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[75].

Biomarker Descriptions (continued)

In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[77], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[309]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[309]. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[310,311,312,313,314,315].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[4,5]. BAP1 biallelic deletions are observed in 11% of mesothelioma[4,5].

Potential relevance: Currently, no therapies are approved for BAP1 aberrations.

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene[1,163]. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage[1,163,164,165]. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction[1,164,166,167]. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[149,167]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[166]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[168]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[168,169].

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

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA[157]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[158]. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[145,146]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[159]. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer[159,160]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[157,161].

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

Biomarker Descriptions (continued)

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy[145,162]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[305,306,307]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[146,305,306,307,308]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[146,307]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[308]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[308].

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma[1,4]. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma[1,4].

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[71] 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[146,308]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[373]. 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)[374,375,376]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[377,378,379].

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

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[71] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FANCF deletion

Fanconi anemia complementation group F

Background: The FANCF gene encodes the FA complementation group F protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[261,262]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[261]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[263,264]. Loss of function mutations in the FA family and HRR pathway, including FANCF, can result in the BRCAness phenotype, characterized by a defect

Biomarker Descriptions (continued)

in the HRR pathway, mimicking BRCA1 or BRCA2 loss[146,265]. 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[266,267].

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[4,5].

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

FBXW7 deletion

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[170]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[170,171,172,173,174,175,176].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[4,5,177,178,179].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[180], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[177]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[176].

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[384]. 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[385,386]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[387]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[388]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[389].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[4,5]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[386,390,391,392,393]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[4,5].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[394,395]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[396] 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.

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases[428,429]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[429,430]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[430,431]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[430,431]. RAD50 contains long coiled-

Biomarker Descriptions (continued)

coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response[430,432]. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[145,146]. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer[433].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[4,5]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[434].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[435]. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression[435]. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype[436].

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs[139]. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)[140]. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)[141]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing[142]. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity[143,144]. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[145,146].

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

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib[71] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation[147]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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)[140]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[141]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[142]. 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[145,146]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[148].

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

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors[145]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit[1]. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36[149,150]. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks[149]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[149]. Together with the rest of the BRCA1-A complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer[149,151].

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

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

APC deletion

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[195]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[196,197]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[195,198]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[199].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[4,5,200]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[201,202].

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

BCL6 amplification

B-cell CLL/lymphoma 6

Background: The BCL6 gene encodes the B-cell lymphoma 6 (BCL6) transcription repressor, a protein that is responsible for inhibiting the expression of several genes including those involved in the DNA damage response, cell cycle checkpoints, and modulating BCL2 expression[450,451,452]. BCL6 is most commonly expressed in germinal center B-cells and is required for germinal cell formation and affinity maturation during T-cell dependent antibody responses[451]. BCL6 is observed to competitively bind DNA motifs recognized by the oncogenic transcription factor STAT6, thereby repressing STAT6 mediated gene transcription[453,454]. Aberrations in BCL6 often lead to altered target gene transcription, including those involved in cell cycle arrest, differentiation, and apoptosis[450,451].

Alterations and prevalence: BCL6 rearrangement most commonly occurs with immunoglobulin H (IGH) partners and results in the truncation or removal the BCL6 promoter region and juxtaposition of BCL6 downstream of the partner gene promoter[455]. Replacement of the BCL6 promoter resulting from such translocations has been observed to lead to aberrant BCL6 expression[456]. BCL6 rearrangement is a common event in lymphoma and has been observed in up to 40% of diffuse large B-cell lymphoma (DLBCL) and 15% of follicle center lymphomas[451,455]. Somatic mutations in BCL6 are observed in 7% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma, and 2% of uterine carcinosarcoma, lung adenocarcinoma, and sarcoma[4,5]. Mutations in the 5' regulatory sequences of BCL6 are observed in 30-40% of germinal center B-cells and are believed to disrupt BCL6 negative autoregulation[451]. Amplifications are observed in 31% of lung squamous cell carcinoma, 16% of esophageal adenocarcinoma and ovarian serous cystadenocarcinoma, and 14% of head and neck and cervical squamous cell carcinoma, 9% of uterine carcinosarcoma, 6% of uterine corpus endometrial carcinoma, and 2-4% of stomach adenocarcinoma, diffuse large B-cell lymphoma, bladder urothelial carcinoma, breast invasive carcinoma, testicular germ cell tumors, liver hepatocellular carcinoma, and pancreatic adenocarcinoma[4,5]. Alterations in BCL6 are rare in pediatric cancers[4,5]. Somatic mutations in BCL6 are observed in 3% of soft tissue sarcoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumors (2 in 332 cases), and glioma (1 in 297 cases)[4,5]. Amplification of BCL6 is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[4,5].

Potential relevance: B-cell lymphoma with BCL6 translocations that co-occur with MYC are referred to as double-hit lymphoma (DHL), while co-occurrence with MYC and BCL2 rearrangements is referred to as triple-hit lymphoma[457]. Such concomitant rearrangements

Biomarker Descriptions (continued)

are recognized by the World Health Organization (WHO) as diagnostic entity of diffuse large B-cell lymphoma/high grade B-cell lymphoma (HGBL) with MYC and BCL2 rearrangements[458]. DHL expressing BCL6 rearrangements are most often aggressive with poor prognosis, involve extra nodal sites, and have a germinal center phenotype[459,460].

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 progression[1]. 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[269,270,271]. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer[297].

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[4,5]. Deletion of chromosome 1p32, where CDKN2C resides, is observed to be recurrent in multiple myeloma with variable frequency (7%-20%), depending on the study[298,299,300].

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

FANCE deletion

Fanconi anemia complementation group E

Background: The FANCE gene encodes the FA complementation group E protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[261,262]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[261]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[263,264]. Loss of function mutations in the FA family and HRR pathway, including FANCE, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[146,265]. 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[266,267].

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

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

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[49]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[49,120]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[121,122]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[49]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[49]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[123]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[124,125,126]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[124,127]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[125,127,128,129]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[130,131,132,133].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[4,5]. Alterations in MLH1 are observed in pediatric cancers[4,5]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[4,5].

Biomarker Descriptions (continued)

Potential relevance: The PARP inhibitor, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[134]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[135,136]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[137,138].

MSH3 deletion

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[1]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[49,50]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[49,50]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[51].

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

Potential relevance: Currently, no therapies are approved for MSH3 aberrations.

MUTYH deletion

mutY DNA glycosylase

Background: The MUTYH gene encodes the mutY DNA glycosylase protein[1]. DNA glycosylases are structurally specific enzymes that function in base excision repair (BER) by removing damaged or incorrect bases in DNA[78]. 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)[78]. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer[79,80].

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[4,5]. Biallelic deletions in MUTYH are observed in 2% of pheochromocytoma and paraganglioma[4,5].

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 genome[181]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[125,127]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[126]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[182]. 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)[182]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[128,183,184,185,186]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[127]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[125,127,128,129].

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[125,127,187,188]. 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[187,188].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[134] (2014) and nivolumab[135] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[134] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[134]. Dostarlimab[189] (2021) is also approved for dMMR recurrent or advanced endometrial

Biomarker Descriptions (continued)

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[184,190]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[136] (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[184,191,192]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[192]. 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[193,194]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[193,194].

PARP2 deletion

poly(ADP-ribose) polymerase 2

Background: The PARP2 gene encodes the poly(ADP-ribose) polymerase 2 protein[1]. PARP2 belongs to the large PARP protein family that also includes PARP1, PARP3, and PARP4[81]. 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[81,82]. PARP enzymes are involved in several DNA repair pathways[81,82]. PARP2 interacts with PARP1 to assist in repair of single-strand breaks through base excision repair (BER)[81,83]. PARP2 has also been observed to promote homologous recombination repair (HRR) of double-strand breaks (DSBs) over non-homologous end joining (NHEJ) by limiting the accumulation of TP53BP1 and preventing TP53BP1 from blocking HRR resection of DNA[83,84]. PARylation of histones H1, H2A, and H2B by PARP2 promotes an open chromatin conformation, which allows DNA repair machinery access to sites of DNA damage[85].

Alterations and prevalence: Somatic mutations in PARP2 are observed in 4% of uterine corpus endometrial carcinoma, and uterine carcinosarcoma, and 2% of stomach adenocarcinoma, and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for PARP2 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[86,87]. Although not indicated for specific alterations in PARP2, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[69] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[70] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[71] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[72] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[81]. 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[81,82]. PARP enzymes are involved in several DNA repair pathways[81,82]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[92,93]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[92].

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

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[86,87].

Biomarker Descriptions (continued)

Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[69] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[70] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[71] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[72] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

PIK3R1 deletion, PIK3R1 p.(Y73*) c.219C>A

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[321]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[321]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[321]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[322,323]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[322,323,324,325]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[326]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[321].

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

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

POLD1 deletion

DNA polymerase delta 1, catalytic subunit

Background: The POLD1 gene encodes the DNA polymerase delta 1, catalytic subunit protein[1]. POLD1 is one of four subunits that make up the DNA polymerase delta (Polδ) enzyme along with POLD2, POLD3, and POLD4[397,398]. Specifically, POLD1 is responsible for the polymerase and 3'-5' exonuclease activity of Polδ in the synthesis of DNA during DNA replication and repair observed in homologous recombination repair (HRR), mismatch repair (MMR), and nucleotide excision repair (NER)[49,397,398,399]. Independent of Polδ, POLD1 associates with γ-tubulin ring complexes to control cytoplasmic microtubule growth[397]. Germline mutations in POLD1 are associated with polymerase proofreading-associated polyposis, which confers predisposition to colorectal adenomas and carcinomas[400,401,402,403,404].

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[4,5].

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 RAD54B[152]. 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[152,153,154]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[152,155]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[156]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[145].

Biomarker Descriptions (continued)

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

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[76], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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 complex[1]. 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[88,89]. 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[88,89]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[90]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[88,89]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,91].

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[4,5]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

SETD2 deletion

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[442,443]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[444]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[445,446]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[443]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[447]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[443,448].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[4,448,449]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[4,442]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[442]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[442].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[348].

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,370]. 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[370,371,372]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[370]. 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 TCF7L2[370].

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[4,5]. Biallelic

Biomarker Descriptions (continued)

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[4,5].

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

TP53 p.(G245V) c.734G>T, TP53 p.(V157F) c.469G>T

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[470]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[471]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[472,473].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[4,5,474,475,476,477]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[4,5]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[478,479,480,481]. Alterations in TP53 are also observed in pediatric cancers[4,5]. 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)[4,5]. 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)[4,5].

Potential relevance: The small molecule p53 reactivator, PC14586[482] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[483], (2019) and breakthrough designation[484] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[485,486]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[487]. 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)[29,32,214,217,243,488]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[318]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[489].

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. 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 cytokines[316]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[316]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[316,317]. 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 survival[316]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[317].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[4,5]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[318]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[319,320].

Biomarker Descriptions (continued)

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,461]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[461,462]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[461,463]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[461,464,465,466,467]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[461,464,465,468,469].

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ERRFI1 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[4,5].

Potential relevance: Currently, no therapies are approved for ERRFI1 aberrations.

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)[1,380]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[380]. 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[380,381,382]. 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[380,381,383]. 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[380,381].

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[4,5]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[4,5]. 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[4,5].

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[1,290]. 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[291,292]. 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[290,293].

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[4,5]. 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[4,5]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5].

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

Biomarker Descriptions (continued)

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor[1]. SPEN plays a role in chromosome X inactivation and regulation of transcription[437,438,439]. 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[437,439]. In ERα-positive breast cancers, SPEN binds ERα in a ligand-independent manner and negatively regulates the transcription of ERα targets, acting as a tumor suppressor gene to regulate cell proliferation, tumor growth, and survival[440,441].

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[4,5]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

EPHA2 deletion

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[1]. 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[94,95]. 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 apoptosis[95]. 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[94,95].

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[4,5].

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

JAK1 deletion

Janus kinase 1

Background: The JAK1 gene encodes Janus kinase 1, a non-receptor protein tyrosine kinase (PTK)[1,13]. JAK1 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[14]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[14]. 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[14,15,16]. 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[16,499,500].

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[501,502,503]. The recurrent somatic mutation V658F observed in JAK1 is homologous to the V617F mutation in JAK2 and is a known driver mutation in myeloproliferative disease[502]. Recurrent activating mutations in JAK1 are infrequently observed in solid cancers, although two variants, S703I and S729C, were reported in hepatocellular carcinomas[504,505,506]. In addition, V658F and R724H were infrequently observed in diverse cancer types[4,5]. Truncating mutations in JAK1, resulting from dispersed or recurrent frameshift mutations, are common in solid cancers and particularly enriched in uterine cancers[4,5,16]. Recurrent truncating mutations in JAK1 are also associated with high tumor mutation burden (TMB) and microsatellite instability (MSI)[499,500]. JAK1 alterations are rare in pediatric cancers[4,5]. 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)[4,5]. JAK1 is amplified in less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[4,5].

Potential relevance: Currently, no therapies are approved for JAK1 aberrations. However, ruxolitinib[31] is a JAK1/2 inhibitor that is FDA approved (2011) for primary myelofibrosis and polycythemia vera. Other JAK inhibitors, including tofacitinib (2012) and baricitinib

Biomarker Descriptions (continued)

(2018), are approved for rheumatoid arthritis. JAK1 mutations and fusions confer poor risk in B-cell ALL[32]. Clinical cases associated with high TMB but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[33].

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[1,256]. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of transcription, translation, and splicing[256]. FUBP1 activates the transcription of targets including the oncogene MYC which functions in cell cycle regulation, metabolism, and apoptosis[256]. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation[256].

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[4,5]. Mutations typically result in inactivation of FUBP1 through alteration of splicing sites, introduction of stop codons, or out-of-frame insertions or deletions[256]. Biallelic loss of FUBP1 is observed in 3% of pheochromocytoma and paraganglioma[4,5]. Co-deletion of 1p and 19q is frequently observed in oligodendrogliomas, which results in the monoallelic loss of FUBP1 and CIC on 19q[256].

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

DPYD deletion

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

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

CASP8 deletion

caspase 8

Background: CASP8 encodes caspase 8, a member of the cysteine-aspartic acid protease (caspase) family consisting of inflammatory caspases and apoptotic caspases. Apoptotic caspases consist of initiator and effector caspases[1,229,230]. CASP8 functions as an initiator caspase and following external stimulation of death receptors, undergoes processing and activation leading to CASP8 mediated cleavage of downstream targets[231]. CASP8 propagates the extrinsic apoptotic pathway by direct cleavage of effector caspases such as CASP3 and activates the intrinsic apoptotic pathway by cleaving BID, a pro-apoptotic proximal substrate of CASP8, resulting in an amplification of the death-inducing signal[231,232]. Certain cancer types have decreased expression or inactivation of CASP8, which results in poor prognosis and metastasis[233,234].

Alterations and prevalence: Somatic mutations in CASP8 are observed in 11% head and neck squamous cell carcinoma, 10% uterine corpus endometrial carcinoma, 5% stomach adenocarcinoma, 4% cervical squamous cell carcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, 3% skin cutaneous melanoma, and 2% diffuse large B-cell lymphoma, lung squamous cell carcinoma, uterine carcinosarcoma, and breast invasive carcinoma[4,5]. Biallelic loss of CASP8 is observed in 2% bladder urothelial carcinoma[4,5].

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

Biomarker Descriptions (continued)

CUL3 deletion

cullin 3

Background: The CUL3 gene encodes cullin 3, a member of the cullin family, which includes CUL1, CUL2, CUL4a, CUL4b, CUL5, CUL7, and Parc[1,9]. 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)[9]. CRLs are involved in diverse biological processes including cell cycle control, DNA replication and repair, and chromatin remodeling[10]. CUL3 is part of the CRL3 complex which is responsible for ubiquitination and degradation of a variety of substrates[10,11,12]. Substrate specificity is dependent on the proteins recruited by CUL3 that have BTB domains, such as KEAP1 and SPOP[10,11,12]. CRL3 substrates include various oncoproteins, tumor suppressors, cell cycle promoters, apoptosis regulators, and signaling molecules, thereby impacting various processes critical to cancer progression and supporting a complex role of CUL3 in oncogenesis[12].

Alterations and prevalence: Somatic mutations in CUL3 are observed in 8% of uterine corpus endometrial carcinoma, 5% of lung squamous cell carcinoma, 4% of kidney renal papillary cell carcinoma, 3% of head and neck squamous cell carcinoma, cholangiocarcinoma, and skin cutaneous melanoma, and 2% of lung adenocarcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and stomach adenocarcinoma[4,5]. Biallelic loss of CUL3 is observed in 2% of sarcoma, cervical squamous cell carcinoma, head and neck squamous cell carcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, and thymoma[4,5]. Amplification of CUL3 is observed in 3% of pancreatic adenocarcinoma and 2% of uterine carcinosarcoma[4,5].

Potential relevance: Currently, no therapies are approved for CUL3 aberrations.

PDCD1 deletion

programmed cell death 1

Background: The PDCD1 gene encodes programmed cell death 1, also known as PD-1 or CD279[1]. PDCD1 is a type I transmembrane inhibitory receptor and member of the CD28/CTLA-4 family, which is part of the immunoglobulin superfamily[301]. PDCD1 is an immune checkpoint molecule that acts as a gatekeeper of immune responses through a balance of signaling suppression, which is critical in the facilitation of self and non-self cell recognition[302]. PDCD1 is expressed in a variety of hematopoietic cells, immune cells, tumor cells, and tumor specific T-cells[301,303]. The two main immunoregulatory ligands of PDCD1 are CD274 (PD-L1) and PDCD1LG2 (PD-L2), which are type I transmembrane proteins expressed in many cells including antigen presenting cells and tumor cells[301]. PDCD1 and CD274 act as co-inhibitors and regulate immune tolerance of central and peripheral T-cells and reduce the proliferation of CD8+ T-cells by inhibitor signals[301,303].

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

Potential relevance: Currently, no therapies are approved for PDCD1 aberrations. Immune checkpoint inhibitor therapy uses immunotherapy to block receptor-ligand interactions and enhance immunity activity against tumor cells[304]. Although not approved for specific PDCD1 aberrations, approved checkpoint inhibitors targeting PDCD1 include the monoclonal antibodies pembrolizumab, nivolumab, and cemiplimab[301].

TGFBR2 deletion

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[44]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[44]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[44]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[45]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[46,47,48].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[4,5]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TGFBR2 aberrations.

Biomarker Descriptions (continued)

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[490]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,491,492]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[493,494]. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3[492].

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

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

PBRM1 deletion

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[96]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[96,97]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[96,98]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[99,100].

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

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

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,341]. The TET enzymes are involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[342,343]. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded ß-helix domain (DSBH)[342,343]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[342,343]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[341,344,345].

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)[217]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[344,346]. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe[4,5]. Alterations in TET2 are also observed in the pediatric population[5]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in

Biomarker Descriptions (continued)

1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[5]. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5].

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[29]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[347]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[348].

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,495]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[496]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[497,498].

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

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

SDHA deletion

succinate dehydrogenase complex flavoprotein subunit A

Background: The SDHA gene encodes succinate dehydrogenase complex flavoprotein subunit A, a major catalytic subunit of the succinate dehydrogenase (SDH) enzyme complex[1,89]. 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[88,89]. 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[88,89]. SDHA is involved in the oxidation of succinate with a coupled reduction of the cofactor FAD[88,89]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[88,89]. Inherited pathogenic mutations in SDHA are known to confer increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[88,89,118,119].

Alterations and prevalence: Somatic mutations in SDHA are observed in 4% of uterine corpus endometrial carcinoma, 3% of colorectal adenocarcinoma, kidney chromophobe, and skin cutaneous melanoma, and 2% of cervical squamous cell carcinoma, stomach adenocarcinoma, uterine carcinosarcoma, bladder urothelial carcinoma, and lung squamous cell carcinoma[4,5]. Biallelic loss of SDHA is observed in 2% of uterine carcinosarcoma[4,5].

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

CDH10 deletion

cadherin 10

Background: The CDH10 gene encodes cadherin 10, a type II classical cadherin and member of the cadherin superfamily[1]. Cadherins are important in calcium-dependent cell-cell adhesion, and are known to mediate cell recognition, cell movement, and maintain structural and functional cell and tissue polarity[6]. CDH10 is classified as an atypical type II cadherin due to its lack of a histidine-alanine-valine (HAV) cell adhesion recognition motif, a hallmark characteristic to type I cadherins[1,6]. Abnormal expression of cadherins results in increased tumor cell invasion, which precedes metastasis of tumors[7,8].

Alterations and prevalence: Somatic mutations of CDH10 are observed in 20% of lung squamous cell carcinoma, 16% of lung adenocarcinoma, 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 8% of stomach adenocarcinoma, and colorectal adenocarcinoma, 6% of head and neck squamous cell carcinoma, 4% of bladder urothelial carcinoma and esophageal adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of pancreatic adenocarcinoma, ovarian serous

Biomarker Descriptions (continued)

cystadenocarcinoma, uterine carcinosarcoma, and sarcoma[4,5]. Amplification of CDH10 is observed in 10% of lung squamous cell carcinoma, 7% of lung adenocarcinoma and esophageal adenocarcinoma, 6% of bladder urothelial carcinoma, 5% of ovarian serous cystadenocarcinoma and cervical squamous cell carcinoma, 4% of sarcoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% uterine corpus endometrial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CDH10 aberrations.

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[1]. Activation of MAPK proteins occurs through a kinase signaling cascade[327,328,330]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[327,328,330]. 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[327,328,330]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[421]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[421]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[421].

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[4,5]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[421]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

RASA1 deletion

RAS p21 protein activator 1

Background: The RASA1 gene encodes the Ras p21 protein activator 1[1]. RASA1 is a member of the RasGAP family, which includes RASA2[110,111]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[110]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[110]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[110]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[110].

Alterations and prevalence: Somatic mutations in RASA1 are observed in 11% of uterine corpus endometrial carcinoma, 6% of lung squamous cell carcinoma, 5% of stomach adenocarcinoma and of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, head and neck squamous cell carcinoma, colorectal carcinoma, and uterine carcinosarcoma, and 3% of esophageal adenocarcinoma[4,5]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for RASA1 aberrations.

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein[1]. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[422,423]. 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[422,424]. 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[422,425,426]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[422,427].

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

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

Biomarker Descriptions (continued)

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[422,423]. 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[422,424]. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic[422].

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

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

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[352]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[353]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[354,355,356]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[357].

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

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[352]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[353]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[354,355,356]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[357].

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

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

NOTCH4 deletion

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[244]. 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[245,246]. In cancer, depending on the tumor type,

Biomarker Descriptions (continued)

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[247,248,249,250].

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

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

TAP2 deletion

transporter 2, ATP binding cassette subfamily B member

Background: The TAP2 gene encodes the transporter 2, ATP binding cassette subfamily B member protein[1]. Along with TAP1, TAP2 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[219,220]. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression[223,224].

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

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

TAP1 deletion

transporter 1, ATP binding cassette subfamily B member

Background: The TAP1 gene encodes the transporter 1, ATP binding cassette subfamily B member protein[1]. Along with TAP2 TAP1 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP-controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[219,220]. TAP1 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression and survival[221,222,223].

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

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

DAXX deletion

death domain associated protein

Background: DAXX encodes the death domain associated protein, a transcription co-repressor known to repress the transcriptional potential of several sumoylated transcription factors[1]. DAXX mediates apoptosis through the death receptor pathway where it interacts and supports a multitude of cellular processes, which include gene regulation, transcriptional mediation through interaction with DNA-binding transcription factors, histones, and chromatin-associated proteins[38]. DAXX is proposed to function as a tumor suppressor due to its potential role in DNA damage repair(DDR) and through facilitating the inhibition of target genes by promoting H3K9 trimethylation[39,40].

Alterations and prevalence: Somatic mutations in DAXX are predominantly missense and truncating and occur in 5% of uterine corpus endometrial carcinoma, 3% skin cutaneous melanoma, adrenocortical carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of colorectal adenocarcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and glioblastoma multiforme[5]. DAXX mutations have also been observed to be enriched in pancreatic neuroendocrine tumors (Pan-NETs) with one study reporting mutations in 25% of 68 cases[41].

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

Biomarker Descriptions (continued)

CDKN1A deletion

cyclin dependent kinase inhibitor 1A

Background: The CDKN1A gene encodes the cyclin-dependent kinase inhibitor 1A protein, also known as p21 or WAF1[1,294]. CDKN1A belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1B (also known as KIP/p27) and CDKN2C (also known as KIP2/p57)[294,295]. Through inhibition of cyclin dependent kinases, including CDK1 and CDK2, CDKN1A impacts several biological processes, including cell cycle arrest, differentiation, gene transcription, apoptosis, and DNA repair[296]. CDKN1A is also capable of binding to proliferating cell nuclear antigen (PCNA) and inhibiting PCNA-dependent DNA polymerase activity[296]. Deregulation of CDKN1A, including loss of expression, is observed in several tumor types, supporting a tumor suppressor role for CDKN1A[296].

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

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

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,13]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[13]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[14]. 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[14,15,16]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[17,18].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[19,20]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[21,22]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[23,24]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[25,26,27,28]. JAK2 fusions are infrequently observed in solid tumors[4]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[4]. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[4,5]. Alterations in JAK2 are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[4,5]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[4,5]. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[4,5].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)[29,30]. Ruxolitinib[31] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[32]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[33]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[25,26,27,28].

LARP4B deletion

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[36]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[36]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[37].

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung

Biomarker Descriptions (continued)

adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[4,5]. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for LARP4B aberrations.

GATA3 deletion

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1, GATA2, and GATA4-6[1,251,252]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[252]. GATA3 functions in the differentiation of immune cells and tissue development[253,254]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[253].

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[4,5]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[4,5]. Alterations in GATA3 are also observed in the pediatric population[5]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[5]. Biallelic deletion is observed in 1% of peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[253,255].

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[327,328,329]. Activation of MAPK proteins occurs through a kinase signaling cascade[327,328,330]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[327,328,330]. 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[327,328,330].

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[4,5]. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma[4,5].

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 protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[34,35]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[35]. ARID5B is known to be essential for the development of hematopoietic cells[35]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[35].

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

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

Biomarker Descriptions (continued)

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,331]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[332,333]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[332,333,334]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[331,332,333,334]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[332]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[332].

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

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

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[235]. 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[236,237]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[238]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and is observed almost exclusively in children less than 3 years of age[239].

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

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

WT1 deletion

Wilms tumor 1

Background: The WT1 gene encodes the Wilms tumor 1 homolog, a zinc-finger transcriptional regulator that plays an important role in cellular growth and metabolism[335,336]. WT1 is endogenously expressed in embryonic kidney cells as well as hematopoietic stem cells and regulates the process of filtration of blood through the kidneys[337]. WT1 protein contains N-terminal proline-glutamine rich regions that are involved in RNA and protein interaction while the C-terminal domain contains Kruppel link cysteine histidine zinc fingers that are involved in DNA binding[335]. WT1 interacts with various genes including TP53, STAT3, and epigenetic modifiers such as TET2 and TET3[335,338]. WT1 is primarily characterized as a tumor suppressor gene involved in the development of renal Wilm's tumor (WT), a rare pediatric kidney cancer[335,339]. Loss of function mutations observed in WT1, including large deletions and intragenic mutations, can impact the zinc finger domain, thereby decreasing the DNA binding activity[335]. WT1 overexpression is observed in acute myeloid leukemia (AML) and lymphoid cancers[335,340].

Alterations and prevalence: Somatic mutations of WT1 occur in 7% of AML, 5% of melanoma, and 1% of mesothelioma[5]. WT1 overexpression is observed in AML, acute lymphoblastic lymphoma (ALL), and myelodysplastic syndrome (MDS)[335]

Potential relevance: Somatic mutations in WT1, including nonsense, frameshift, and splice-site mutations, are associated with poor prognosis in MDS[217]. Overexpression of WT1 in MDS is associated with a higher risk of progression to AML. WT1 overexpression is also associated with poor prognosis, resistance to chemotherapy, and poor overall survival in AML[338].

Biomarker Descriptions (continued)

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors, which also includes RUNX2 and RUNX3[203]. All RUNX proteins share several conserved regions with similar functionality, including a highly conserved N-terminal 'runt' domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein-interacting motifs, and a nuclear matrix targeting signal[204]. Each of these proteins interacts with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex[204]. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF[205]. Specifically, CBFβ binds to the 'runt' domain of RUNX1, leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[206,207]. RUNX1 is frequently mutated in various hematological malignancies[207]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML)[208,209]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[207].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[210]. RUNX1 translocations occur in 4% of all AML[4,5]. A recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[211]. The RUNX1::RUNX1T1 fusion, consists of the runt-homology domain (RHD) of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[207,211]. Another translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 2% of adult ALL[212]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[207]. RUNX1 somatic mutations are observed in approximately 10% of AML, 10-15% of MDS, 5% of uterine corpus endometrial carcinoma, 4% of breast invasive carcinoma, 3% of bladder urothelial carcinoma, and 2% of colorectal adenocarcinoma[4,5,207]. Biallelic deletion of RUNX1 is observed in 7% of esophageal adenocarcinoma and 2% of stomach adenocarcinoma[4,5]. Alterations in RUNX1 are common in pediatric cancers, particularly the ETV6::RUNX1 fusion, which is observed in 20-25% of childhood ALL[212,213]. Overall, RUNX1 fusions are observed in 12% of B-lymphoblastic leukemia/lymphoma[4,5]. Somatic mutations in RUNX1 are observed in 5% of T-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[4,5]. Biallelic deletion of RUNX1 is observed in 5% of leukemia and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[4,5].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[30]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1, is associated with favorable risk in AML[214]. The translocation t(12;21)(q34;q11) that results in ETV6::RUNX1 fusion is associated with standard risk in adult ALL and favorable risk in pediatric ALL[32,215,216]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[214,217,218].

ZRSR2 deletion

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

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3' intron splice site[240]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[240,241]. 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[240,242].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[5,217].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[214,217,243].

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[405,406]. 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 BCL6[406]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[407,408,409].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[4,217,410,411]. 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[4,5]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[412,413,414]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[415,416]. Alterations in BCOR are also observed in pediatric cancers[4,5]. 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)[4,5]. Other alterations have been reported in clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, with one study reporting the presence of BCOR ITDs in more than 90% of cases[412].

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[280,417]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[280]. 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[30,214,217,243,410]. 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%)[411]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[418,419].

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-lined protein[1]. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases[42]. DUBs are responsible for protein deubiquitination, thereby counter-regulating post-transcriptional ubiquitin modification of proteins within the cell[42,43]. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X[43]. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its subtrates[43]. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair[43].

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

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

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[1,358]. 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)[358,359,360,361]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[358]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[362,363,364,365,366,367,368,369]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[362].

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

Biomarker Descriptions (continued)

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

KDM6A deletion

lysine demethylase 6A

Background: The KDM6A gene encodes the lysine demethylase 6A protein[1]. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C[257]. Methylation of histone lysine and arginine residues functions to regulate transcription and the DNA damage response, specifically in the recruitment of DNA repair proteins and transcriptional repression[258]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[257,259]. KDM6A also interacts with various transcription factors as well as KMT2C, KMT2D, and CBP/p300 chromatin-modifying enzymes, and the SWI/SNF chromatin-remodeling complex to facilitate transcriptional regulation[257]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[257]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[257,260].

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[4,5]. 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[4,5].

Potential relevance: Currently, no therapies are approved for KDM6A aberrations. Pre-clinical data suggest that KDM6A loss of function or inactivating mutations may respond to EZH2 inhibitors[260].

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,225]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[225,226]. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression[225]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[227,228].

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[4,5]. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[4,5]. 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[4,5].

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[1,259]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[258]. 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[258,259]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[420].

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

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

Biomarker Descriptions (continued)

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[1,101,102]. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis[101,103]. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization[101]. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition[102,104].

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[4,5]. 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[4,5]. Biallelic loss of SMC1A is found in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[4,5].

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 1[1]. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway[1,112]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[113,114]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[114]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[115]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[112].

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

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

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)[116].

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[4,5]. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively[117]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[4,5].

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

BRCA2 deletion

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462	✖	✖	✖	✖	● (I/II)
AMG 193, pembrolizumab	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

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

ARID1A deletion

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

BRCA1 deletion

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

BAP1 deletion

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

BARD1 deletion

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

BRIP1 deletion

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

CDK12 deletion

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

CHEK2 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)

* 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

FBXW7 deletion

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

PTEN deletion

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

RAD50 deletion

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

RAD51C deletion

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

RAD51D deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***60.93%***
BRCA1	***CNV, CN:1.0***
BRCA1	***LOH, 17q21.31(41197602-41276231)x1***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***
BARD1	***CNV, CN:1.0***
BARD1	***LOH, 2q35(215593375-215674382)x1***
BARD1	***SNV, E655K, AF:0.64***
BRIP1	***CNV, CN:1.0***
BRIP1	***LOH, 17q23.2(59760627-59938976)x1***
CDK12	***CNV, CN:1.0***
CDK12	***LOH, 17q12(37618286-37687519)x1***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130729)x1***
RAD51C	***CNV, CN:1.0***
RAD51C	***LOH, 17q22(56769933-56811619)x1***
RAD51D	***CNV, CN:1.0***
RAD51D	***LOH, 17q12(33427950-33446720)x1***
RAD54L	***CNV, CN:1.0***
RAD54L	***LOH, 1p34.1(46714017-46743978)x1***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. 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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