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Patient Name: 박병록
Gender: Male
Sample ID: N26-32

Primary Tumor Site: Lung
Collection Date: 2026.01.16.

Sample Cancer Type: Lung Cancer

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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	***2.84 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PIK3CA p.(C420R) c.1258T>C* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 6.95% Locus: chr3:178927980 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1, 2 / I] **alpelisib + hormone therapy** [1, 2 / II+] **capivasertib + hormone therapy** [1, 2 / II+]	4
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*	17

*** 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	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5
IIC	*ARID1A deletion* AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	2
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	2
IIC	*PIK3CA amplification* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Locus: chr3:178916680	None*	None*	2
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	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	*FANCA deletion* Fanconi anemia complementation group A Locus: chr16:89804984	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	*NBN deletion* nibrin Locus: chr8:90947783	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, CDKN2C deletion, CUL4A deletion, JAK1 deletion, LATS2 deletion, MAP2K4 deletion, MAP2K7 deletion, MLH3 deletion, MSH3 deletion, MUTYH deletion, Microsatellite stable, PARP3 deletion, PARP4 deletion, PIK3R1 deletion, PPP2R2A deletion, RAD51B deletion, RAD54L deletion, RNASEH2B deletion, RPA1 deletion, SDHB deletion, SETD2 deletion, STK11 deletion, TP53 deletion, TP53 p.(Q144) c.430C>T, XRCC3 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, FUBP1 deletion, DPYD deletion, NOTCH2 deletion, CUL3 deletion, PDCD1 deletion, DOCK3 deletion, PBRM1 deletion, MECOM amplification, TP63 deletion, TET2 deletion, INPP4B deletion, FAT1 deletion, MAP3K1 deletion, RASA1 deletion, ERAP1 deletion, ERAP2 deletion, HLA-A deletion, HLA-B deletion, NOTCH4*

deletion, TAP2 deletion, TAP1 deletion, DAXX deletion, CSMD3 deletion, LARP4B deletion, GATA3 deletion, WT1 deletion, TPP2 deletion, DICER1 deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1 deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, GPS2 deletion, RUNX1 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(C420R)	c.1258T>C	COSM757	chr3:178927980	6.95%	NM_006218.4	missense
TP53	p.(Q144*)	c.430C>T	.	chr17:7578500	80.47%	NM_000546.6	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	90.40%	NM_000903.3	missense
NTRK1	p.(V426I)	c.1276G>A	.	chr1:156844722	52.35%	NM_002529.3	missense
BRIP1	p.(S1115C)	c.3344C>G	.	chr17:59761063	42.45%	NM_032043.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.54
MTAP	chr9:21802646	0.11	0.1
CDKN2A	chr9:21968178	0.09	0.09
ARID1A	chr1:27022875	1.17	0.61
CDKN2B	chr9:22005728	0.08	0.09
PIK3CA	chr3:178916680	9.43	4.53
RB1	chr13:48877953	1.11	0.57
BAP1	chr3:52436290	1.12	0.58
BARD1	chr2:215593375	1	0.55
FANCA	chr16:89804984	1.06	0.55
FANCF	chr11:22646196	1.06	0.56
FBXW7	chr4:153243999	1.08	0.56
NBN	chr8:90947783	0.98	0.52
ABRAXAS1	chr4:84383635	1.16	0.6
CDKN2C	chr1:51434849	1.05	0.55
CUL4A	chr13:113863977	1.01	0.53
JAK1	chr1:65300225	1.11	0.57
LATS2	chr13:21548922	1.02	0.54
MAP2K4	chr17:11924164	1.34	0.68
MAP2K7	chr19:7968792	1.26	0.65
MLH3	chr14:75483761	1.08	0.57
MSH3	chr5:79950540	1.07	0.56
MUTYH	chr1:45794962	1.05	0.55

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
PARP3	chr3:51976651	0.95	0.5
PARP4	chr13:25000551	1.01	0.53
PIK3R1	chr5:67522468	1.05	0.55
PPP2R2A	chr8:26149298	1.15	0.59
RAD51B	chr14:68290164	1	0.58
RAD54L	chr1:46714017	1	0.6
RNASEH2B	chr13:51484145	1.07	0.56
RPA1	chr17:1733385	1.08	0.56
SDHB	chr1:17345303	1.17	0.6
SETD2	chr3:47058542	1.07	0.56
STK11	chr19:1206847	0.97	0.51
TP53	chr17:7572848	1.15	0.59
XRCC3	chr14:104165043	0.84	0.45
TNFRSF14	chr1:2488070	0.81	0.44
ERRFI1	chr1:8073246	1.21	0.62
ENO1	chr1:8921399	1.22	0.63
PGD	chr1:10459132	1.11	0.58
SPEN	chr1:16174516	1.11	0.57
EPHA2	chr1:16451707	1.02	0.54
FUBP1	chr1:78414385	1.08	0.57
DPYD	chr1:97544504	1.11	0.57
NOTCH2	chr1:120457903	1.11	0.58
CUL3	chr2:225338933	1.14	0.59
PDCD1	chr2:242793161	0.8	0.43
DOCK3	chr3:51101879	1	0.53
PBRM1	chr3:52582040	1.07	0.56
MECOM	chr3:168802636	11.58	5.55
TP63	chr3:189456442	1.09	0.57
TET2	chr4:106155068	1.07	0.56
INPP4B	chr4:142949914	1	0.53
FAT1	chr4:187509708	1.15	0.59
MAP3K1	chr5:56111388	1.09	0.57
RASA1	chr5:86564256	1.06	0.56
ERAP1	chr5:96112128	1.07	0.56

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ERAP2	chr5:96219500	0.79	0.43
HLA-A	chr6:29910229	0.86	0.46
HLA-B	chr6:31322252	0.6	0.34
NOTCH4	chr6:32163187	1	0.52
TAP2	chr6:32796585	1.05	0.55
TAP1	chr6:32814849	0.95	0.5
DAXX	chr6:33286486	1.12	0.58
CSMD3	chr8:113237020	0.86	0.46
LARP4B	chr10:858847	1.01	0.53
GATA3	chr10:8097519	0.93	0.49
WT1	chr11:32410528	0.99	0.52
TPP2	chr13:103249399	0.99	0.52
DICER1	chr14:95556791	1.08	0.57
CYLD	chr16:50783549	1.09	0.57
CBFB	chr16:67063242	0.94	0.5
CTCF	chr16:67644720	1	0.52
CDH1	chr16:68771249	1.13	0.59
ZFHX3	chr16:72820995	0.94	0.5
GPS2	chr17:7216071	1.2	0.62
RUNX1	chr21:36164357	1.18	0.61
MYCL	chr1:40362966	1.14	0.59
MPL	chr1:43803495	1.17	0.61
MAGOH	chr1:53692690	1.12	0.58
NRAS	chr1:115251152	1.09	0.57
ERBB4	chr2:212248561	1.04	0.55
MITF	chr3:69788729	1.05	0.55
BCL6	chr3:187440209	0.98	0.51
FGFR3	chr4:1801456	0.78	0.42
DDR1	chr6:30852922	1.17	0.61
FGFR1	chr8:38271452	0.98	0.52
RUNX1T1	chr8:92982878	0.76	0.41
NTRK2	chr9:87549097	1.16	0.6
HRAS	chr11:532637	0.76	0.41
FGF9	chr13:22245989	1.06	0.55

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
FLT3	chr13:28578185	1.01	0.53
AKT1	chr14:105236628	0.66	0.37

Biomarker Descriptions

PIK3CA amplification, PIK3CA p.(C420R) c.1258T>C

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[188]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[189,190]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[189]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[191,192]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[191,192,193,194]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[195,196,197].

Alterations and prevalence: Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[198,199]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[200,201,202]. Somatic mutations in PIK3CA are observed in 50% of uterine corpus endometrial carcinoma, 35% of uterine carcinosarcoma, 32% of breast invasive carcinoma, 29% of cervical squamous cell carcinoma, 28% of colorectal adenocarcinoma, 22% of bladder urothelial carcinoma, 17% of head and neck squamous cell carcinoma, 16% of stomach adenocarcinoma, 11% of lung squamous cell carcinoma, 9% of esophageal adenocarcinoma, 8% of brain lower grade glioma, 6% of cholangiocarcinoma, 5% of skin cutaneous melanoma and lung adenocarcinoma, 4% of liver hepatocellular carcinoma, 3% of pancreatic adenocarcinoma and sarcoma, and 2% of mesothelioma, prostate adenocarcinoma, testicular germ cell tumors, and ovarian serous cystadenocarcinoma[4,5]. PIK3CA is amplified in 38% of lung squamous cell carcinoma, 20% of ovarian serous cystadenocarcinoma, 18% of esophageal adenocarcinoma, 16% of head and neck squamous cell carcinoma, 15% of cervical squamous cell carcinoma, 11% of uterine carcinosarcoma, 7% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma, 4% of bladder urothelial carcinoma, 3% of breast invasive carcinoma and pancreatic adenocarcinoma, and 2% of prostate adenocarcinoma, lung adenocarcinoma, and kidney renal clear cell carcinoma[4,5]. Alterations in PIK3CA are also observed in pediatric cancers[5]. Somatic mutations in PIK3CA are observed in 6% of non-Hodgkin Lymphoma (1 in 17 cases), 4% of glioma (11 in 297 cases), 3% of soft tissue sarcoma (1 in 38 patients), 2% of embryonal tumors (6 in 332 cases), 1% of leukemia (5 in 354 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), and peripheral nervous system tumors (1 in 1158 cases)[5].

Potential relevance: The PI3K inhibitor, alpelisib[203], is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations[204]. However, alpelisib did not improve response when administered with letrozole in patients with ER + early breast cancer with PIK3CA mutations[205]. The FDA also approved the kinase inhibitor, capivasertib (2023)[206] in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib[207], is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[208,209]. In colorectal cancers, PIK3CA mutations predict significantly improved survival and reduced disease recurrence with adjuvant aspirin therapy, compared to no benefit in wild-type PIK3CA tumors[173,182,210,211]. In 2025, the FDA granted fast track designation to the PI3Kα inhibitor and degrader, ETX-636[212], for the treatment of PIK3CA-mutant, HR-positive/HER-negative advanced breast cancer.

Biomarker Descriptions (continued)

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[57,58]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[57,58]. 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[59,60,61]. 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%[59,62].

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[63,64,65,66,67,68,69,70]. 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)[71]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[72,73]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[74] (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[74] 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[75] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[48] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[48] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA2. Niraparib[76] (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[77] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib[78] received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[79]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[80]. 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[31], 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.

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[327,328]. 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[328].

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[328,329]. 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,

Biomarker Descriptions (continued)

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)[262]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[263,264,265]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[266]. 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[1,266,267]. CDKN2A aberrations commonly co-occur with CDKN2B[262]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[268]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[269,270].

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[271]. 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[272,273,274]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[275]. 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[276,277,278]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[279]. 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[280,281,282,283].

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[1,111]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[106,111]. 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[106]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[106,112]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[111]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[111].

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[112]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[111]. Somatic mutations in ARID1A have been identified in several cancers including 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[4,5,106]. 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[113]. Biallelic deletion of ARID1A is observed in 3% of cholangiocarcinoma and stomach adenocarcinoma, and 2% of pheochromocytoma and paraganglioma[4,5].

Biomarker Descriptions (continued)

Alterations in ARID1A are also observed in pediatric cancers[5]. Somatic mutations in ARID1A are observed in 12% of non-Hodgkin lymphoma (2 in 17 cases), 8% of Hodgkin lymphoma (5 in 61 cases), 5% of T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of embryonal tumors (5 in 332 cases), 1% of glioma (4 in 297 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and peripheral nervous system tumors (2 in 1158 cases)[5]. Biallelic deletion of ARID1A is observed in 2% of peripheral nervous system cancers (2 in 91 cases), 1% of leukemia (3 in 250 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[5].

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[114], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[115], 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.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,262]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[262]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[263,264,265]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[262]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,288,289].

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

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma[275].

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer[118]. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[118,119]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[120]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[118,119,121]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[122].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in 20% of bladder urothelial carcinoma, 13% of uterine corpus endometrial carcinoma, and 10% of sarcoma and glioblastoma multiforme[4,5]. Biallelic loss of RB1 is also observed in several cancers including 15% of sarcoma, 10% of prostate adenocarciona, 9% of uterine carcinosarcoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma, 5% of liver hepatocellular carcinoma and adrenocortical carcinoma, and 4% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[4,5]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[123,124,125]. Alterations in RB1 are also observed in pediatric cancers[5]. Somatic mutations in RB1 are observed in 52% of retinoblastoma (16 in 31 cases), 3% of bone cancer (10 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (2 in 311 cases)[5]. Biallelic deletion of RB1 is observed in 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (28 in 731 cases), 3% of leukemia (7 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[5]. Structural variants in RB1 are observed in 3% of bone cancer (5 in 150 cases)[5].

Biomarker Descriptions (continued)

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

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[298]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[298]. 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[299,300,301,302,303,304].

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[1,147]. 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[1,147,148,149]. 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[1,148,150,151]. 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[139,151]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[150]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[152]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[152,153].

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[74] 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[31], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FANCA deletion

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, 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[86,87]. 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[86]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[88,89]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[45,90]. 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[91,92]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[87,92,93,94,95].

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

Biomarker Descriptions (continued)

Potential relevance: The PARP inhibitor, talazoparib[48] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[96,97]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[95].

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[86,87]. 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[86]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[88,89]. Loss of function mutations in the FA family and HRR pathway, including FANCF, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[45,90]. 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[91,92].

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[1,154]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes[155]. 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[154,155,156,157,158,159,160].

Alterations and prevalence: Somatic mutations in FBXW7 occur at high frequencies in various malignancies, including 39% of uterine carcinosarcoma, 19% of uterine corpus endometrial carcinoma, 17% of colorectal adenocarcinoma, 12% of cervical squamous cell carcinoma, 8% of stomach adenocarcinoma and bladder urothelial carcinoma, 6% of head and neck squamous cell carcinoma and esophageal adenocarcinoma, 4% of lung squamous cell carcinoma and skin cutaneous melanoma, 3% of pancreatic adenocarcinoma, and 2% of lung adenocarcinoma and breast invasive carcinoma[4,5,161,162,163]. Biallelic deletion is observed in 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and brain lower grade glioma[4,5]. Alterations in FBXW7 are also observed in pediatric cancers[5]. Somatic mutations in FBXW7 are observed in 15% of T-lymphoblastic leukemia/lymphoma (6 in 41 cases), 2% of embryonal tumor (5 in 332 cases), and less than 1% of glioma (2 in 297 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and bone cancer (1 in 327 cases)[5]. Biallelic deletion of FBXW7 is observed in 2% of B-lymphoblastic leukemia/lymphoma (12 in 731 cases) and less than 1% of leukemia (2 in 250 cases)[5].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[164], 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[161]. 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[165].

NBN deletion

nibrin

Background: The NBN gene encodes nibrin, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) protein complex, which is necessary for the maintenance of genomic stability[39,40]. The MRN complex is involved in repair of double-stranded breaks (DSB) by homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[41,42,43]. Specifically, NBN contains a nuclear localization signaling motif responsible for translocation of the MRN complex into the nucleus and contributes to DNA repair by mediating protein-protein interactions at the site of DNA damage[39]. NBN is a tumor suppressor gene. Loss of function mutations in NBN are implicated in the BRCAness phenotype, which is characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2

Biomarker Descriptions (continued)

loss[44,45]. Germline mutations in NBN are associated with Nijmegen breakage syndrome, an autosomal recessive disorder resulting in microcephaly at birth, immunodeficiency, radiosensitivity, and cancer predisposition[46,47].

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

Potential relevance: The PARP inhibitor, talazoparib[48] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Loss of function mutations in one or more HRR genes, including NBN, may confer sensitivity to platinum agents and PARP inhibitors[44,45,49]. NBN overexpression has been shown to be associated with poor prognosis in uveal melanoma, head and neck cancer, and ovarian cancer[50,51,52,53].

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[139,140]. 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[139]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[139]. 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[139,141].

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.

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[263,264,265]. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer[290].

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[291,292,293].

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

CUL4A deletion

cullin 4A

Background: The CUL4A gene encodes cullin 4A, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4b, CUL5, CUL7, and Parc[1,14]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[18]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[18,19]. 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)[14]. CUL4A is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[19]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4A in oncogenesis[18,19].

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

Biomarker Descriptions (continued)

squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[4,5]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[4,5].

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

JAK1 deletion

Janus kinase 1

Background: The JAK1 gene encodes Janus kinase 1, a non-receptor protein tyrosine kinase (PTK)[1,454]. JAK1 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[455]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[455]. 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[455,456,457]. 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[457,458,459].

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[460,461,462]. 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[461]. Recurrent activating mutations in JAK1 are infrequently observed in solid cancers, although two variants, S703I and S729C, were reported in hepatocellular carcinomas[463,464,465]. 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[4,5,457]. Recurrent truncating mutations in JAK1 are also associated with high tumor mutation burden (TMB) and microsatellite instability (MSI)[458,459]. 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[466] is a JAK1/2 inhibitor that is FDA approved (2011) for primary myelofibrosis and polycythemia vera. Other JAK inhibitors, including tofacitinib (2012) and baricitinib (2018), are approved for rheumatoid arthritis. JAK1 mutations and fusions confer poor risk in B-cell ALL[236]. Clinical cases associated with high TMB but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[467].

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2[1]. LATS2 is a serine/threonine protein kinase and, along with LATS1, is a member of the AGC kinase family comprised of more than 60 members[358,359]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[360]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[360]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[361].

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

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

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[342]. Activation of MAPK proteins occurs through a kinase signaling cascade[342,343,344]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[342,343,344]. 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[342,343,344]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[345].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[4,5]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[4,5]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[346,347].

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

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7[1]. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10[342,344,375]. Activation of MAPK proteins occurs through a kinase signaling cascade[342,343,344]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[342,343,344]. 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[342,343,344].

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma[4,5]. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[1]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[33]. MLH3 is considered a mismatch repair (MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[33,34,35]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[36].

Alterations and prevalence: Somatic mutations in MLH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, skin cutaneous melanoma, and stomach adenocarcinoma[4,5]. Biallelic deletions are observed in 2% of kidney chromophobe[4,5].

Potential relevance: Currently, no therapies are approved for MLH3 aberrations.

MSH3 deletion

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[1]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[33,37]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[33,37]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[38].

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[54]. 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-

Biomarker Descriptions (continued)

formamidopyrimidine)[54]. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer[55,56].

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[166]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[167,168]. 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[169]. 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[170]. 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)[170]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[171,172,173,174,175]. 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[168]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[167,168,172,176].

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[167,168,177,178]. 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[177,178].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[179] (2014) and nivolumab[180] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[179] 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[179]. Dostarlimab[181] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[173,182]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[183] (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[173,184,185]. 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[185]. 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[186,187]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[186,187].

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[98]. 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[98,99]. PARP enzymes are involved in several DNA repair pathways[98,99]. 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)[100,101]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[100].

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[102,103].

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[74] (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[74] 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[75] (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[48] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[76] (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.

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein[1]. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3[98]. 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[98,99]. PARP enzymes are involved in several DNA repair pathways[98,99]. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins[366].

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

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (HRR) deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[102,103]. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[74] (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[74] 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[75] (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[48] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[76] (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

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[310]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[310]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[310]. 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[191,192]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[191,192,193,194]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[311]. 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[310].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 10% of glioblastoma multiforme, 6% of colorectal adenocarcinoma, 4% of brain lower grade glioma, and skin cutaneous melanoma, 3% of cervical squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, and breast invasive carcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial

Biomarker Descriptions (continued)

carcinoma, esophageal adenocarcinoma, thymoma, head and neck squamous cell carcinoma, and kidney chromophobe[4,5]. Additionally, biallelic loss of PIK3R1 is observed in 4% of prostate adenocarcinoma and 3% of ovarian serous cystadenocarcinoma[4,5]. Alterations in PIK3R1 are also observed in pediatric cancers[5]. Somatic mutations in PIK3R1 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 leukemia (7 in 354 cases), 1% of glioma (3 in 297 cases) and bone cancer (3 in 327 cases), and less than 1% of embryonal tumors (2 in 332 cases) and peripheral nervous system tumors (1 in 1158 cases)[5]. Biallelic deletion of PIK3R1 is observed in 3% of leukemia (8 of 250 cases) and in less than 1% of B-lymphoblastic leukemia/lymphoma (4 of 731 cases), while structural alterations in PIK3R1 occur in fewer than 1% of leukemia (1 of 107 cases)[5].

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

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[26,27]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[28]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[26].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[26,27,29,30]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[4].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[31], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[26]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[32].

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[134]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[135]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[136]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[44,45]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[137]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[138].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[4,5]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[138].

Potential relevance: The PARP inhibitor, olaparib[74] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[31], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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[142]. 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[142,143,144]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven

Biomarker Descriptions (continued)

conserved sequence motifs for identifying helicases[142,145]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[146]. 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[44].

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

Potential relevance: The PARP inhibitor, olaparib[74] 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[31], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[372,373]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[372]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[372].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[4,5]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[4,5].

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

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[374]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[374]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[374].

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

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

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[82,83]. 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[82,83]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[84]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[82,83]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,85].

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

Biomarker Descriptions (continued)

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)[404,405]. 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[406]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[407,408]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[405]. 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)[409]. 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[405,410].

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[4,410,411]. 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[4,404]. 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[404]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[404].

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)[130].

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression[213]. STK11 preserves hematopoietic stem cell homeostasis, and its loss drives metabolic dysfunction and promotes leukemic progression in myeloproliferative neoplasms via ROS and HIF-1α activation[214,215]. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development[216,217].

Alterations and prevalence: Somatic mutations in STK11 are observed in 13% of lung adenocarcinoma, 4% of cervical squamous cell carcinoma, 3% of cholangiocarcinoma and uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, pancreatic adenocarcinoma, adrenocortical carcinoma, and esophageal adenocarcinoma[4,5,218,219]. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer[4,5]. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others[4,5,216,219,220]. Biallelic loss of STK11 is observed in 3% of sarcoma, cervical squamous cell carcinoma, and ovarian serous cystadenocarcinoma[4,5]. Alterations in STK11 are also observed in pediatric cancers[221]. Biallelic loss of STK11 is observed in 6% of B-lymphoblastic leukemia/lymphoma (45 in 731 cases), 2% of leukemia (4 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[221]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and glioma (1 in 297 cases)[221].

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260[222] in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors[223]. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)[224].

Biomarker Descriptions (continued)

TP53 deletion, TP53 p.(Q144*) c.430C>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[428]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[429]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[430,431].

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%)[4,5,218,432,433,434]. 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[435,436,437,438]. 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[439] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[440,441]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[442]. 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)[235,236,239,325,443]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[307]. 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[444].

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[1,139]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[139,247]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[248].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[4,5]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[248].

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[305]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[305]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[305,306]. 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[305]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[306].

Biomarker Descriptions (continued)

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[307]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[308,309].

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,419]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[419,420]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[419,421]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[419,422,423,424,425]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[419,422,423,426,427].

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)[1,362]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[362]. 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[362,363,364]. 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[362,363,365]. 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[362,363].

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[1,284]. 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[285,286]. 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[284,287].

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].

Biomarker Descriptions (continued)

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

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[399,400,401]. 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[399,401]. 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[402,403].

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[104,105]. 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[105]. 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[104,105].

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.

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[1,261]. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of transcription, translation, and splicing[261]. FUBP1 activates the transcription of targets including the oncogene MYC which functions in cell cycle regulation, metabolism, and apoptosis[261]. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation[261].

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[261]. 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[261].

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

Biomarker Descriptions (continued)

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.

NOTCH2 deletion

notch 2

Background: The NOTCH2 gene encodes the notch receptor 2 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[249]. 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[250,251]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[252,253,254,255].

Alterations and prevalence: Somatic mutations observed in NOTCH2 are primarily missense or truncating and are found in about 11% of uterine cancer, 6% of melanoma and stomach cancer, as well as 3-5% diffuse large B-cell lymphoma (DLBCL), lung, colorectal, bladder, cervical, and head and neck cancers[4].

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

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[1,14]. 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)[14]. CRLs are involved in diverse biological processes including cell cycle control, DNA replication and repair, and chromatin remodeling[15]. CUL3 is part of the CRL3 complex which is responsible for ubiquitination and degradation of a variety of substrates[15,16,17]. Substrate specificity is dependent on the proteins recruited by CUL3 that have BTB domains, such as KEAP1 and SPOP[15,16,17]. 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[17].

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.

Biomarker Descriptions (continued)

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[294]. 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[295]. PDCD1 is expressed in a variety of hematopoietic cells, immune cells, tumor cells, and tumor specific T-cells[294,296]. 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[294]. 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[294,296].

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[297]. Although not approved for specific PDCD1 aberrations, approved checkpoint inhibitors targeting PDCD1 include the monoclonal antibodies pembrolizumab, nivolumab, and cemiplimab[294].

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[445]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,446,447]. 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[448,449]. 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[447].

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[106]. 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[106,107]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[106,108]. 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[109,110].

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.

Biomarker Descriptions (continued)

MECOM amplification

MDS1 and EVI1 complex locus

Background: The MECOM gene encodes the MDS1 and EVI1 complex locus (MECOM), a zinc-finger transcriptional factor that regulates hematopoietic cell differentiation[376]. The MECOM locus encodes multiple alternative splice variants that result in MDS1-EVI1, MDS1, and EVI1 protein isoforms[377]. The EVI1 isoform is the most abundant and oncogenic form of MECOM that is expressed in various cancers including acute myeloid leukemia (AML)[377,378]. MECOM is a frequent target of chromosomal translocation which can lead to MECOM overexpression and leukemogenesis[379].

Alterations and prevalence: Somatic mutations MECOM are observed in up to 22% of malignant melanoma; 75% of these mutations are missense and the remaining 25% are truncating mutations[4,5,380]. MECOM amplifications are observed in up to 35% of lung squamous cell carcinoma, 30% of ovarian serous cystadenocarcinoma, and 20% of esophageal adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[4,5]. MECOM rearrangements occur with various partner genes including ETV6, RUNX1, and H2AFY[381]. The t(3;21)(q26;q22) translocation that results in the MECOM::RUNX1 fusion is most commonly observed in chronic myeloid leukemia (CML) in blast crisis. The t(3;3)(q21.3;q26.2)/ inv(3)(q21.3;q26.3) translocation, also referred to as inv(3)/t(3;3), results in a GATA2::MECOM fusion and is observed in AML, primary myelofibrosis (PMF), and myelodysplastic syndrome (MDS)[239,325,371]. The inv(3)/t(3;3) translocation repositions the distal GATA enhancer element and activates MECOM expression while simultaneously causing GATA2 haploinsufficiency[382].

Potential relevance: AML with MECOM rearrangement is considered a distinct molecular subtype of AML as defined by the World Health Organization (WHO)[234]. MECOM rearrangements, including GATA2::MECOM fusions, are associated with poor/adverse risk in AML[235,371]. Inv(3) is associated with poor cytogenetic risk in MDS as defined by the revised international prognostic scoring system (IPSS-R) scoring system[239]. In PMF, inv(3) is considered an unfavorable karyotype associated with intermediate risk as defined by the dynamic international prognostic scoring system (DIPSS)-Plus scoring system[325]. MECOM overexpression is observed in 10% of de novo AML associated with poor prognosis, and is commonly found in MLL-rearranged cases[383,384]. Amplification of MECOM is associated with favorable prognosis in ovarian cancer[385].

TP63 deletion

tumor protein p63

Background: The TP63 gene encodes tumor protein p63, a member of the p53 family of transcription factors that regulates cancer development and progression[1]. TP63 transcription generates two N-terminally different isoforms, a full-length TAp63 containing the N-terminal transactivation domain and ΔNp63 with a truncated N-terminal domain[126]. Consistent with a tumor suppressor, TAp63 induces cell cycle arrest and apoptosis, while ΔNp63 functions more like an oncogene by governing epithelial morphogenesis by maintaining the self-renewing capacity of progenitor cells[126,127]. Amplification of chromosomal region 3q26-3qter is the most common genetic alteration identified in squamous cell carcinoma (SCC), with the most frequent amplified region being 3q26-3q28, where p63 resides[128]. Consequently, p63 is found to be overexpressed in SCC, with ΔNp63α being the predominantly expressed isoform[129].

Alterations and prevalence: Somatic mutations in TP63 are predominantly missense or truncating and occur in 18% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma and stomach adenocarcinoma, 3% of cervical squamous cell carcinoma, kidney chromophobe, and colorectal adenocarcinoma, and 2% of lung adenocarcinoma, head and neck squamous cell carcinoma, lung squamous cell carcinoma, and glioblastoma multiforme[4,5]. Amplification of TP63 is observed in 32% of lung squamous cell carcinoma, 20% of esophageal adenocarcinoma, 16% of cervical squamous cell carcinoma, ovarian serous cystadenocarcinoma and head and neck squamous cell carcinoma, 11% of uterine carcinosarcoma, 6% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, 3% of bladder urothelial carcinoma, and 2% of lung adenocarcinoma, testicular germ cell tumors, breast invasive carcinoma, pancreatic adenocarcinoma, and sarcoma[4,5]. Biallelic deletion of TP63 is observed in 1% of prostate adenocarcinoma, lung adenocarcinoma, and brain lower grade glioma[4,5]. Alterations in TP63 are also observed in pediatric cancers[5]. Somatic mutations in TP63 are observed in 3% of soft tissue sarcoma (1 in 38 cases) and less than 1% of bone cancer (2 in 327 cases), embryonal tumors (2 in 332 cases), and glioma (1 in 297 cases)[5]. TP63 is amplified in less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[5]. Biallelic deletion of TP63 is observed in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases) and leukemia (1 in 250 cases)[5].

Potential relevance: Currently, no therapies are approved for TP63 aberrations. TBL1XR1::TP63 fusion is considered a diagnostic marker for ALK-negative anaplastic large cell lymphoma[130].

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[1,319]. The TET enzymes are involved in DNA demethylation, specifically in the conversion of 5-

Biomarker Descriptions (continued)

methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[320,321]. 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)[320,321]. 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[320,321]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[319,322,323].

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)[239]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[322,324]. 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 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[325]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[326]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[130].

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[1,450]. 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[451]. 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[452,453].

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.

FAT1 deletion

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,318]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[318]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[318]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[318]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[318].

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

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for FAT1 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[342,343,344]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[342,343,344]. 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[342,343,344]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[386]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[386]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[386].

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[386]. 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[116,117]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[116]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[116]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[116]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[116].

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[387,388]. 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[387,389]. 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[387,390,391]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[387,392].

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[387,388]. 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[387,389]. 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[387].

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[336]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[337]. 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[338,339,340]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[341].

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[336]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[337]. 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[338,339,340]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[341].

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[249]. 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[250,251]. 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[252,253,254,255].

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[241,242]. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression[245,246].

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[241,242]. TAP1 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression and survival[243,244,245].

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[22]. 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[23,24].

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[25].

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

Biomarker Descriptions (continued)

CSMD3 deletion

CUB and Sushi multiple domains 3

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2[1,6]. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the transmembrane and extracellular proteins[6,7]. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation[6,7]. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)[6,8].

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma, 19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma[4,5]. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma[4,5]. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

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[20]. 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[20]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[21].

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 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[1,256,257]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[257]. GATA3 functions in the differentiation of immune cells and tissue development[258,259]. 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[258].

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[258,260].

Biomarker Descriptions (continued)

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[312,313]. 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[314]. 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[312]. WT1 interacts with various genes including TP53, STAT3, and epigenetic modifiers such as TET2 and TET3[312,315]. WT1 is primarily characterized as a tumor suppressor gene involved in the development of renal Wilm's tumor (WT), a rare pediatric kidney cancer[312,316]. 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[312]. WT1 overexpression is observed in acute myeloid leukemia (AML) and lymphoid cancers[312,317].

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)[312]

Potential relevance: Somatic mutations in WT1, including nonsense, frameshift, and splice-site mutations, are associated with poor prognosis in MDS[239]. 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[315].

TPP2 deletion

tripeptidyl peptidase 2

Background: The TPP2 gene encodes the tripeptidyl peptidase 2[1]. TPP2 is a serine peptidase that becomes activated upon homopolymer complex formation[81]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[81]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[81].

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

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

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[330]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[330,331]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[330]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[330,331]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[331,332,333,334]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[335].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[4,5], 3% of lung squamous cell carcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, and stomach adenocarcinoma, and 2% of head and neck squamous cell carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, kidney chromophobe, and glioblastoma multiforme[5]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% of kidney chromophobe[4,5]. Alterations in DICER1 are also observed in pediatric cancers[5]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases), 1% of glioma (4 in 297 cases), and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), peripheral nervous system cancers (2 in 1158 cases), and Wilms tumor (1 in 710 cases)[5]. Biallelic deletion of DICER1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for DICER1 aberrations.

Biomarker Descriptions (continued)

CYLD deletion

CYLD lysine 63 deubiquitinase

Background: The CYLD gene encodes CYLD lysine 63 deubiquitinase, which is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) family of deubiquitinases[1,9]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[10]. CLYD contains a USP domain with a catalytic triad formed by Cys601, His871, and Asp889 that selectively hydrolyses K63-linked ubiquitin chains from signaling molecules and regulates cell survival, proliferation, and tumorigenesis[11,12]. CYLD plays a tumor suppressor role by negatively regulating NF-κB activation by deubiquitinating multiple NF-κB signaling components, including NEMO, Tak1, TRAF2, TRAF6, and RIP1[13]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[12,13]. CYLD has also been found to be downregulated in melanoma, salivary gland tumors, head and neck cancer, colon and hepatocellular carcinoma, cervical cancer, lung cancer, and renal cell carcinoma[12].

Alterations and prevalence: Somatic mutations in CYLD have been observed in 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of thymoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[4,5]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[4,5].

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

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[1]. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CFB) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis[367,368,369]. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation[368,369]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[369]

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma[4]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[4]. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with bone barrow eosinophilia (M4Eo) subtype[370]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[370].

Potential relevance: Currently, no therapies are approved for CBFB aberrations. In AML, CBFB translocations, including inv(16) and t(16;16) which result in CBFB::MYH11 fusion, are associated with favorable prognosis and define a distinct molecular subtype of AML according to the World Health Organization (WHO)[234,235,371].

CTCF deletion

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[131]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[131,132,133]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[131].

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

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

Biomarker Descriptions (continued)

CDH1 deletion

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,412]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[413]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[414,415]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[416].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[4,5,417,418]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[4,5]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[4,5].

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

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,348,349]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[349,350]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[351,352,353,354,355]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[351,354,356,357].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[4,5]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[4,5].

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

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[393]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[393,394]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[395,396,397].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[4,5]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[4,5,398]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[398].

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

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[225]. 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[226]. Each of these proteins interacts with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex[226]. 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[227]. 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[228,229]. RUNX1 is frequently mutated in various hematological malignancies[229]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML)[230,231]. 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)[229].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[232]. 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[199]. 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[199,229]. Another translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 2% of adult ALL[233]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[229]. 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[4,5,229]. 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[221,233]. 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)[234]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1, is associated with favorable risk in AML[235]. 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[236,237,238]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[235,239,240].

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1,

Genes Assayed (continued)

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

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

PIK3CA p.(C420R) c.1258T>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✖
capivasertib + fulvestrant	○	○	○	✖	✖

* 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

PIK3CA p.(C420R) c.1258T>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
inavolisib + palbociclib + fulvestrant	○	○	○	✖	✖
ETX-636	✖	✖	✖	✖	● (I/II)
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (I)

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*
MRTX-1719, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II/III)
AMG 193	✖	✖	✖	✖	● (II)
CTS-3497	✖	✖	✖	✖	● (I/II)
IDE397	✖	✖	✖	✖	● (I/II)
PH020-803	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462, pembrolizumab	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)
AMG 193, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (I)
GH-56	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
HSK-41959	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

MTAP deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
S-095035, TNG-462	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

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

ARID1A deletion

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

CDKN2B deletion

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

PIK3CA amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, gedatolisib	✖	✖	✖	✖	● (I)
TOS-358	✖	✖	✖	✖	● (I)

RB1 deletion

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

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

Relevant Therapy Summary (continued)

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

RB1 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CID-078	✖	✖	✖	✖	● (I)

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)

FANCA deletion

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

FANCF deletion

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

FBXW7 deletion

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

NBN 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	***40.56%***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***
BARD1	***CNV, CN:1.0***
BARD1	***LOH, 2q35(215593375-215674382)x1***
BRIP1	***SNV, S1115C, AF:0.42***
RAD51B	***CNV, CN:1.0***
RAD51B	***LOH, 14q24.1(68290164-69061406)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 (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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