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Patient Name: 이연섭
Gender: F
Sample ID: N25-300

Primary Tumor Site: Ovary
Collection Date: 2025.10.23.

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	***8.54 Mut/Mb measured***
Genomic Instability	***GIM 23 (High)***

HRD Status: ***HR Deficient (HRD+)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Genomic Instability* GIM 23 (High)	**bevacizumab + olaparib** [1, 2 / II+] **niraparib** [1 / II+]	None*	15
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib [II+] olaparib [II+] rucaparib [II+]	1
IIC	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	2

*** 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	*ARID1A deletion* AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	1
IIC	*BRCA1 deletion* BRCA1, DNA repair associated Locus: chr17:41197602	None*	None*	1
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	1
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	1
IIC	*TP53 deletion* tumor protein p53 Locus: chr17:7572848	None*	None*	1

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

Alerts informed by public data sources: ⊘ Contraindicated, Resistance, Breakthrough, Fast Track

Genomic Instability	**pidnarulex** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

*ABRAXAS1 deletion, ARID1B deletion, AXIN1 deletion, AXIN2 deletion, BARD1 deletion, BRIP1 deletion, CDK12 deletion, CDKN1B deletion, CHEK2 deletion, CREBBP deletion, CUL4A deletion, ERCC2 deletion, FANCA deletion, LATS1 deletion, LATS2 deletion, MAP2K4 deletion, NF1 deletion, NF2 p.(A448Pfs*7) c.1342delG, PARP4 deletion, PIK3R1 deletion, PMS2 deletion, POLD1 deletion, PPP2R2A deletion, PTCH1 p.(L62Gfs*27) c.184_185delCT, RAD51C deletion, RAD51D deletion, RAD52 deletion, RNASEH2B deletion, RPA1 deletion, SDHB deletion, SLX4 deletion, TP53 p.(L265P) c.794T>C, TSC1 deletion, TSC2 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, DNMT3A deletion, ASXL2 deletion, ACVR2A deletion, CASP8 deletion, BMPR2 deletion, CUL3 deletion, TET2 deletion, MAP3K1 deletion, RASA1 deletion, ADAMTS2 deletion, HDAC2 deletion, TNFAIP3 deletion, MAP3K4 deletion, HDAC9 deletion, NOTCH1 deletion, ETV6 deletion, TPP2 deletion, CBFB deletion, CTCF deletion, CDH1 deletion, ZFHX3 deletion, GPS2 deletion, NCOR1 deletion, SPOP deletion, RNF43 deletion, PPM1D deletion, PRKAR1A deletion, CIC deletion, ARHGAP35 deletion, EP300 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NF2	p.(A448Pfs*7)	c.1342delG	.	chr22:30070823	55.91%	NM_000268.4	frameshift Deletion
PTCH1	p.(L62Gfs*27)	c.184_185delCT	.	chr9:98270458	31.53%	NM_000264.5	frameshift Deletion
TP53	p.(L265P)	c.794T>C	.	chr17:7577144	53.62%	NM_000546.6	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PBRM1	p.(L526F)	c.1578A>C	.	chr3:52651518	34.33%	NM_018313.5	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGC GGCCGCAGCGGC	.	chr5:79950707	52.11%	NM_002439.5	nonframeshift Deletion
HLA-B	p.(E176T)	c.526_527delGAinsAC	.	chr6:31324036	5.02%	NM_005514.8	missense
PTCH1	p.(F60S)	c.179T>C	.	chr9:98270465	32.68%	NM_000264.5	missense
WT1	p.(S69C)	c.206C>G	.	chr11:32456701	37.25%	NM_024426.6	missense
CBL	p.(H398Q)	c.1194C>A	.	chr11:119148974	6.67%	NM_005188.4	missense
PDIA3	p.(E334D)	c.1002G>C	.	chr15:44059082	37.67%	NM_005313.5	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.64
SMARCB1	chr22:24129273	1.08	0.65
ARID1A	chr1:27022875	1.11	0.66
BRCA1	chr17:41197602	1	0.67
NF2	chr22:29999923	1.07	0.64
RB1	chr13:48877953	1.07	0.64
TP53	chr17:7572848	1.14	0.67
ABRAXAS1	chr4:84383635	1.08	0.65
ARID1B	chr6:157099057	1.05	0.64
AXIN1	chr16:338145	1.08	0.65
AXIN2	chr17:63526027	0.99	0.61
BARD1	chr2:215593375	1	0.63
BRIP1	chr17:59760627	1	0.64
CDK12	chr17:37618286	1	0.61
CDKN1B	chr12:12870763	0.79	0.54
CHEK2	chr22:29083868	1	0.65
CREBBP	chr16:3777679	0.96	0.61
CUL4A	chr13:113863977	1.04	0.64
ERCC2	chr19:45854865	1.12	0.67
FANCA	chr16:89804984	1.07	0.65
LATS1	chr6:149982844	1.09	0.66
LATS2	chr13:21548922	1.05	0.64
MAP2K4	chr17:11924164	1.11	0.66

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
NF1	chr17:29422233	1.01	0.63
PARP4	chr13:25000551	0.95	0.6
PIK3R1	chr5:67522468	1.04	0.64
PMS2	chr7:6012922	0.96	0.61
POLD1	chr19:50902079	1.09	0.65
PPP2R2A	chr8:26149298	1.08	0.65
RAD51C	chr17:56769933	1	0.7
RAD51D	chr17:33427950	1	0.7
RAD52	chr12:1022494	0.95	0.6
RNASEH2B	chr13:51484145	0.96	0.61
RPA1	chr17:1733385	1.04	0.63
SDHB	chr1:17345303	1.13	0.67
SLX4	chr16:3632292	1.07	0.64
TSC1	chr9:135771600	1.03	0.63
TSC2	chr16:2098579	1.01	0.63
TNFRSF14	chr1:2488070	1.13	0.67
ERRFI1	chr1:8073246	1.05	0.64
ENO1	chr1:8921399	1.03	0.63
PGD	chr1:10459132	1.03	0.63
SPEN	chr1:16174516	1.04	0.64
EPHA2	chr1:16451707	1.17	0.68
DNMT3A	chr2:25457069	0.96	0.6
ASXL2	chr2:25964858	0.99	0.62
ACVR2A	chr2:148602708	1.09	0.65
CASP8	chr2:202122934	1.01	0.62
BMPR2	chr2:203329535	1.05	0.64
CUL3	chr2:225338933	1.04	0.63
TET2	chr4:106155068	1.03	0.63
MAP3K1	chr5:56111388	1.05	0.64
RASA1	chr5:86564256	1.03	0.63
ADAMTS2	chr5:178549645	1.05	0.64
HDAC2	chr6:114262171	0.91	0.58
TNFAIP3	chr6:138192315	1.05	0.64
MAP3K4	chr6:161412931	1.09	0.66

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
HDAC9	chr7:18201905	0.92	0.59
NOTCH1	chr9:139390441	0.89	0.58
ETV6	chr12:11803059	0.95	0.6
TPP2	chr13:103249399	0.95	0.6
CBFB	chr16:67063242	0.86	0.57
CTCF	chr16:67644720	0.95	0.6
CDH1	chr16:68771249	1.04	0.64
ZFHX3	chr16:72820995	0.93	0.6
GPS2	chr17:7216071	1	0.62
NCOR1	chr17:15935586	0.97	0.61
SPOP	chr17:47677716	1	0.62
RNF43	chr17:56432226	1.08	0.65
PPM1D	chr17:58677747	1.01	0.63
PRKAR1A	chr17:66511464	0.97	0.61
CIC	chr19:42775916	0.05	0.26
ARHGAP35	chr19:47421913	0.96	0.6
EP300	chr22:41489001	1.03	0.63
BARD1	chr2:215593375	1	0.63
ATM	chr11:108098341	3	1.33
BRCA2	chr13:32890491	1	0.64
RAD51D	chr17:33427950	1	0.7
CDK12	chr17:37618286	1	0.61
BRCA1	chr17:41197602	1	0.67
RAD51C	chr17:56769933	1	0.7
BRIP1	chr17:59760627	1	0.64
CHEK2	chr22:29083868	1	0.65
MYCN	chr2:16082167	1.04	0.64
ALK	chr2:29416263	1.17	0.69
SF3B1	chr2:198256951	1.08	0.65
CTLA4	chr2:204732664	1.05	0.64
ERBB4	chr2:212248561	1.11	0.66
FLT4	chr5:180030092	1.08	0.65
FYN	chr6:111982890	1.01	0.62
ROS1	chr6:117622071	1.18	0.69

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ESR1	chr6:152163831	1.04	0.63
CARD11	chr7:2949684	1.12	0.66
RAC1	chr7:6426823	1.11	0.66
GLI3	chr7:42003880	1.01	0.63
FGFR1	chr8:38271452	1.13	0.67
FGFR2	chr10:123239426	1.12	0.66
HRAS	chr11:532637	0.89	0.58
CCND2	chr12:4383227	0.96	0.6
FGF23	chr12:4479456	1	0.62
CHD4	chr12:6692405	1.12	0.67
FGF9	chr13:22245989	1.03	0.63
FLT3	chr13:28578185	1.2	0.69
RARA	chr17:38487425	1.07	0.64
STAT5B	chr17:40354722	0.92	0.59
STAT3	chr17:40467740	0.89	0.58
RPS6KB1	chr17:57970507	0.89	0.58
GNA13	chr17:63010302	0.99	0.61
SOX9	chr17:70117435	1.07	0.64
H3-3B	chr17:73772413	0.91	0.58
RPTOR	chr17:78519448	1.01	0.63
AXL	chr19:41725295	1.18	0.69
BCL2L12	chr19:50169053	1.03	0.63
MAPK1	chr22:22123473	1.16	0.68

Biomarker Descriptions

Genomic Instability

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA[408]. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs[408,409]. HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2[126,410,411,412]. A consequence of HRD due to the failure to repair DSBs is genomic instability[413,414]. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division[415,416,417,418,419,420]. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)[416,421,422]. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability[415]. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible[423,424,425]. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars[426,427]. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)[408,428]. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors

Biomarker Descriptions (continued)

varies depending on the cancer type[408]. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)[408,413,429,430].

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation[431]. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma[431]. 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[36,37,38,39,40,41,42,43]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[6,7]. 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[6,7].

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies[34,432,433]. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality[304,305,408,434]. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib[47] was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer[47]. In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L[47,411,435]. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers[47]. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib[48] (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib[50] (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib[49] (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability[436]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex[15] causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported[52]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[53]. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations[53,437,438,439].

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[30,31]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[30,31]. 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[32,33,34]. 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%[32,35].

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[36,37,38,39,40,41,42,43]. Somatic alterations in BRCA2 are observed in 5-15% of

Biomarker Descriptions (continued)

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[6,7].

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)[44]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[45,46]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[47] (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[47] 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[48] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[49] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[49] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib[50] (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[51] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[52]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[53]. 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[15], 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.

SMARCB1 deletion

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

Background: The SMARCB1 gene encodes SWI/SNF related BAF chromatin remodeling complex subunit B1[1]. SMARCB1, also known as SNF5 or INI1, is a core member of the ATP-dependent, multi-subunit SWI/SNF chromatin-remodeling complex, along with SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1, and SMARCA2/BRM[78]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[78,79]. Independent of its functions in chromatin remodeling, SMARCB1 acts as a tumor suppressor and inhibits MYC activation, so loss of function in SMARCB1 enhances MYC activity[93]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[94,95].

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[79]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[93]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[6,7]. Alterations in SMARCB1 are also observed in pediatric cancers[6,7]. Somatic mutations in SMARCB1 are observed in 10% of pediatric rhabdoid tumors, 6% of non-Hodgkin lymphoma, 4% of embryonal tumors, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and Ewing sarcoma (1 in 354 cases)[6,7]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[6,7].

Potential relevance: Currently, no therapies are approved for SMARCB1 aberrations. Mutations and deletions of SMARCB1 are considered diagnostic markers of epithelioid sarcoma and SMARCB1-deficient renal medullary carcinoma[96,97].

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[1,77]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[77,78]. 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[78]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[78,79]. ARID1A binds to transcription

Biomarker Descriptions (continued)

factors and coactivator/corepressor complexes to alter transcription[77]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[77].

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[79]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[77]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[6,7,78]. 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[80].

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[81], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[82], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

BRCA1 deletion

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[30,31]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[30,31]. 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[32,33,34]. 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%[32,35].

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[36,37,38,39,40,41,42,43]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[6,7].

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)[44]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[45,46]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[47] (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[47] 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[48] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[49] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[49] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[50] (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[51] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[52]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[53]. 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[15], 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.

Biomarker Descriptions (continued)

NF2 deletion, NF2 p.(A448Pfs*7) c.1342delG

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells. NF2 is structurally and functionally related to the Ezrin, Radixin, Moesin (ERM) family which is known to control plasma membrane function, thereby influencing cell shape, adhesion, and growth[142,143,144]. NF2 regulates several cellular pathways including the RAS/RAF/MEK/ERK, PI3K/AKT, and Hippo-YAP pathways, thus impacting cell motility, adhesion, invasion, proliferation, and apoptosis[142,143,144,145]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[143,144,146]. Specifically, deleterious germline mutations or deletion of NF2 leading to loss of heterozygosity (LOH) is causal of neurofibromatosis type 2, a tumor prone disorder characterized by early age onset of multiple Schwannomas and meningiomas[143,144,146].

Alterations and prevalence: Somatic mutations in NF2 are predominantly misssense or truncating and are observed in about 23% of mesothelioma, 5% of cholangiocarcinoma and uterine cancer, and about 3% of papillary renal cell carcinoma (pRCC), bladder, and cervical cancers[6]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[6].

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

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[85,86]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[87]. 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[85,86,88]. 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[89].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[7]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[7]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[90,91,92].

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

TP53 deletion, TP53 p.(L265P) c.794T>C

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[391]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[392]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[393,394].

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%)[6,7,287,395,396,397]. 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[6,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[398,399,400,401]. Alterations in TP53 are also observed in pediatric cancers[6,7]. 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)[6,7]. 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)[6,7].

Potential relevance: The small molecule p53 reactivator, PC14586[402] (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[403,404]. TP53 mutation are a diagnostic marker

Biomarker Descriptions (continued)

of SHH-activated, TP53-mutant medulloblastoma[405]. 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)[27,202,227,246,406]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[28]. 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[407].

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[126,127]. 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[126]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[126]. 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[126,128].

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[6,7].

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

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[1]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[1,77]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[77,78].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[78]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[78,79]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[77].

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[79]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[6,7]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases[217,372].

AXIN1 deletion

axin 1

Background: The AXIN1 gene encodes the axis inhibition protein 1, a cytoplasmic protein that contains a regulation of G-protein signaling (RGS) domain and a disheveled and axin (DIX) domain, which are responsible for a variety of protein-protein interactions and signaling regulation[1,147,148,149]. AXIN1 functions as a negative regulator of the WNT signaling pathway through facilitating β-catenin degradation[1,155,156,157]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[150,151]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[151]. AXIN1 has also been observed to function in complex with DAXX, HIPK2, and TP53 to regulate cell growth, apoptosis, and cellular development[158].

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

Biomarker Descriptions (continued)

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

AXIN2 deletion

axin 2

Background: The AXIN2 gene encodes the axis inhibition protein 2, a cytoplasmic protein that contains a regulation of G-protein signaling (RGS) domain and a disheveled and axin (DIX) domain, which are responsible for a variety of protein-protein interactions and signaling regulation[1,147,148,149]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[150,151]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[151]. AXIN2 has been observed to be involved the regulation of the cell cycle through its involvement in WNT signaling and has been suggested to promote mitochondrial-associated apoptosis[152,153]. Loss of AXIN2 expression has been observed to contribute to the development of gastric cancer[154].

Alterations and prevalence: Somatic mutations of AXIN2 are observed in 7% of uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma and skin cutaneous melanoma[6,7]. Biallelic deletion of AXIN2 is observed in 4% of diffuse large B-cell lymphoma[6,7].

Potential relevance: Currently, no therapies are approved for AXIN2 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[1,135]. 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[1,135,136,137]. 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[1,136,138,139]. 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[126,139]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[138]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[140]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[140,141].

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[6,7]. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer[6,7].

Potential relevance: The PARP inhibitor, olaparib[47] 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[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

BRIP1 deletion

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA[129]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[130]. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[66,121]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[131]. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer[131,132]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[129,133].

Alterations and prevalence: Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma[6,7].

Potential relevance: The PARP inhibitor, olaparib[47] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors

Biomarker Descriptions (continued)

or platinum therapy[121,134]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDK12 deletion

cyclin dependent kinase 12

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[179,180,181]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[66,179,180,181,182]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[66,181]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[182]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[182].

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

Potential relevance: The PARP inhibitor, olaparib[47] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[49] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors[66,182]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDKN1B deletion

cyclin dependent kinase inhibitor 1B

Background: The CDKN1B gene encodes the cyclin-dependent kinase inhibitor 1B protein and is also known as p27 or KIP1. CDKN1B belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1A (also known as WAF1/p21) and CDKN2C (also known as KIP2/p57)[170,171]. CDKN1B is involved in controlling G1/S cell cycle progression, cell proliferation, and apoptosis[1,170,171]. Specifically, in the nucleus, CDKN1B acts as a tumor suppressor by binding with the cyclin E-CDK2 and cyclin D-CDK4 complexes[172]. However, cytoplasmic localization of the CDKN1B/p27 is associated with invasiveness and metastasis in melanoma thereby giving it potential oncogenic function[173]. Germline mutations of CDKN1B are commonly associated with multiple endocrine neoplasia type 4 (MEN4), a hereditary disease characterized by parathyroid, anterior pituitary, or neuroendocrine tumors[171,174].

Alterations and prevalence: Somatic aberrations commonly observed in CDKN1B are mutations, copy number loss and amplification. Mutations that lead to a truncated form of CDKN1B are observed in 2% of endometrial carcinoma[6,7,171]. CDKN1B copy number loss is observed in 4% of prostate adenocarcinoma, and 2% of mature B-cell neoplasm[6,7]. Amplifications of CDKN1B are observed in 4% of ovarian epithelial tumors, 5% of seminoma, and 3% of non-seminomatous germ cell tumor[6,7].

Potential relevance: Currently, no targeted therapies are approved for CDKN1B aberrations.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[290]. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)[291,292,293]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[294,295,296].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[6,7]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[6,7].

Potential relevance: The PARP inhibitor, olaparib[47] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[49] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA

Biomarker Descriptions (continued)

granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CREBBP deletion

CREB binding protein

Background: The CREBBP gene encodes the CREB binding protein (also known as CBP), a highly conserved and ubiquitously expressed tumor suppressor. CREBBP is a member of the KAT3 family of lysine acetyl transferases, which, along with EP300, interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[17,18]. CREBBP functions as a global transcriptional coactivator through the modification of lysines on nuclear proteins[17]. CREBBP binds to cAMP-response element binding protein (CREB) and is known to play a role in embryonic development, growth, and chromatin remodeling[17]. Upon disruption of normal CREBBP functions through genomic alterations, cells become susceptible to defects in differentiation and malignant transformation[19]. Inherited CREBBP mutations and deletions result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[20].

Alterations and prevalence: Mutations in CREBBP are observed in up to 12% of bladder urothelial carcinoma, uterine corpus endometrial carcinoma, and skin cutaneous melanoma, and in 5-10% of stomach adenocarcinoma, lung squamous cell carcinoma, and cervical squamous cell carcinoma[6,7]. CREBBP is frequently mutated in 15-17% of small cell lung cancer (SCLC)[21]. Inactivating mutations and deletions of CREBBP account for over 70% of all B-cell non-Hodgkin lymphoma diagnoses including 60% of follicular lymphoma and 30% of diffuse large-B-cell lymphoma (DLBCL)[17]. The rare t(11;16)(q23;p13) translocation fuses CREBBP with the partner gene KMT2A/MLL, in 0.2% secondary AML and 0.1% myelodysplastic syndrome (MDS)[22,23,24]. Elevated expression of CBP was detected in lung cancer cells and tumor tissue as compared to normal lung cells in one study[25].

Potential relevance: The t(8;16)(p11.2;p13.3) translocation resulting in KAT6A::CREBBP fusion is associated with poor/adverse risk in AML[26,27]. A mutation in CREBBP is a diagnostic marker of diffuse large B-cell lymphoma[28]. SCLC patients with CREBBP-positive tumors demonstrate lower overall survival (OS) and disease-free survival (DFS) compared to those with CREBBP-negative tumors[29].

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[1,2]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[8]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[8,9]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[2]. 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[9]. 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[8,9].

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[6,7]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[6,7]. Amplification of CUL4A is observed in 4% of sarcoma and uterine carcinosarcoma, 3% of colorectal adenocarcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[6,7]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[6,7].

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

ERCC2 deletion

ERCC excision repair 2, TFIIH core complex helicase subunit

Background: The ERCC2 gene encodes ERCC excision repair 2, TFIIH core complex helicase subunit, also known as XPD[1]. ERCC2 is a protein involved in the nucleotide excision repair (NER) pathway responsible for repairing bulky DNA lesions caused by UV radiation, environmental mutagens, chemical agents, and cyclopurines generated by reactive oxygen species[264]. ERCC2 functions as a helicase along with ERCC3/XPB in the TFIIH core complex[264]. During repair of bulky lesions by NER, the TFIIH core complex binds to the lesion, followed by DNA damage verification by ERCC2, which is essential for NER[264]. Following lesion binding and verification, ERCC2 unwinds DNA in the 5’-3’ direction[264]. Mutations in ERCC2 lead to stalled RNA polymerase, resulting in persistent block of transcription[264]. Germline ERCC2 mutations can lead to hereditary disorders including: Cockayne syndrome, characterized by skin cancer susceptibility and neurodegeneration; xeroderma pigmentosum (XP), characterized by neurodegeneration and developmental

Biomarker Descriptions (continued)

defects; and trichothiodystrophy (TTD), characterized by brittle hair due to sulfur deficiency as well as other developmental defects[264,265].

Alterations and prevalence: Somatic mutations in ERCC2 are predominantly missense and occur in 9% of bladder urothelial carcinoma, 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of lung squamous cell carcinoma[6,7]. The missense mutation, N238S, is observed to be recurrent in bladder urothelial carcinoma and is predicted to result in ERCC2 loss of function[6,7,266]. Biallelic loss of ERCC2 is observed in 2% of brain lower grade glioma and diffuse large B-cell lymphoma, as well as 1% of sarcoma and ovarian serous cystadenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for ERCC2 aberrations. In one study, ERCC2 mutations correlated with enhanced response to cisplatin based chemotherapy compared to wild-type ERCC2 in patients with muscle-invasive urothelial carcinoma[267].

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[62,63]. 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[62]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[64,65]. 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[66,67]. 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[68,69]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[63,69,70,71,72].

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

Potential relevance: The PARP inhibitor, talazoparib[49] 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[73,74]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[72].

LATS1 deletion

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1[1]. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members[229,230]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[231]. 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[231]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[232].

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma[6,7]. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma[6,7].

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

Biomarker Descriptions (continued)

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[229,230]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[231]. 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[231]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[232].

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[6,7]. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma[6,7].

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[258]. Activation of MAPK proteins occurs through a kinase signaling cascade[258,259,260]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[258,259,260]. 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[258,259,260]. 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[261].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[6,7]. 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[6,7]. 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[262,263].

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

NF1 deletion

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[199]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[199,200]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[199]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[199,201,202].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[199]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[199,203]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[199,202].

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)[97].

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[301]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-

Biomarker Descriptions (continued)

ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[301,302]. PARP enzymes are involved in several DNA repair pathways[301,302]. 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[303].

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[6,7]. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)[6,7].

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[304,305]. 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[47] (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[47] 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[48] (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[49] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[50] (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[190]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[190]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[190]. 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[195]. 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[190].

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

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

PMS2 deletion

PMS1 homolog 2, mismatch repair system component

Background: The PMS2 gene encodes the PMS1 homolog 2 protein[1]. PMS2 is a tumor suppressor gene that heterodimerizes with MLH1 to form the MutLα complex[98]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process[1]. Mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[99]. PMS2, along with MLH1, MSH6, and MSH2, form the core components of the MMR pathway[98,99]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[98]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[100]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[101,102,103]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[101,104]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[102,104,105,106].

Alterations and prevalence: Somatic mutations in PMS2 are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, and 4% of adrenocortical carcinoma[6,7]. Iterations in PMS2 are observed in pediatric cancers[6,7]. Somatic

Biomarker Descriptions (continued)

mutations are observed in 3% of soft tissue sarcoma, 2% of B-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)[6,7].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[107]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[108,109]. PMS2 mutations are consistent with high grade in pediatric diffuse gliomas[110,111].

POLD1 deletion

DNA polymerase delta 1, catalytic subunit

Background: The POLD1 gene encodes the DNA polymerase delta 1, catalytic subunit protein[1]. POLD1 is one of four subunits that make up the DNA polymerase delta (Polδ) enzyme along with POLD2, POLD3, and POLD4[306,307]. Specifically, POLD1 is responsible for the polymerase and 3'-5' exonuclease activity of Polδ in the synthesis of DNA during DNA replication and repair observed in homologous recombination repair (HRR), mismatch repair (MMR), and nucleotide excision repair (NER)[98,264,306,307]. Independent of Polδ, POLD1 associates with γ-tubulin ring complexes to control cytoplasmic microtubule growth[306]. Germline mutations in POLD1 are associated with polymerase proofreading-associated polyposis, which confers predisposition to colorectal adenomas and carcinomas[308,309,310,311,312].

Alterations and prevalence: Somatic mutations in POLD1 are observed in 8% of uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for POLD1 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)[10,11]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[12]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[10].

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[10,11,13,14]. 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[6].

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[15], 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[10]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[16].

PTCH1 p.(L62Gfs*27) c.184_185delCT

patched 1

Background: The PTCH1 gene encodes the patched 1 protein, a transmembrane protein that along with PTCH2, belongs to the patched gene family[1]. PTCH1 is involved in the Hedgehog (Hh) signaling pathway that plays a significant role in embryonic development, cell proliferation, and cell differentiation[388,389]. PTCH1 is a tumor suppressor gene that inhibits the transmembrane receptor Smoothened (SMO) and prevents downstream Hh signaling pathway activation[388,389]. The Hh pathway is activated when one of the Hh ligands including Sonic hedgehog (SHh), Indian hedgehog (IHh), or Desert Hedgehog (DHh) bind to PTCH1 and disrupt SMO inhibition[389]. Inactivating mutations in PTCH1 lead to ligand-independent signaling of Hh, as PTCH1 no longer prevents SMO activity[389]. Germline mutations in PTCH1 are associated with basal cell nevus syndrome (BCNS) or Gorlin Syndrome with a predisposition to non-cancerous and cancerous tumors including basal cell carcinoma[389,390].

Biomarker Descriptions (continued)

Alterations and prevalence: Inactivating mutations in PTCH1 are observed in 85% of sporadic basal cell carcinomas[390]. Somatic mutations in PTCH1 are also observed in 11% of uterine corpus endometrial carcinoma and 4-5% of stomach adenocarcinoma, skin cutaneous melanoma, cholangiocarcinoma, esophagus adenocarcinoma, colorectal adenocarcinoma, and mesothelioma[6,7].

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

RAD51C deletion

RAD51 paralog C

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs[115]. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)[116]. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)[117]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing[118]. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity[119,120]. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[66,121].

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers[6].

Potential relevance: The PARP inhibitor, olaparib[47] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib[49] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation[122]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51D deletion

RAD51 paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[116]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[117]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[118]. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[66,121]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[123].

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer[6].

Potential relevance: The PARP inhibitor, olaparib[47] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors[121]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[15], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD52 deletion

RAD52 homolog, DNA repair protein

Background: The RAD52 gene encodes the RAD52 homolog, DNA repair protein[1]. RAD52 binds to single- and double-stranded DNA and enables strand exchange for double-strand break (DSB) repair by binding to RAD51[320]. RAD52 also promotes DSB repair through homologous recombination repair (HRR) by recruiting BRCA1 to sites of DSBs, which leads to the removal of TP53BP1 and prevents DSB repair by non-homologous end joining (NHEJ)[321].

Alterations and prevalence: Somatic mutations in RAD52 are observed in 2% of uterine corpus endometrial carcinoma, uterine carcinosarcoma, and skin cutaneous melanoma[6,7].

Potential relevance: Currently, no therapies are approved for RAD52 aberrations.

Biomarker Descriptions (continued)

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[322,323]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[322]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[322].

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

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)[329]. 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)[329]. 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[329].

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[6,7]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[6,7].

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[55,56]. 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[55,56]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[57]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[55,56]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,58].

Alterations and prevalence: Somatic mutations in SDHB are observed in 1% cervical squamous cell carcinoma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, stomach adenocarcinoma, thymoma, lung squamous cell carcinoma, and kidney renal clear cell carcinoma[6,7]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[6,7].

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

SLX4 deletion

SLX4 structure-specific endonuclease subunit

Background: The SLX4 gene encodes the SLX4 structure-specific endonuclease subunit[1]. SLX4, also known as FANCP, is a tumor suppressor protein that functions as a scaffold for DNA repair endonucleases[362]. SLX4 functions in DNA repair mechanisms including double-strand break (DSB) repair and interstrand crosslink repair[362,363,364]. Specifically, SLX4 localizes at DSB sites and recruits and interacts with other repair proteins such as ERCC1-XPF, MUS81-EME1, and SLX1[362,363,364]. Germline SLX4 mutations are associated

Biomarker Descriptions (continued)

with Fanconi Anemia, a genetic condition characterized by genomic instability and congenital abnormalities, including bone marrow failure and cancer predisposition[363].

Alterations and prevalence: Recurrent somatic mutations in SLX4 are observed in 11% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of stomach adenocarcinoma, and 4% of bladder urothelial carcinoma[6,7].

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

TSC1 deletion

tuberous sclerosis 1

Background: The TSC1 gene encodes the hamartin protein. TSC1 and TSC2 (also known as tuberin) form a complex through their respective coiled-coil domains[59]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[60]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[59,61]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[59].

Alterations and prevalence: Somatic mutations are observed in up to 8.5% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, and up to 6% of skin cutaneous melanoma[6,7].

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

TSC2 deletion

tuberous sclerosis 2

Background: The TSC2 gene encodes the tuberin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains[59]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[60]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[59,61]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[59].

Alterations and prevalence: Somatic mutations are observed in up to 8% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma[6,7].

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

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[183]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[183]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[183,184]. 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[183]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[184].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[6,7]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[6,7].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[28]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[185,186].

Biomarker Descriptions (continued)

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,373]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[373,374]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[373,375]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[373,376,377,378,379]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[373,376,377,380,381].

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[6,7]. 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[6,7].

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)[1,297]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[297]. 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[297,298,299]. 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[297,298,300]. 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[297,298].

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[6,7]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[6,7]. 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[6,7].

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[1,175]. 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[176,177]. 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[175,178].

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[6,7]. 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[6,7]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[6,7].

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

Biomarker Descriptions (continued)

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor[1]. SPEN plays a role in chromosome X inactivation and regulation of transcription[353,354,355]. 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[353,355]. 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[356,357].

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[6,7]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[6,7].

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[75,76]. 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[76]. 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[75,76].

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[6,7].

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

DNMT3A deletion

DNA methyltransferase 3 alpha

Background: The DNMT3A gene encodes the DNA methyltransferase 3 alpha which functions as a de novo methyltransferase (DNMT) with equal methylation efficiency for unmethylated and hemimethylated DNA[204]. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression[205,206].

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)[6,26,207,208,209,210,211]. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer[6,202]. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported[6,207]. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations[212,213]. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation[214,215]. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity[216].

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML[207,210,211,213]. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)[217].

Biomarker Descriptions (continued)

ASXL2 deletion

additional sex combs like 2, transcriptional regulator

Background: The ASXL2 gene encodes the ASXL transcriptional regulator 2 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,124]. ASXL2 belongs to the ASXL gene family, which also includes ASXL1 and ASXL3[124]. ASXL proteins contain a conserved C-terminal plant homeodomain (PHD), which facilitates interaction with DNA and histones[124]. ASXL2 influences chromatin remodeling and transcription through interaction with BAP1 as well as other transcriptional activators and repressors[124].

Alterations and prevalence: Somatic mutations in ASXL2 are observed in 8% of uterine corpus endometrial carcinoma and bladder urothelial carcinoma, 7% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and uterine carcinosarcoma[6,7]. ASXL2 mutations in acute myeloid leukemia (AML) are observed to co-occur with t(8;21)(q22;q22)/ RUNX1::RUNX1T1[125]. ASXL2 deletions are observed in 4% diffuse large B-cell lymphoma (DLBCL) and 2% of uterine carcinosarcoma[6,7].

Potential relevance: Currently, no therapies are approved for ASXL2 aberrations. ASXL2 mutations have been shown to be associated with better prognosis in pediatric AML with t(8;21)[125].

ACVR2A deletion

activin A receptor type 2A

Background: The ACVR2A gene encodes the activin A type 2A receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family[1,218]. ACVR2A is a type II receptor that forms heterotetrametric complex with at least two type I receptors (ACVR1 and ACVR1B) and two type II receptors (including BMPR2 and ACVR2B)[218,219]. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrametric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream signaling[218,219]. Downregulation of ACVR2A has been associated with increased cell migration, tumor progression, and metastases in colon cancer[220].

Alterations and prevalence: Somatic mutations of ACVR2A are observed in 11% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 7% of colorectal adenocarcinoma, 3% of liver hepatocellular carcinoma, skin cutaneous melanoma, and cholangiocarcinoma, 2% of cervical squamous cell carcinoma, and 1% of kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, and glioblastoma multiforme, and esophageal adenocarcinoma[6,7]. Biallelic deletion of ACVR2A is observed in 4% of prostate adenocarcinoma, 2% of liver hepatocellular carcinoma, and 1% of stomach adenocarcinoma, thymoma, testicular germ cell tumors, esophageal adenocarcinoma, and colorectal adenocarcinoma[6,7].

Potential relevance: Currently, no therapies are approved for ACVR2A aberrations.

CASP8 deletion

caspase 8

Background: CASP8 encodes caspase 8, a member of the cysteine-aspartic acid protease (caspase) family consisting of inflammatory caspases and apoptotic caspases. Apoptotic caspases consist of initiator and effector caspases[1,159,160]. CASP8 functions as an initiator caspase and following external stimulation of death receptors, undergoes processing and activation leading to CASP8 mediated cleavage of downstream targets[161]. CASP8 propagates the extrinsic apoptotic pathway by direct cleavage of effector caspases such as CASP3 and activates the intrinsic apoptotic pathway by cleaving BID, a pro-apoptotic proximal substrate of CASP8, resulting in an amplification of the death-inducing signal[161,162]. Certain cancer types have decreased expression or inactivation of CASP8, which results in poor prognosis and metastasis[163,164].

Alterations and prevalence: Somatic mutations in CASP8 are observed in 11% head and neck squamous cell carcinoma, 10% uterine corpus endometrial carcinoma, 5% stomach adenocarcinoma, 4% cervical squamous cell carcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, 3% skin cutaneous melanoma, and 2% diffuse large B-cell lymphoma, lung squamous cell carcinoma, uterine carcinosarcoma, and breast invasive carcinoma[6,7]. Biallelic loss of CASP8 is observed in 2% bladder urothelial carcinoma[6,7].

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

Biomarker Descriptions (continued)

BMPR2 deletion

bone morphogenetic protein receptor type 2

Background: BMPR2 encodes bone morphogenetic protein receptor type 2, a member of the bone morphogenetic protein (BMP) receptor family and TGFβ receptor superfamily[1,278,279]. BMPR2 is a type II serine/threonine kinase receptor that functions as part of BMP receptor complexes for BMP proteins[278]. BMP receptor complexes consist of two type I and two type II receptors that are activated upon BMP binding, leading to SMAD activation and transcription of proteins involved in various aspects of growth and development[278]. BMPR2 is expressed in a variety of tissues including pulmonary vascular endothelium, pulmonary vascular smooth muscle, cerebellum, and hippocampus, and organs such as the thyroid gland, adrenal gland, heart, liver, pancreas, and kidney[278]. BMPR2 is observed to be mutated or down-regulated in cancer, including prostate cancer and microsatellite instable colorectal cancer[278].

Alterations and prevalence: Somatic mutations of BMPR2 are observed in 7% of colorectal adenocarcinoma, 6% of stomach adenocarcinoma, uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 3% of cervical squamous cell carcinoma, 2% of bladder urothelial carcinoma, lung squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and lung adenocarcinoma[6,7]. Biallelic deletion of BMPR2 is observed in 1% of cervical squamous cell carcinoma, uveal melanoma, head and neck squamous cell carcinoma, stomach adenocarcinoma, and glioblastoma multiforme[6,7].

Potential relevance: Currently, no therapies are approved for BMPR2 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[1,2]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[2]. CRLs are involved in diverse biological processes including cell cycle control, DNA replication and repair, and chromatin remodeling[3]. CUL3 is part of the CRL3 complex which is responsible for ubiquitination and degradation of a variety of substrates[3,4,5]. Substrate specificity is dependent on the proteins recruited by CUL3 that have BTB domains, such as KEAP1 and SPOP[3,4,5]. 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[5].

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[6,7]. 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[6,7]. Amplification of CUL3 is observed in 3% of pancreatic adenocarcinoma and 2% of uterine carcinosarcoma[6,7].

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

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,221]. The TET enzymes are involved in DNA demethylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[222,223]. 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)[222,223]. 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[222,223]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[221,224,225].

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)[202]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[224,226]. 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[6,7]. Alterations in TET2 are also observed in the pediatric population[7]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than

Biomarker Descriptions (continued)

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)[7]. 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)[7].

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[227]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[228]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[217].

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[258,259,260]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[258,259,260]. 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[258,259,260]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[330]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[330]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[330].

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[6,7]. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[330]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[6,7].

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[83,84]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[83]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[83]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[83]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[83].

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[6,7]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[6,7].

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

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[331]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[331]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[331,332]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[331]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[331]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[331,333].

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[6,7]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[6,7].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[334]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[335]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[336]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[337].

TNFAIP3 deletion

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3[1]. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity[196]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[196,197]. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions[196]. TNFAIP3 deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[196,198].

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma[6,7]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[6,7,196].

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

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4[1]. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10[258]. Activation of MAPK proteins occurs through a kinase signaling cascade[258,259,260]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[258,259,260]. 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[258,259,260]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[338].

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

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

HDAC9 deletion

histone deacetylase 9

Background: The HDAC9 gene encodes the histone deacetylase 9 protein[1]. HDAC9 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[331]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[331,332]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[331]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[331,333].

Alterations and prevalence: Somatic mutations in HDAC9 are observed in 16% of skin cutaneous melanoma, 8% of lung adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma and lung squamous cell carcinoma, 4% of esophageal adenocarcinoma, 3% of esophageal adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and kidney chromophobe[6,7]. Biallelic deletion of HDAC9 is observed in 2% of diffuse large B-cell lymphoma[7]. Alterations in HDAC9 are also observed in pediatric cancers[7]. Somatic mutations in HDAC9 are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone

Biomarker Descriptions (continued)

cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[7]. Biallelic deletion of HDAC9 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[7].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat[334] (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies. The pan-HDAC inhibitor, romidepsin[335] (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy. The pan-HDAC inhibitor, belinostat[336] (2014), is approved for the treatment of relapsed or refractory PTCL. The FDA granted fast track designation to the pan-HDAC inhibitor, panobinostat[339] (2024), for the treatment of recurrent glioblastoma.

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[280]. 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[281,282]. 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[283,284,285,286].

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers[6,7,287]. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia[288,289].

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

ETV6 deletion

ETS variant 6

Background: The ETV6 gene encodes the E twenty-six (ETS) variant 1 transcription factor[233]. ETV6 contains an N-terminal pointed (PNT) domain responsible for protein-protein interactions and a C-terminal ETS domain involved in DNA binding[233]. ETV6 plays a critical role in embryonic development as well as hematopoiesis and is the target of chromosomal rearrangement and missense mutations in hematological malignancies and solid tumors[234,235]. Hereditary mutations in ETV6 are associated with a predisposition to hematological cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS)[27,236,237,238,239].

Alterations and prevalence: ETV6 translocations are prevalent in hematological malignancies and have been observed with numerous fusion partners[240]. The most recurrent translocation is t(12;21)(p13;q22), which results in the ETV6::RUNX1 fusion and is observed in 20-25% of childhood acute lymphoblastic leukemia (ALL) and 2% of adult ALL[240,241]. The t(5;12)(q33;p13) translocation, which results in the ETV6::PDGFRB fusion, is recurrent in chronic myelomonocytic leukemia (CMML)[240,242]. Other ETV6 fusions, including ETV6::PDGFRA, ETV6::NTRK2, ETV6::NTRK3, and ETV6::ABL1, are reported in hematological malignancies and solid tumors[235,240,243]. ETV6 fusions involving a receptor tyrosine kinase (RTK) fusion partner retains the ETV6 PNT domains and the tyrosine kinase domain of the RTK, leading to constitutive kinase activation[240,243]. Mutations in ETV6 are primarily missense, nonsense, or frameshift and are observed in 5% of diffuse large B-cell lymphoma (DLBCL) and uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of colorectal adenocarcinoma and stomach adenocarcinoma, and 2% of bladder urothelial carcinoma and uterine carcinosarcoma[6,7,233,244]. ETV6 mutations occur in the PNT and ETS domain of ETV6 and may impair ETV6 oligomerization or DNA-binding, respectively[233]. Biallelic deletion of ETV6 is observed in 4% of DLBCL, 3% of prostate adenocarcinoma, and 2% of lung adenocarcinoma[6,7]. Alterations in ETV6, in addition to ETV6::RUNX1 fusion, are also observed in pediatric cancers[240,243]. ETV6 fusions occur in 12% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[240,243]. Somatic mutations in ETV6 are observed in 2% of B-lymphoblastic leukemia/lymphoma and less than 1% of leukemia (3 in 354 cases), embryonal tumors (1 in 332 cases), and bone cancer (1 in 327 cases)[240,243]. Biallelic deletion of ETV6 is observed in 11% of B-lymphoblastic leukemia/lymphoma and 4% of leukemia[240,243].

Potential relevance: ETV6::NTRK3 fusion is useful as an ancillary diagnostic marker in congenital/infantile fibrosarcoma and inflammatory myofibroblastic tumors[97,245]. Nonsense or frameshift mutations in ETV6 are independently associated with poor prognosis in MDS[202]. However, ETV6::RUNX1 fusions are associated with standard risk in adults and favorable outcomes in children with ALL[246,247,248]. ETV6 fusions that partner with RTKs demonstrate response to various tyrosine kinase inhibitors such as imatinib, nilotinib, and entrectinib[249]. Specifically, individual case reports of an ETV6::PDGFRA fusion chronic eosinophilic leukemia patient and an ETV6::PDGFRB fusion CMML patient treated with imatinib demonstrated complete cytogenetic response (CCyR) and complete hematological responses, respectively[250,251]. Additionally, an ETV6::ABL1 fusion Ph-negative CML patient treated with nilotinib

Biomarker Descriptions (continued)

demonstrated CCyR and major molecular response (MMR) at 22 months from diagnosis[252]. In another case report, an ETV6::NTRK3 fusion mammary analogue secretory carcinoma (MASC) patient demonstrated partial response to entrectinib with an 89% reduction in tumor burden[253].

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[54]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[54]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[54].

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[6,7]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[6,7].

Potential relevance: Currently, no therapies are approved for TPP2 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[313,314,315]. 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[314,315]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[315]

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[6]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[6]. 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[316]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[316].

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)[26,27,239].

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[112]. 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[112,113,114]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[112].

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[6,7].

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)[1,365]. 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[366]. 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[367,368]. 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[369].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[6,7,370,371]. 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[6,7]. 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[6,7].

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[1,268,269]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[269,270]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[271,272,273,274,275]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[271,274,276,277].

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[6,7]. 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[6,7].

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[347]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[347,348]. 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[349,350,351].

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[6,7]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[6,7]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[6,7,352]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[352].

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

Biomarker Descriptions (continued)

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,324,325]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[324,325,326,327]. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[325]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types, including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[325,328].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[6,7]. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[6,7]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[6,7]. Alterations in NCOR1 are also observed in pediatric cancer[7]. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[7]. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)[7].

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

SPOP deletion

speckle type BTB/POZ protein

Background: The SPOP gene encodes the speckle type BTB/POZ protein[1]. SPOP is an E3 ligase substrate adaptor, with specificity for cullin3-RING ubiquitin ligase (CRL3), which recruits substrates for ubiquitination[254]. Substrates recruited by SPOP include proteins involved in epigenetic modification, hormone signaling effectors, and cascade effectors, such as androgen receptor (AR), estrogen receptor (ER), CCNE1, MYC, and PTEN[254]. Mutations in SPOP meprin and TRAF-C homology (MATH) domains have been implicated to have loss of function as well as gain of function roles that are cancer-type dependent and are based on SPOP's specificity for its various substrates[254,255,256,257]. In prostate cancer, mutations in the SPOP substrate-binding cleft of the MATH domain, involving residues F133, F102, W131 and Y87, lead to increased levels of AR. In endometrial cancer, mutations in the SPOP substrate-binding face of the MATH domain, involving residues M117, E47, R121 and E50, lead to decreased levels of estrogen and progesterone receptors[254,255,256,257]. Moreover, improved overall survival has been observed from hormonal therapies in patients with SPOP mutated prostate cancer[257].

Alterations and prevalence: Somatic mutations in SPOP are observed in 11% of prostate adenocarcinoma, 10% of uterine corpus endometrial carcinoma, 7% of uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma[6,7]. Amplification of SPOP is observed in 6% of breast invasive carcinoma, 5% of mesothelioma, and 2% of esophageal adenocarcinoma and pancreatic adenocarcinoma[6,7].

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

RNF43 deletion

ring finger protein 43

Background: The RNF43 gene encodes the ring finger protein 43[1]. RNF43 is a transmembrane E3 ubiquitin ligase and a negative regulator of the Wnt signaling pathway[358,359]. Wnt signaling leads to the expression of genes that control cell proliferation, migration, and cell polarity formation[358]. RNF43 functions as a tumor suppressor and inhibits the Wnt pathway by ubiquitination and degradation of the Wnt receptor frizzled (FZD)[358,359].

Alterations and prevalence: Somatic mutations in RNF43 are observed in 14% endometrial carcinoma, 8% gastroesophageal junction cancer and colorectal adenocarcinoma, and 6% pancreatic adenocarcinoma[6,7]. Somatic frameshift mutations in RNF43 including R117fs and G659fs are frequently observed in colorectal and endometrial cancers with microsatellite instability[358,360,361].

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

Biomarker Descriptions (continued)

PPM1D deletion

protein phosphatase, Mg2+/Mn2+ dependent 1D

Background: The PPM1D gene encodes the protein phosphatase, Mg2+/Mn2+ dependent 1D, also known as wild-type p53-induced phosphatase 1 (WIP1) or protein phosphatase 2C delta (PP2Cδ)[340]. PPM1D is a member of the PP2C family of Ser/Thr protein phosphatases[1]. PPM1D negatively regulates several key tumor suppressor pathways including ATM, CHK2, P38 MARK and P53, which are involved in cell stress, cell cycle regulation, DNA damage repair and tumor cell metabolism[340,341]. PPM1D amplification/overexpression and/or mutations occur in various solid cancers, including breast cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, ovarian carcinoma and neuroblastoma[341]. Truncating mutations in the last exon of PPM1D lead to the production of a stable, enzymatically active protein and are commonly associated with clonal hematopoiesis, a condition that has been shown to be present in patients with therapy-related myeloid neoplasm such as therapy-related acute myeloid leukemia (t-AML) or therapy-related myelodysplastic syndrome (t-MDS)[342,343].

Alterations and prevalence: Somatic mutations in PPM1D are predominantly truncating or missense and are observed in 6% of uterine corpus endometrial carcinoma, 2% of stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[6,7]. Amplification of PPM1D is observed in 8% of breast invasive carcinoma, 5% of mesothelioma, 4% of liver hepatocellular carcinoma, 3% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of adrenocortical carcinoma, skin cutaneous melanoma, ovarian serous cystadenocarcinoma, pheochromocytoma and paraganglioma, esophageal adenocarcinoma, pancreatic adenocarcinoma, thymoma, sarcoma, and lung adenocarcinoma[6,7]. Alterations in PPM1D are also observed in pediatric cancers[7]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma and glioma, and less than 1% of leukemia (1 in 311 cases), embryonal tumor (1 in 332 cases), and peripheral nervous system cancers (3 in 1158 cases)[7]. PPM1D amplification is observed in 2% of peripheral nervous system cancers, and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[7].

Potential relevance: Currently, no therapies are approved for PPM1D aberrations. Overexpression of PPM1D has been associated with tumor progression and poor prognosis in non-small cell lung cancer, nasopharyngeal carcinoma and prostate cancer[344,345,346].

PRKAR1A deletion

protein kinase cAMP-dependent type I regulatory subunit alpha

Background: The PRKAR1A gene encodes the protein kinase cAMP-dependent type I regulatory subunit alpha of protein kinase A (PKA), an inactive tetrameric holoenzyme with two regulatory (R) subunits and two catalytic (C) subunits (namely PRKACA and PRKACB)[1,382]. PKA is a cAMP-dependent protein kinase involved in the phosphorylation of several downstream targets and an essential regulator of several cell signaling pathways involved in differentiation, proliferation, and apoptosis[1,383,384]. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins[1,383]. Mutations in PRKAR1A lead to increased availability of free catalytical subunits and increased PKA activity[385,386]. Loss of PRKAR1A has been shown to promote tumor cell proliferation and migration in lung cancer cell lines suggesting a tumor suppressor role in cancer[387].

Alterations and prevalence: Somatic mutations in PRKAR1A are observed in 5% of adrenocortical carcinoma, 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[6,7]. Biallelic loss of PRKAR1A is observed in 4% of adrenocortical carcinoma[6,7].

Potential relevance: Currently, no therapies are approved for PRKAR1A aberrations.

CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,317]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,317]. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5[317]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[317].

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[6,7]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[6,7]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[317,318].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma[97,319].

ARHGAP35 deletion

Rho GTPase activating protein 35

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription[1]. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell membrane[165,166]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[167,168].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[6,7]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[169]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[6,7]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[6,7].

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

EP300 deletion

E1A binding protein p300

Background: The EP300 gene encodes the E1A binding protein p300[1]. EP300 is a member of the KAT3 family of lysine acetyl transferases, which, along with CREBBP (also known as CBP), interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[17,18]. EP300 functions as a transcriptional coactivator and has been observed to activate members of the E2F transcription factor family, thereby regulating expression of genes required for cell cycle G1/S phase transition[187,188]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[187]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[20].

Alterations and prevalence: Somatic mutations in EP300 are observed in 15% of bladder urothelial carcinoma, 14% of uterine corpus endometrial carcinoma, 12% of cervical squamous cell carcinoma, 8% of skin cutaneous melanoma, 7% of head and neck squamous cell carcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and colorectal adenocarcinoma[6,7]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[189].

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

Genomic Instability

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer **Variant class:** HR Deficient

Supporting Statement:
The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

https://www.senhwabio.com//en/news/20220125

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed (continued)

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

Genomic Instability

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	●	●	✖	●	● (II)
bevacizumab + olaparib	●	✖	●	●	✖
olaparib	✖	✖	✖	✖	● (IV)
fluzoparib, bevacizumab	✖	✖	✖	✖	● (III)
IMNN-001, chemotherapy, olaparib, niraparib	✖	✖	✖	✖	● (III)
olaparib, bevacizumab	✖	✖	✖	✖	● (III)
atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
fluzoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
HS-10502	✖	✖	✖	✖	● (I)
MOMA-313, olaparib	✖	✖	✖	✖	● (I)
pidnarulex	✖	✖	✖	✖	● (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

Genomic Instability (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
SIM-0501	✖	✖	✖	✖	● (I)
XL-309, olaparib	✖	✖	✖	✖	● (I)

BRCA2 deletion

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

SMARCB1 deletion

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

ARID1A deletion

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

BRCA1 deletion

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

NF2 deletion

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

* 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

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

TP53 deletion

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

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

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

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