삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Patient Name: 조은희
Gender: F
Sample ID: N25-28

Primary Tumor Site: soft tissue
Collection Date: 2025.01.24

Sample Cancer Type: Leiomyosarcoma

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Relevant Leiomyosarcoma Findings

Gene	Finding
BRAF	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***2.84 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	*CCND1 amplification* cyclin D1 Locus: chr11:69455949	None*	None*	4
IIC	*CHEK1 deletion* checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1

*** Public data sources included in relevant therapies: FDA**1, NCCN, **EMA**2, 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	*FANCA deletion* Fanconi anemia complementation group A Locus: chr16:89804984	None*	None*	1
IIC	*LATS2 deletion* large tumor suppressor kinase 2 Locus: chr13:21548922	None*	None*	1
IIC	*MLH1 p.(V384D) c.1151T>A* mutL homolog 1 Allele Frequency: 52.50% Locus: chr3:37067240 Transcript: NM_000249.4	None*	None*	1
IIC	*PALB2 deletion* partner and localizer of BRCA2 Locus: chr16:23614759	None*	None*	1
IIC	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	1
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

ARID1B deletion, ARID2 deletion, CUL4A deletion, CUL4B deletion, ERCC2 deletion, FGF19 amplification, KMT2A deletion, MAP2K4 deletion, MRE11 deletion, Microsatellite stable, PMS2 deletion, POLD1 deletion, RNASEH2B deletion, RPA1 deletion, TCF7L2 deletion, TP53 deletion, TP53 p.(V143M) c.427G>A, XRCC2 deletion, ELF3 deletion, HLA-A deletion, HLA-B deletion, MAP3K4 deletion, HDAC9 deletion, POT1 deletion, EZH2 deletion, KMT2C deletion, LARP4B deletion, GATA3 deletion, MAPK8 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, MEN1 deletion, KMT2D deletion, ACVR1B deletion, TPP2 deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1 deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, GPS2 deletion, NCOR1 deletion, CIC deletion, ARHGAP35 deletion, RUNX1 deletion, ZMYM3 deletion, STAG2 deletion, PHF6 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MLH1	p.(V384D)	c.1151T>A	.	chr3:37067240	52.50%	NM_000249.4	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.45%	NM_000903.3	missense
TP53	p.(V143M)	c.427G>A	.	chr17:7578503	75.79%	NM_000546.6	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	34.57%	NM_002439.5	nonframeshift Insertion
RAB11FIP1	p.([A651V;L652=])	c.1952_1954delCCCinsTCT	.	chr8:37730366	67.50%	NM_001002814.3	missense, synonymous

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FANCA	p.(S309G)	c.925A>G	.	chr16:89862395	90.56%	NM_000135.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ELF3	chr1:201980251	0.81	0.47
HLA-A	chr6:29910229	1.07	0.59
HLA-B	chr6:31322252	0.95	0.54
ARID1B	chr6:157099057	1.01	0.56
MAP3K4	chr6:161412931	1.05	0.58
PMS2	chr7:6012922	0.88	0.51
HDAC9	chr7:18201905	0.94	0.54
POT1	chr7:124464001	1.11	0.61
EZH2	chr7:148506391	0.83	0.48
KMT2C	chr7:151833866	0.91	0.52
XRCC2	chr7:152345702	0.97	0.55
LARP4B	chr10:858847	0.84	0.49
GATA3	chr10:8097519	0.85	0.5
MAPK8	chr10:49609682	1	0.56
ARID5B	chr10:63661463	0.82	0.48
PTEN	chr10:89623659	0.93	0.53
CYP2C9	chr10:96698378	0.94	0.54
SUFU	chr10:104263903	0.93	0.53
TCF7L2	chr10:114710485	0.97	0.55
MEN1	chr11:64571785	1.1	0.6
CCND1	chr11:69455949	4.98	2.31
FGF19	chr11:69513948	5.08	2.36
MRE11	chr11:94153270	1.08	0.6
ATM	chr11:108098341	1	0.57
KMT2A	chr11:118307146	1.03	0.58
CHEK1	chr11:125496639	1	0.63
ARID2	chr12:46123536	0.98	0.55
KMT2D	chr12:49415529	0.94	0.53
ACVR1B	chr12:52345528	1.13	0.62
LATS2	chr13:21548922	1.02	0.57

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.57
RB1	chr13:48877953	0.98	0.55
RNASEH2B	chr13:51484145	1.01	0.56
TPP2	chr13:103249399	1.02	0.57
CUL4A	chr13:113863977	0.94	0.54
PALB2	chr16:23614759	1	0.57
CYLD	chr16:50783549	1.17	0.63
CBFB	chr16:67063242	0.94	0.54
CTCF	chr16:67644720	1.08	0.6
CDH1	chr16:68771249	0.95	0.54
ZFHX3	chr16:72820995	0.95	0.54
FANCA	chr16:89804984	0.95	0.54
RPA1	chr17:1733385	1.03	0.58
GPS2	chr17:7216071	0.99	0.56
TP53	chr17:7572848	1.07	0.59
MAP2K4	chr17:11924164	1.13	0.61
NCOR1	chr17:15935586	0.99	0.55
CIC	chr19:42775916	1.05	0.58
ERCC2	chr19:45854865	1.01	0.56
ARHGAP35	chr19:47421913	0.95	0.54
POLD1	chr19:50902079	1.08	0.6
RUNX1	chr21:36164357	0.93	0.53
ZMYM3	chrX:70460753	0.84	0.49
CUL4B	chrX:119660593	0.02	0.13
STAG2	chrX:123156472	0.99	0.55
PHF6	chrX:133511628	0.9	0.52
FGFR3	chr4:1801456	1.05	0.58
CARD11	chr7:2949684	1	0.56
RAC1	chr7:6426823	1.06	0.59
ABCB1	chr7:87145849	1	0.56
CDK6	chr7:92244380	1.02	0.57
MET	chr7:116339789	1.05	0.58
SMO	chr7:128845103	0.95	0.54
RET	chr10:43609070	1.05	0.58

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
FGFR2	chr10:123239426	0.95	0.54
FGF4	chr11:69588019	0.88	0.51
FGF3	chr11:69625020	1	0.56
EMSY	chr11:76157926	0.78	0.47
YAP1	chr11:101981594	0.93	0.53
KRAS	chr12:25362709	0.9	0.52
ERBB3	chr12:56477596	0.94	0.54
STAT6	chr12:57490294	0.91	0.52
CDK4	chr12:58142242	0.94	0.53
KLF5	chr13:73633435	1.02	0.57
ERCC4	chr16:14013959	5.38	2.49
RPTOR	chr17:78519448	0.93	0.53
AKT2	chr19:40739751	1.09	0.6
AXL	chr19:41725295	0.94	0.53

Biomarker Descriptions

CUL4B deletion

cullin 4B

Background: The CUL4B gene encodes cullin 4B, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4a, CUL5, CUL7, and Parc[1,2]. CUL4B belongs to the CUL4 subfamily which also includes CUL4A[3]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[3,4]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[2]. CUL4B is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[4]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4B in oncogenesis[3,4].

Alterations and prevalence: Somatic mutations in CUL4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 2% of bladder urothelial carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, uterine carcinosarcoma, brain lower grade glioma, and lung squamous cell carcinoma[5,6]. Amplification of CUL4B is observed in 2% of diffuse large B-cell lymphoma[5,6]. Biallelic loss of CUL4B is observed in 1% sarcoma and testicular germ cell tumors[5,6].

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

CYLD deletion

CYLD lysine 63 deubiquitinase

Background: The CYLD gene encodes CYLD lysine 63 deubiquitinase, which is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) family of deubiquitinases[1,7]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[8]. CLYD contains a USP domain with a catalytic triad formed by Cys601, His871, and Asp889 that selectively hydrolyses K63-linked ubiquitin chains from signaling molecules and regulates cell survival, proliferation, and tumorigenesis[9,10]. CYLD plays a tumor suppressor role by negatively regulating NF-κB activation by deubiquitinating multiple NF-κB signaling components, including NEMO, Tak1, TRAF2, TRAF6, and RIP1[11]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin

Biomarker Descriptions (continued)

appendage tumors[10,11]. CYLD has also been found to be downregulated in melanoma, salivary gland tumors, head and neck cancer, colon and hepatocellular carcinoma, cervical cancer, lung cancer, and renal cell carcinoma[10].

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

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

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[12,13]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[13]. ARID5B is known to be essential for the development of hematopoietic cells[13]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[13].

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

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

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[3]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[3,4]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[2]. 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[4]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4A in oncogenesis[3,4].

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[5,6]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[5,6]. 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[5,6]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[5,6].

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

LARP4B deletion

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[14]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[14]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[15].

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[5,6]. Biallelic deletions

Biomarker Descriptions (continued)

in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[5,6].

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

ELF3 deletion

E74 like ETS transcription factor 3

Background: The ELF3 gene encodes the E74 like ETS transcription factor 3 protein[1]. ELF3 is a transcription factor that has been observed to function as a negative regulator of the epithelial-mesenchymal transition (EMT) process, specifically in ovarian cancer cells[16]. ELF3 has also been proposed to act as an antagonist of oncogenic-signaling induced ZEB1 expression in colorectal cancer, supporting a tumor suppressor role for ELF3[16,17].

Alterations and prevalence: Somatic mutations in ELF3 are observed in 13% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 3% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine corpus endometrial carcinoma, and cervical squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ELF3 aberrations.

MRE11 deletion

MRE11 homolog, double strand break repair nuclease

Background: The MRE11 gene encodes the meiotic recombination 11 protein, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) complex, which is necessary for the maintenance of genomic stability[18]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through two mechanisms namely homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[19,20,21]. Dimerization of MRE11 is required for DNA binding of the MRN complex, and it acts as a 3'–5' exonuclease and ssDNA endonuclease upon binding DNA[18]. MRE11 is a tumor suppressor gene and loss of function mutations are implicated in the BRCAness phenotype, characterized by a defect in the HRR pathway mimicking BRCA1 or BRCA2 loss[22,23]. Germline mutations in MRE11 have been identified as candidate susceptibility aberrations in colorectal cancer and a hallmark of ataxia-telangiectasia-like disorder (ALTD), a heritable disease resulting in progressive cerebellar degeneration and cancer predisposition[24,25,26,27].

Alterations and prevalence: Somatic mutations in MRE11 are observed in 6-7% of uterine cancer as well as 2-3% of lung adenocarcinoma and melanoma[5]. Mutations in the T11 polypyrimidine tract of MRE11 intron 5 are associated with aberrant splicing and reduced MRE11 protein expression. The presence of MRE11 splice variants is frequently observed in mismatch repair deficient (dMMR)/microsatellite instability (MSI-H) colorectal and endometrial cancers[28,29,30,31]

Potential relevance: The PARP inhibitor, talazoparib[32] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors[22,23]. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro[33,34,35].

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[36]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[36]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[36].

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[5,6]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[5,6].

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

Biomarker Descriptions (continued)

EZH2 deletion

enhancer of zeste 2 polycomb repressive complex 2 subunit

Background: The EZH2 gene encodes the enhancer of zeste homolog 2 protein, a histone methyltransferase that functions as both a transcriptional suppressor and co-activator[37]. EZH2 mediates methylation of histone H3 at Lys 27 (H3K27me3) and promotes tumor growth and metastasis through regulation of the cell cycle[37,38]. Since EZH2 loss-of-function is associated with the development of cancer, it is considered a tumor suppressor. EZH2 is overexpressed in various cancer types, consequently, it can also function as an oncogene[37].

Alterations and prevalence: Diverse EZH2 alterations including missense, nonsense, frameshift mutations, and inactivating deletions are observed in 18-25% of T-cell acute lymphocytic leukemia (T-ALL), 3-13% of myeloproliferative neoplasms (MPN), 8-12% of myelodysplastic/myeloproliferative neoplasms overlap disorders (MDS/MPN), and 6% of diverse MDS[38,39]. Heterozygous gain-of-function mutations at tyrosine 641 (Y641) are observed in 22% of germinal center B-cell (GBC) and diffuse large B-cell lymphoma (DLBCL), and 7-17% of follicular lymphoma (FL)[38,40]. In solid tumors, EZH2 mutations are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 3% of cholangiocarcinoma[5,6]. Amplifications are observed in up to 7% of ovarian carcinoma[5,6]. Increased EZH2 copy number corresponds with enhanced protein expression and is observed in over 50% of hormone-refractory prostate cancers[41].

Potential relevance: The methyltransferase inhibitor tazemetostat[42] was FDA approved (2020) for EZH2 mutated relapsed or refractory follicular lymphoma after at least 2 prior systemic therapies. Tazemetostat was also granted FDA fast track designation in 2016 for DLBCL harboring EZH2 activating mutations[43]. Somatic mutation in EZH2 is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR)[44]. EZH2 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and MDS/MPN[45]. EZH2 mutations also confer poor prognosis in essential thrombocythemia (ET), primary myelofibrosis (PMF), and AML[46,47,48]. EZH2 overexpression correlates with malignancy, poor prognosis, and poor survival, and has been detected in MDS and acute myeloid leukemia (AML)[37,49]. Several studies have shown that EZH2 overexpression enhances chemoresistance in solid tumor types[50,51].

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[52,53]. 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[52]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[54,55]. 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[23,56]. 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[57,58]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[53,58,59,60,61].

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

Potential relevance: The PARP inhibitor, talazoparib[32] 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[62,63]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[61].

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes the lysine methyltransferase 2A protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily. KMT2A influences epigenetic regulation by means of its methyltransferase activity, which regulates a variety of cellular functions including neurogenesis, hematopoiesis, and osteogenesis[64]. Located at the chromosomal position 11q23, KMT2A is the

Biomarker Descriptions (continued)

target of recurrent chromosomal rearrangements observed in several leukemia subtypes including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[65]. Such translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[65]. Loss of methyltransferase activity along with partner gene gain of function contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[65,66,67,68].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[47,65,69]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[65]. In infant acute leukemic cases, KMT2A rearrangement is reported in up to 70% of those diagnosed with either AML or ALL[65,70,71]. Mutations in KMT2A are also reported in diverse solid tumors including 10-20% of melanoma, stomach, bladder, and uterine cancers and around 5% of lung and head and neck cancers[5]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations which result in KMT2A truncation and loss of methyltransferase activity[5,72].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[47,48]. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML[73,74,75]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[46]. KMT2A fusion is also associated with poor risk in ALL[76]. In 2024, the FDA approved the oral menin inhibitor, revumenib[77], for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also grant fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[78].

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)[79].

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[5,6]. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively[80]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[5,6].

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

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[81,82]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[83]. 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[81,82,84]. 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[85].

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%)[6]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[6]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[86,87,88].

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

Biomarker Descriptions (continued)

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[89]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process. Mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[90]. PMS2, along with MLH1, MSH6, and MSH2, form the core components of the MMR pathway[89,90]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. 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[91,92,93]. 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[91,94]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[92,94,95,96].

Alterations and prevalence: Somatic mutations in PMS2 are observed in 7% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, and 4% of adrenocortical carcinoma[5,6].

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[97]. 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[98,99].

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[100]. 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[100,101,102]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[100].

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

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

ARID2 deletion

AT-rich interaction domain 2

Background: The ARID2 gene encodes the AT-rich interaction domain 2 protein[1]. ARID2, also known as BAF200, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID5B[103]. ARID2 is an essential member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[103,104]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[104,105]. ARID2 may alter the expression of IFN responsive genes, which suppress cell proliferation[103]. Loss of function mutations in ARID2 may promote cell proliferation, suggesting a tumor suppressor role of ARID2[103].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[106]. Somatic mutations in ARID2 are observed in 17% of skin cutaneous melanoma, 11% of uterine corpus endometrial carcinoma, 8% of bladder urothelial carcinoma and stomach adenocarcinoma, 7% of colorectal adenocarcinoma, and 5% of liver hepatocellular carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[5,6]. ARID2 biallelic deletions are observed in 2% of mesothelioma[5,6].

Potential relevance: Currently, no therapies are approved for ARID2 aberrations.

ATM deletion

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[107]. ATM and ATR act as master regulators of

Biomarker Descriptions (continued)

DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[108]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[108,109]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[110]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[22,23]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[111].

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

Potential relevance: The PARP inhibitor, olaparib[112] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[32] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[22,113,114]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[115]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[116], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

MLH1 p.(V384D) c.1151T>A

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[89]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[89,90]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates to mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[117,118]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[89]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. 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[91,92,93]. 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[91,94]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[92,94,95,96]. Specifically, MLH1 mutations are associated with increased risk of ovarian and pancreatic cancer[119,120,121,122].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[5,6].

Potential relevance: The PARP inhibitor, talazoparib[32] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[97]. 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[98,99].

PALB2 deletion

partner and localizer of BRCA2

Background: The PALB2 gene encodes the partner and localizer of BRCA2 protein that binds to and promotes intranuclear localization of the breast cancer 2 early onset (BRCA2) protein[123]. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA) complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCM. FA genes are tumor suppressors that play a role in interstrand cross-link (ICL) DNA repair through homologous recombination repair (HRR) of double-strand breaks (DSB) and nucleotide excision repair (NER)[52]. Loss of function mutations of genes in the FA family and HRR pathway, including PALB2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[23,56]. 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[57,58]. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric

Biomarker Descriptions (continued)

malignancies[124,125]. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer[124,126].

Alterations and prevalence: Somatic alterations in PALB2 include missense or truncating mutations and are observed in 2-6% of melanoma, uterine, bladder, breast, lung, stomach and colorectal cancers[5].

Potential relevance: The PARP inhibitor, olaparib[112] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes PALB2. Additionally, talazoparib[32] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes PALB2. In a phase II trial of patients with metastatic, castration-resistant prostate cancer, one patient exhibiting a somatic PALB2 frameshift mutation exhibited durable response to olaparib for 39 weeks[115,127]. However, olaparib resistance was observed following 9-months of treatment due to the emergence of a secondary deletion which restored the PALB2 reading frame, a resistance mechanism similar to that observed in PARPi treated BRCA mutated patients[127,128]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[116], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Rucaparib is recommended as a maintenance therapy for germline or somatic PALB2 mutations in metastatic pancreatic cancer[129].

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[130]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[92,94]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[93]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[131]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[131]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[95,132,133,134,135]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[94]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[92,94,95,96].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[92,94,136,137]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[136,137].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[97] (2014) and nivolumab[98] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[97] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[97]. Dostarlimab[138] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[133,139]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[99] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[133,140,141]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[141]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[142,143]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[142,143].

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[144]. All RUNX proteins share several conserved regions with similar functionality including a highly conserved N-terminal ‘runt’ domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[145]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved

Biomarker Descriptions (continued)

in hematopoietic differentiation and cell cycle regulation[146,147]. RUNX1 is frequently mutated in various hematological malignancies[147]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[148,149]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[147].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[150]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 20-25% of childhood ALL[151,152]. This translocation is also observed in adult ALL at a lower frequency (2%)[152]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[153]. The RUNX1::RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[147,153]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[147]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[5,45,47,147].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[44,47]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1 in AML and t(12;21)(q34;q11)/ETV6::RUNX1 in ALL, are associated with favorable risk[48,76]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[45,48,154].

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[155]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[156,157]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[158]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and is observed almost exclusively in children less than 3 years of age[159].

Alterations and prevalence: Somatic mutations are observed in 4% endometrial carcinoma, 2% esophageal adenocarcinoma, and stomach adenocarcinoma[6]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[6].

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

STAG2 deletion

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[160,161]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[162,163]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[162,164].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[45]. Somatic mutations in STAG2 are observed in various solid tumors including 14% of bladder cancer, 10% of uterine cancer, 3% of stomach cancer, and 4% of lung adenocarcinoma[6]. In addition, mutations in STAG2 are observed in 5-10% of myelodysplastic syndrome(MDS), 3% of acute myeloid leukemia, and 2% of diffuse large B-cell lymphoma[6,45].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and Acute Myeloid Leukemia[45,47,48]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[165].

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

Biomarker Descriptions (continued)

membrane[166,167]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[168,169].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[5,6]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[170]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[5,6].

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

GATA3 deletion

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3[1]. GATA3 is a zinc-finger transcription factor that functions in the differentiation of immune cells and tissue development[171,172]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[171].

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma, skin cutaneous melanoma[5,6]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[5,6].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[171,173].

MEN1 deletion

menin 1

Background: The MEN1 gene encodes the menin 1 protein[1]. MEN1 is a tumor suppressor that functions as a scaffold protein and is known to play a role in histone modification and epigenetic gene regulation through alteration of chromatin structure[1,174]. MEN1 also interacts with several proteins involved in transcription, signaling pathways, and cell division, including JUND, NF-κB, SMAD3, and estrogen receptor α[174,175,176]. Germline mutations in MEN1 result in multiple endocrine neoplasia type 1 (also referred to as MEN1), which is an inherited familial cancer syndrome that causes a predisposition to endocrine tumors, including pituitary, parathyroid, and pancreatic cancer[175,176].

Alterations and prevalence: Somatic mutations in MEN1 are observed in 8% of adrenocortical carcinoma, 5% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and skin cutaneous melanoma[5,6]. Biallelic deletion of MEN1 is observed in 1% of adrenocortical carcinoma and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for MEN1 aberrations.

KMT2C deletion

lysine methyltransferase 2C

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2C belongs to the SET domain protein methyltransferase superfamily[177]. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type[178]. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes[179,180]. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes[179,180]. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation[178].

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma[5,6]. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma[5,6].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for KMT2C aberrations.

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2[1]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[181]. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)[182,183]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[182]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[182,184].

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases[5,185]. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases[5,185].

Potential relevance: The PARP inhibitor, olaparib[112] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[116], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[186,187,188]. Activation of MAPK proteins occurs through a kinase signaling cascade[186,187,189]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[186,187,189]. 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[186,187,189].

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

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

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,190]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[191,192]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[191,192,193]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[190,191,192,193]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[191]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[191].

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

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

Biomarker Descriptions (continued)

ACVR1B deletion

activin A receptor type 1B

Background: The ACVR1B gene encodes the activin A type 1B receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family[1,194]. ACVR1B is a type I receptor that forms a heterotetrametric complex with at least two type I receptors (including ACVR1) and two type II receptors (including BMPR2, ACVR2A, and ACVR2B)[194,195]. 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[194,195]. Loss of function mutations and homozygous deletion in ACVR1B has been observed in pancreatic cancer and is associated with increased cell growth, colony formation, and tumorigenicity[196,197].

Alterations and prevalence: Somatic mutations of ACVR1B are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, 3% of stomach adenocarcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and kidney chromophobe, and 1% of head and neck squamous cell carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, brain lower grade glioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma, and acute myeloid leukemia[5,6]. Biallelic deletion of ACRV1B is observed in 1% of stomach adenocarcinoma, brain lower grade glioma, and pancreatic adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ACVR1B aberrations.

PHF6 deletion

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[198,199].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[198,200,201,202]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[200,202]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[200]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[198,200].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[203].

KMT2D deletion

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2D belongs to the SET domain protein methyltransferase superfamily[177]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[177]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[177].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KMT2D aberrations.

XRCC2 deletion

X-ray repair cross complementing 2

Background: The XRCC2 gene encodes the X-ray repair cross complementing 2 protein, also known as FANCU, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC3 paralogs[1,204,205]. XRCC2 forms the BCDX2 complex with other RAD51 paralogs, RAD51B, RAD51C, and RAD51D[204,205]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze

Biomarker Descriptions (continued)

ATP[206]. XRCC2 regulates the assembly of RAD51 filaments to assist in strand-exchange activity during homologous recombination repair (HRR)[204,205]. XRCC2 germline biallelic mutations result in Fanconi Anemia (FA) complementation group U, an atypical form of FA associated with defects in HRR[207].

Alterations and prevalence: Somatic mutations in XRCC2 are observed in 3% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[5,6]. Biallelic deletions in XRCC2 are observed in 2% of acute myeloid leukemia (AML), sarcoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for XRCC2 aberrations. Pre-clinical evidence suggests that XRCC2 biallelic mutations may demonstrate sensitivity to the PARP inhibitor olaparib[208].

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[209]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[210]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[211,212,213]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[214].

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

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

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[209]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[210]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[211,212,213]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[214].

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

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

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[186]. Activation of MAPK proteins occurs through a kinase signaling cascade[186,187,189]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[186,187,189]. 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[186,187,189]. 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[215].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[5,6]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[5,6]. Nonsense, frameshift, and missense

Biomarker Descriptions (continued)

mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[216,217].

Potential relevance: Currently, no therapies are approved for MA2PK4 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[218]. ERCC2 functions as a helicase along with ERCC3/XPB in the TFIIH core complex[218]. 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[218]. Following lesion binding and verification, ERCC2 unwinds DNA in the 5'-3' direction[218]. Mutations in ERCC2 lead to stalled RNA polymerase, resulting in persistent block of transcription[218]. Germline ERCC2 mutations can lead to hereditary disorders including: Cockayne syndrome, characterized by skin cancer susceptibility and neurodegerneration; xeroderma pigmentosum (XP), characterized by neurodegeneration and developmental defects; and trichothiodystrophy (TTD), characterized by brittle hair due to sulfur deficiency as well as other developmental defects[218,219].

Alterations and prevalence: Somatic mutations in ERCC2 are predominantly missense and occur in 9% of bladder urothelial carcinoma, 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of lung squamous cell carcinoma[5,6]. The missense mutation, N238S, is observed to be recurrent in bladder urothelial carcinoma and is predicted to result in ERCC2 loss of function[5,6,220]. Biallelic loss of ERCC2 is observed in 2% of brain lower grade glioma and diffuse large B-cell lymphoma, as well as 1% of sarcoma and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ERCC2 aberrations. In one study, ERCC2 mutations correlated with enhanced response to cisplatin based chemotherapy compared to wild-type ERCC2 in patients with muscle-invasive urothelial carcinoma[221].

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[1,222,223]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[223,224]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[225,226,227,228,229]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[225,228,230,231].

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

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

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[232,233]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[234]. 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[234]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[235].

Biomarker Descriptions (continued)

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

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

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,236]. Through its interaction with β-catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC[236,237,238]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[236]. Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2[236].

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

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

CCND1 amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[239,240,241]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[239,240]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[239,240,242]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[241,243].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[5,6,244,245]. These mutations block phosphorylation-dependent nuclear export and proteolysis[246,247,248,249]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[5,6,250]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[251,252].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma[253].

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[254]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[255,256]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[257]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[258]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[259].

Biomarker Descriptions (continued)

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[5,6]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[256,260,261,262,263]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[5,6].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[264,265]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[116], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[266] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

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[267,268]. 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)[89,218,267,268]. Independent of Polδ, POLD1 associates with γ-tubulin ring complexes to control cytoplasmic microtubule growth[267]. Germline mutations in POLD1 are associated with polymerase proofreading-associated polyposis, which confers predisposition to colorectal adenomas and carcinomas[269,270,271,272,273].

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

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

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[274,275,276]. 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[275,276]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[276]

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[5]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[5]. 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[277]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[277].

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)[44,47,48].

CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,278]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,278]. 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[278]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[278].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[5,6]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[5,6]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[278,279].

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[280,281].

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[282,283]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[282]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[282].

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

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

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)[1,284,285]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[284,285,286,287]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[285]. 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[285,288].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[5,6]. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[5,6]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for NCOR1 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)[289]. 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)[289]. 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[289].

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

Biomarker Descriptions (continued)

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

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

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[186]. Activation of MAPK proteins occurs through a kinase signaling cascade[186,187,189]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[186,187,189]. 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[186,187,189]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[290].

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma[5,6]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[5,6].

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

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)[291]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[291,292]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[291]. 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[291,293].

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, and 4% of esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for HDAC9 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[294]. 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[295]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[296]. 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[297].

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[298]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[298,299]. 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[300,301,302].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[5,6]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[5,6]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[5,6,303]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[303].

Biomarker Descriptions (continued)

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

CDH1 deletion

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,304]. 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[305]. 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[306,307]. 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[308].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[5,6,309,310]. 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[5,6]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[5,6].

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

POT1 deletion

protection of telomeres 1

Background: The POT1 gene encodes the protection of telomeres 1 protein, a nuclear protein and member of the Shelterin complex along with TERF1, TERF2, TPP1, TINF2, and TERF2IP[311]. The Shelterin complex is responsible for the protection and maintenance telomeres[1,311,312]. POT1 mediates the association of the Shelterin complex with single-stranded telomeric DNA, resulting in the prevention of telomerase binding and subsequent telomere elongation[311,313]. POT1 also inhibits inappropriate DNA damage response at telomeres by preventing the binding of RPA and inhibiting recruitment of ATR, thereby protecting telomeres from erroneous repair[312]. Loss of function POT1 germline mutations have been observed in melanoma, chronic lymphocytic leukemia (CLL), angiosarcoma, and glioma[312].

Alterations and prevalence: Somatic mutations in POT1 are observed in 5% of uterine corpus endometrial carcinoma, 3% of bladder urothelial carcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for POT1 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[1,314]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[105,314].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[105]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[105,106]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[314].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[106]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[5,6]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[5,6].

Biomarker Descriptions (continued)

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[315,316].

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. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[317,318]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer[319] and in men for breast and prostate cancer[320,321]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer[322].테스트 입니다.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer[323,324,325,326,327,328,329]. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers[5,6].

Potential clinical 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)[330]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[331,332]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[] (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 who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Rucaparib[] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with two or more chemotherapies. Talazoparib[] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Due to efficacy in both gBRCAm and non-gBRCAm patients, Niraparib (2017) is another PARPi approved for maintenance of epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of BRCA status[333]. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[334]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[128].

TP53 deletion, TP53 p.(V143M) c.427G>A

tumor protein p53

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[335]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[336,337].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[5,6,250,338,339,340]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[341,342,343,344].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[345]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[346] and breakthrough designation[347] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[348,349]. 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)[45,46,47,48,76,350]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell

Biomarker Descriptions (continued)

transplant[253]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[351].

FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members[352,353]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[352,353]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival[354,355,356]. FGF19 is specifically observed to bind FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation[357,358]. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma[357,359].

Alterations and prevalence: FGF19 amplification is observed in about 35% of esophageal cancer, 23% of head and neck cancer, 10-15% of invasive breast carcinoma, cholangiocarcinoma, squamous lung, and bladder cancers as well as 5-7% of melanoma, liver, ovarian, and stomach cancers[5]. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma[360].

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. Selective, irreversible FGFR4 inhibitors, including fisogatinib (BLU-554), are under current clinical trial evaluation. In a phase-I clinical study of fisogatinib in patients with advanced hepatocellular carcinoma, 63% of the 115 patients enrolled were FGF19-positive by IHC[361]. Additionally, in 53 patients with tissue available for evaluation, 96% also exhibited mRNA-expression of FGFR4 and KLB. The total overall response rate observed for fisogatinib in FGF19-positive patients evaluable for response was 17% (11/66)[361].

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,

Genes Assayed (continued)

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

NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

BRCA2 deletion

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

* 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

ATM deletion

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

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)
PF-07220060, midazolam	✖	✖	✖	✖	● (I/II)

CHEK1 deletion

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

FANCA deletion

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

LATS2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IAG-933	✖	✖	✖	✖	● (I)

MLH1 p.(V384D) c.1151T>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ipilimumab + nivolumab, atezolizumab + talazoparib	✖	✖	✖	✖	● (II)

PALB2 deletion

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

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

Relevant Therapy Summary (continued)

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

PTEN deletion

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

RB1 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***27.93%***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***
CHEK1	***CNV, CN:1.0***
CHEK1	***LOH, 11q24.2(125496639-125525271)x1***
PALB2	***CNV, CN:1.0***
PALB2	***LOH, 16p12.2(23614759-23652528)x1***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.0.2 data version 2025.04(004)). 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 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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