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Patient Name: 김수훈
Gender: Male
Sample ID: N26-8

Primary Tumor Site: unknown
Collection Date: 2025.11.17

Sample Cancer Type: Unknown Primary Origin

Report Highlights

7 Relevant Biomarkers
3 Therapies Available
16 Clinical Trials

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+	4
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	4
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	2
IIC	*CDKN2A p.(H83R) c.248A>G* cyclin dependent kinase inhibitor 2A Allele Frequency: 76.30% Locus: chr9:21971110 Transcript: NM_001195132.2	None*	None*	6
IIC	*TP53 deletion* tumor protein p53 Locus: chr17:7572848	None*	None*	2
IIC	*ARID2 deletion* AT-rich interaction domain 2 Locus: chr12:46123536	None*	None*	1
IIC	*FANCD2 deletion* Fanconi anemia complementation group D2 Locus: chr3:10070306	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

CDKN1A deletion, CUL4A deletion, FANCE deletion, LATS2 deletion, MAP2K4 deletion, MLH1 deletion, Microsatellite stable, PARP3 deletion, PARP4 deletion, PMS2 deletion, RNASEH2B deletion, RPA1 deletion, SETD2 deletion, TP53 c.783-1G>T, XRCC3 deletion, TGFBR2 deletion, DOCK3 deletion, PBRM1 deletion, FAT1 p.(Y1145) c.3435C>A, TPMT p.(Y240C) c.719A>G, HLA-A deletion, HLA-B deletion, NOTCH4 deletion, TAP2 deletion, TAP1 deletion, DAXX deletion, HDAC9 deletion, KMT2D deletion, ACVR1B deletion, TPP2 deletion, DICER1 deletion, CYLD deletion, CYLD p.(E857*) c.2569G>T, NQO1 p.(P187S) c.559C>T, GPS2 deletion, NCOR1 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CDKN2A	p.(H83R)	c.248A>G	COSM13253	chr9:21971110	76.30%	NM_001195132.2	missense
TP53	p.(?)	c.783-1G>T	.	chr17:7577156	60.19%	NM_000546.6	unknown
FAT1	p.(Y1145*)	c.3435C>A	.	chr4:187584598	73.81%	NM_005245.4	nonsense
TPMT	p.(Y240C)	c.719A>G	COSM4986703	chr6:18130918	18.53%	NM_000367.5	missense
CYLD	p.(E857*)	c.2569G>T	.	chr16:50828231	59.11%	NM_001042355.2	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.25%	NM_000903.3	missense
OR2M3	p.(G249V)	c.746G>T	.	chr1:248367115	37.93%	NM_001004689.1	missense
TET2	p.(D1427V)	c.4280A>T	.	chr4:106193818	75.28%	NM_001127208.3	missense
FBXW7	p.(D560H)	c.1678G>C	.	chr4:153245513	76.45%	NM_033632.3	missense
HCN1	p.(A520Cfs*9)	c.1557_1558insT	.	chr5:45303761	38.22%	NM_021072.4	frameshift Insertion
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	83.64%	NM_005514.8	missense, missense
MALRD1	p.(T906A)	c.2716A>G	.	chr10:19498334	52.40%	NM_001142308.3	missense
MGA	p.(N1217K)	c.3651T>A	.	chr15:42019598	37.37%	NM_001164273.1	missense
MAP2K2	p.(R231L)	c.692G>T	.	chr19:4101030	41.83%	NM_030662.4	missense
USP9X	p.(E635K)	c.1903G>A	.	chrX:41022048	72.90%	NM_001039590.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.64
BAP1	chr3:52436290	0.97	0.62
RB1	chr13:48877953	1.05	0.65
TP53	chr17:7572848	1.16	0.69
ARID2	chr12:46123536	0.93	0.61
FANCD2	chr3:10070306	1.03	0.64
CDKN1A	chr6:36645655	0.88	0.58
CUL4A	chr13:113863977	0.97	0.62

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
FANCE	chr6:35420188	1.11	0.67
LATS2	chr13:21548922	0.93	0.6
MAP2K4	chr17:11924164	1.03	0.64
MLH1	chr3:37034957	1.03	0.64
PARP3	chr3:51976651	1.05	0.65
PARP4	chr13:25000551	0.96	0.61
PMS2	chr7:6012922	0.97	0.62
RNASEH2B	chr13:51484145	1.05	0.65
RPA1	chr17:1733385	1.01	0.64
SETD2	chr3:47058542	1	0.63
XRCC3	chr14:104165043	0.93	0.6
TGFBR2	chr3:30648337	0.96	0.61
DOCK3	chr3:51101879	0.84	0.57
PBRM1	chr3:52582040	1.03	0.64
HLA-A	chr6:29910229	0.72	0.52
HLA-B	chr6:31322252	0.35	0.39
NOTCH4	chr6:32163187	0.91	0.59
TAP2	chr6:32796585	0.97	0.62
TAP1	chr6:32814849	0.88	0.59
DAXX	chr6:33286486	0.97	0.62
HDAC9	chr7:18201905	0.93	0.6
KMT2D	chr12:49415529	0.95	0.61
ACVR1B	chr12:52345528	1.19	0.7
TPP2	chr13:103249399	1	0.63
DICER1	chr14:95556791	0.97	0.62
CYLD	chr16:50783549	1.07	0.65
GPS2	chr17:7216071	1.08	0.66
NCOR1	chr17:15935586	0.99	0.63
RAF1	chr3:12625930	0.97	0.62
MYD88	chr3:38180156	1.12	0.68
MITF	chr3:69788729	1.12	0.68
DDR1	chr6:30852922	1.08	0.66
PIM1	chr6:37138341	1.18	0.69
CCND3	chr6:41903600	0.96	0.61

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CARD11	chr7:2949684	1.03	0.64
RAC1	chr7:6426823	1.18	0.7
GLI3	chr7:42003880	0.91	0.6
EGFR	chr7:55211010	1	0.63
ERBB3	chr12:56477596	0.95	0.61
STAT6	chr12:57490294	1.07	0.65
CDK4	chr12:58142242	1.11	0.67
FGF9	chr13:22245989	0.95	0.61
FLT3	chr13:28578185	1.08	0.66
KLF5	chr13:73633435	1.03	0.64
AKT1	chr14:105236628	0.86	0.58

Biomarker Descriptions

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[37,38]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[37,38]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[39,40,41]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[39,42].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[43,44,45,46,47,48,49,50]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[7,8].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[51]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[52,53]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[54] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[54] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[55] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[56] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[56] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA2. Niraparib[57] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[58]

Biomarker Descriptions (continued)

received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib[59] received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[60]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[61]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[62], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[217]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[217]. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[218,219,220,221,222,223].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[7,8]. BAP1 biallelic deletions are observed in 11% of mesothelioma[7,8].

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

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer[82]. 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[82,83]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[84]. 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[82,83,85]. 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[86].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in 20% of bladder urothelial carcinoma, 13% of uterine corpus endometrial carcinoma, and 10% of sarcoma and glioblastoma multiforme[7,8]. Biallelic loss of RB1 is also observed in several cancers including 15% of sarcoma, 10% of prostate adenocarciona, 9% of uterine carcinosarcoma, ovarian serous cystadenocarcinoma, and bladder urothelial carcinoma, 5% of liver hepatocellular carcinoma and adrenocortical carcinoma, and 4% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[7,8]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[87,88,89]. Alterations in RB1 are also observed in pediatric cancers[8]. Somatic mutations in RB1 are observed in 52% of retinoblastoma (16 in 31 cases), 3% of bone cancer (10 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), and leukemia (2 in 311 cases)[8]. Biallelic deletion of RB1 is observed in 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (28 in 731 cases), 3% of leukemia (7 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[8]. Structural variants in RB1 are observed in 3% of bone cancer (5 in 150 cases)[8].

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

CDKN2A p.(H83R) c.248A>G

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[180]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[181,182,183]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[184]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,184,185]. CDKN2A aberrations commonly co-occur with CDKN2B[180]. Loss of CDKN2A/p16 results in downstream

Biomarker Descriptions (continued)

inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[186]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[187,188].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[189]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[7,8]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[7,8]. Alterations in CDKN2A are also observed in pediatric cancers[8]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[8]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[8].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[190,191,192]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[193]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[194,195,196]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[197]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[198,199,200,201].

TP53 c.783-1G>T, TP53 deletion

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[224]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[225]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[226,227].

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%)[7,8,228,229,230,231]. 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[7,8]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[232,233,234,235]. Alterations in TP53 are also observed in pediatric cancers[7,8]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[7,8]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[7,8].

Potential relevance: The small molecule p53 reactivator, PC14586[236] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[237,238]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[239]. 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)[240,241,242,243,244]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[245]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[246].

Biomarker Descriptions (continued)

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[110]. ARID2 is an essential member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[71,110]. 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[70,71]. ARID2 may alter the expression of IFN responsive genes, which suppress cell proliferation[110]. Loss of function mutations in ARID2 may promote cell proliferation, suggesting a tumor suppressor role of ARID2[110].

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[111]. 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[7,8]. ARID2 biallelic deletions are observed in 2% of mesothelioma[7,8].

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

FANCD2 deletion

Fanconi anemia complementation group D2

Background: The FANCD2 gene encodes the FA complementation group D2 protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), 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[26,27]. 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[26]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[28,29]. Loss of function mutations in the FA family and HRR pathway, including FANCD2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[30,31]. 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[32,33].

Alterations and prevalence: Somatic mutations in FANCD2 are observed in 4-8% of diffuse large B-cell lymphoma (DLBCL), melanoma, bladder, and uterine cancer[7].

Potential relevance: Currently, no therapies are approved for FANCD2 aberrations. Consistent with other genes that contribute to the BRCAness phenotype, FANCD2 deficiency or loss of function has been shown to confer enhanced sensitivity to PARP inhibitors in vitro[34,35,36].

CDKN1A deletion

cyclin dependent kinase inhibitor 1A

Background: The CDKN1A gene encodes the cyclin-dependent kinase inhibitor 1A protein, also known as p21 or WAF1[1,177]. CDKN1A belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1B (also known as KIP/p27) and CDKN2C (also known as KIP2/p57)[177,178]. Through inhibition of cyclin dependent kinases, including CDK1 and CDK2, CDKN1A impacts several biological processes, including cell cycle arrest, differentiation, gene transcription, apoptosis, and DNA repair[179]. CDKN1A is also capable of binding to proliferating cell nuclear antigen (PCNA) and inhibiting PCNA-dependent DNA polymerase activity[179]. Deregulation of CDKN1A, including loss of expression, is observed in several tumor types, supporting a tumor suppressor role for CDKN1A[179].

Alterations and prevalence: Somatic mutations in CDKN1A are observed in 10% of bladder urothelial carcinoma, 3% of kidney chromophobe, and 2% of skin cutaneous melanoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[7,8]. Biallelic deletion of CDKN1A is observed in 2% of kidney chromophobe and 1% of sarcoma[7,8].

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

Biomarker Descriptions (continued)

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[1,9]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[10]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[10,11]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[9]. 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[11]. 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[10,11].

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[7,8]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[7,8]. 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[7,8]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[7,8].

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

FANCE deletion

Fanconi anemia complementation group E

Background: The FANCE gene encodes the FA complementation group E protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[26,27]. 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[26]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[28,29]. Loss of function mutations in the FA family and HRR pathway, including FANCE, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[30,31]. 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[32,33].

Alterations and prevalence: Somatic mutations in FANCE are observed in 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL), skin cutaneous melanoma, and uterine carcinosarcoma[7,8].

Potential relevance: Currently, no therapies are approved for FANCE 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[141,142]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[143]. 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[143]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[144].

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[7,8]. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma[7,8].

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

Biomarker Descriptions (continued)

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[118]. Activation of MAPK proteins occurs through a kinase signaling cascade[118,119,120]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[118,119,120]. 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[118,119,120]. 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[121].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[7,8]. 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[7,8]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[122,123].

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

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[90]. 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[90,91]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[112,113]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[90]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[90]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[92]. 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[93,94,95]. 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[93,96]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[94,96,97,98]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[114,115,116,117].

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[7,8]. Alterations in MLH1 are observed in pediatric cancers[7,8]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[7,8].

Potential relevance: The PARP inhibitor, talazoparib[56] 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[99]. 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[100,101]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[102,103].

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[124]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[94,96]. 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[95]. 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[125]. 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)[125]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[97,126,127,128,129]. 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[96].

Biomarker Descriptions (continued)

LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[94,96,97,98].

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[94,96,130,131]. 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[130,131].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[99] (2014) and nivolumab[100] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[99] 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[99]. Dostarlimab[132] (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[127,133]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[101] (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[127,134,135]. 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[135]. 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[136,137]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[136,137].

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[64]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[64,65]. PARP enzymes are involved in several DNA repair pathways[64,65]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[66,67]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[66].

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma[7,8]. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma[7,8].

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[68,69]. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[54] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[54] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[55] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[56] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[57] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein[1]. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3[64]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis,

Biomarker Descriptions (continued)

nucleic acid metabolism, and regulation of chromatin structure[64,65]. PARP enzymes are involved in several DNA repair pathways[64,65]. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins[150].

Alterations and prevalence: Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma[7,8]. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)[7,8].

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (HRR) deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[68,69]. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[54] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[54] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[55] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[56] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[57] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

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[90]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process[1]. Mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[91]. PMS2, along with MLH1, MSH6, and MSH2, form the core components of the MMR pathway[90,91]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[90]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[92]. 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[93,94,95]. 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[93,96]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[94,96,97,98].

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[7,8]. Iterations in PMS2 are observed in pediatric cancers[7,8]. Somatic mutations are observed in 3% of soft tissue sarcoma, 2% of B-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)[7,8].

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[99]. 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[100,101]. PMS2 mutations are consistent with high grade in pediatric diffuse gliomas[102,103].

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[155,156]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[155]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[155].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[7,8]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[7,8].

Biomarker Descriptions (continued)

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

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[169]. 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)[169]. 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[169].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[7,8]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[7,8].

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

SETD2 deletion

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[208,209]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[210]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[211,212]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[209]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[213]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[209,214].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[7,214,215]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[7,208]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[208]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[208].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[216].

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[1,152]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[152,153]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[154].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[7,8]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[7,8].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[154].

Biomarker Descriptions (continued)

TGFBR2 deletion

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[20]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[20]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[20]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[21]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[22,23,24].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[7,8]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[7,8].

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

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[247]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,248,249]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[250,251]. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3[249].

Alterations and prevalence: Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe[7,8]. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma[7,8].

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

PBRM1 deletion

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[70]. 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[70,71]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[70,72]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[73,74].

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[7,8]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[7,8].

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

Biomarker Descriptions (continued)

FAT1 p.(Y1145*) c.3435C>A

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,25]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[25]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[25]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[25]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[25].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[7,8]. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma[7,8]. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma[7,8].

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

TPMT p.(Y240C) c.719A>G

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,138,139]. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine[138,139,140]. Inherited TPMT polymorphisms, including TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, and TPMT*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure[138,140].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[7,8]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[7,8]. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[7,8]. Alterations in TPMT are also observed in pediatric cancers[8]. Somatic mutations are observed in less than 1% of peripheral nervous system tumors (1 in 1158 cases)[8]. Amplification of TPMT is observed in 1% of peripheral nervous system tumors (1 in 91 cases)[8].

Potential relevance: Currently, no therapies are approved for TPMT 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[104]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[105]. 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[106,107,108]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[109].

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[7,8]. Biallelic loss of HLA-A is observed in 4% of DLBCL[7,8].

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

Biomarker Descriptions (continued)

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[104]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[105]. 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[106,107,108]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[109].

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[7,8]. Biallelic loss of HLA-B is observed in 5% of DLBCL[7,8].

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

NOTCH4 deletion

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[162]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[163,164]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[165,166,167,168].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[7].

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

TAP2 deletion

transporter 2, ATP binding cassette subfamily B member

Background: The TAP2 gene encodes the transporter 2, ATP binding cassette subfamily B member protein[1]. Along with TAP1, TAP2 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[145,146]. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression[149,151].

Alterations and prevalence: Somatic mutations in TAP2 are predominantly missense or truncating and have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and stomach adenocarcinoma, and 2% of lung adenocarcinoma[7,8]. Biallelic deletion of TAP2 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)[7,8].

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

TAP1 deletion

transporter 1, ATP binding cassette subfamily B member

Background: The TAP1 gene encodes the transporter 1, ATP binding cassette subfamily B member protein[1]. Along with TAP2 TAP1 is a member of the superfamily of ATP-binding cassette (ABC) transporters[1]. Together, TAP1 and TAP2 are capable of ATP-controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[145,146]. TAP1 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression and survival[147,148,149].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in TAP1 are predominantly missense or truncating and have been observed in 6% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma and thymoma[7,8]. Biallelic deletion of TAP1 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)[7,8].

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

DAXX deletion

death domain associated protein

Background: DAXX encodes the death domain associated protein, a transcription co-repressor known to repress the transcriptional potential of several sumoylated transcription factors[1]. DAXX mediates apoptosis through the death receptor pathway where it interacts and supports a multitude of cellular processes, which include gene regulation, transcriptional mediation through interaction with DNA-binding transcription factors, histones, and chromatin-associated proteins[12]. DAXX is proposed to function as a tumor suppressor due to its potential role in DNA damage repair(DDR) and through facilitating the inhibition of target genes by promoting H3K9 trimethylation[13,14].

Alterations and prevalence: Somatic mutations in DAXX are predominantly missense and truncating and occur in 5% of uterine corpus endometrial carcinoma, 3% skin cutaneous melanoma, adrenocortical carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of colorectal adenocarcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and glioblastoma multiforme[8]. DAXX mutations have also been observed to be enriched in pancreatic neuroendocrine tumors (Pan-NETs) with one study reporting mutations in 25% of 68 cases[15].

Potential relevance: Currently, no therapies are approved for DAXX 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)[170]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[170,171]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[170]. 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[170,172].

Alterations and prevalence: Somatic mutations in HDAC9 are observed in 16% of skin cutaneous melanoma, 8% of lung adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma and lung squamous cell carcinoma, 4% of esophageal adenocarcinoma, 3% of esophageal adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and kidney chromophobe[7,8]. Biallelic deletion of HDAC9 is observed in 2% of diffuse large B-cell lymphoma[8]. Alterations in HDAC9 are also observed in pediatric cancers[8]. Somatic mutations in HDAC9 are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[8]. Biallelic deletion of HDAC9 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[8].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat[173] (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies. The pan-HDAC inhibitor, romidepsin[174] (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy. The pan-HDAC inhibitor, belinostat[175] (2014), is approved for the treatment of relapsed or refractory PTCL. The FDA granted fast track designation to the pan-HDAC inhibitor, panobinostat[176] (2024), for the treatment of recurrent glioblastoma.

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[81]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[81]. Mutations

Biomarker Descriptions (continued)

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[81].

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[7,8].

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

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[1,16]. 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)[16,17]. 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[16,17]. 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[18,19].

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[7,8]. Biallelic deletion of ACRV1B is observed in 1% of stomach adenocarcinoma, brain lower grade glioma, and pancreatic adenocarcinoma[7,8].

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

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[63]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[63]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[63].

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[7,8]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[7,8].

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

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[75]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[75,76]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[75]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[75,76]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[76,77,78,79]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[80].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[7,8], 3% of lung squamous cell carcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, and stomach adenocarcinoma, and 2% of head and neck squamous cell carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma,

Biomarker Descriptions (continued)

liver hepatocellular carcinoma, kidney chromophobe, and glioblastoma multiforme[8]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% of kidney chromophobe[7,8]. Alterations in DICER1 are also observed in pediatric cancers[8]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of Hodgkin lymphoma (1 in 61 cases) and bone cancer (5 in 327 cases), 1% of glioma (4 in 297 cases), and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), peripheral nervous system cancers (2 in 1158 cases), and Wilms tumor (1 in 710 cases)[8]. Biallelic deletion of DICER1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[8].

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

CYLD deletion, CYLD p.(E857*) c.2569G>T

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[1,2]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[3]. 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[4,5]. 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[6]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[5,6]. 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[5].

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[7,8]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[7,8].

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

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[202]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[202,203]. 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[204,205,206].

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[7,8]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[7,8]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[7,8,207]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[207].

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

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,157,158]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[157,158,159,160]. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[158]. 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[158,161].

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

Biomarker Descriptions (continued)

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[7,8]. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[7,8]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[7,8]. Alterations in NCOR1 are also observed in pediatric cancer[8]. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)[8]. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)[8].

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

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

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed (continued)

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)
olaparib, pembrolizumab	✖	✖	✖	✖	○ (II)

BAP1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	◑ (II)
olaparib, pembrolizumab	✖	✖	✖	✖	○ (II)
tulmimetostat	✖	✖	✖	✖	○ (I/II)

RB1 deletion

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

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

Relevant Therapy Summary (continued)

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

CDKN2A p.(H83R) c.248A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ficlatuzumab, cetuximab	✖	✖	✖	✖	○ (III)
chemotherapy, cetuximab, radiation therapy, atezolizumab	✖	✖	✖	✖	○ (II/III)
niraparib, dostarlimab	✖	✖	✖	✖	○ (II)
pembrolizumab, nogapendekin alfa inbakicept, PD-L1 t-haNK	✖	✖	✖	✖	○ (II)
prexasertib, chemotherapy	✖	✖	✖	✖	○ (II)
ipatasertib, chemotherapy, radiation therapy	✖	✖	✖	✖	○ (I)

TP53 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
hormone therapy, hormone therapy + chemotherapy	✖	✖	✖	✖	○ (II)
A2A-252	✖	✖	✖	✖	○ (I)

ARID2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, pembrolizumab	✖	✖	✖	✖	○ (II)

FANCD2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, pembrolizumab	✖	✖	✖	✖	○ (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	***27.92%***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***

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

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

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