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Patient Name: 김선진
Gender: Male
Sample ID: N26-36

Primary Tumor Site: Skin
Collection Date: 2025.11.25

Sample Cancer Type: Cutaneous Squamous Cell Carcinoma

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Report Highlights

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Relevant Cutaneous Squamous Cell Carcinoma Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	***4.73 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PIK3CA p.(E542K) c.1624G>A* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 25.22% Locus: chr3:178936082 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1, 2 / I] **alpelisib + hormone therapy** [1, 2 / II+] **capivasertib + hormone therapy** [1, 2 / II+] aspirin [II+]	5
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	*CHEK1 deletion* checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	*FANCA deletion* Fanconi anemia complementation group A Locus: chr16:89804984	None*	None*	1

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

ABRAXAS1 deletion, KMT2A deletion, MLH3 deletion, MRE11 deletion, Microsatellite stable, PPP2R2A deletion, RAD51B deletion, STK11 c.735-1G>A, XRCC3 deletion, UGT1A1 p.(G71R) c.211G>A, HLA-B deletion, MEN1 deletion, DICER1 deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1 deletion, ZFHX3 deletion, PRKACA amplification, RUNX1 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(E542K)	c.1624G>A	COSM760	chr3:178936082	25.22%	NM_006218.4	missense
STK11	p.(?)	c.735-1G>A	COSM5732040	chr19:1221211	57.05%	NM_000455.5	unknown
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.78%	NM_000463.3	missense
OR2L8	p.(G196C)	c.586_588delGGCinsTGT	.	chr1:248112745	2.11%	NM_001001963.1	missense
PECR	p.(E149D)	c.447G>C	.	chr2:216923677	53.10%	NM_018441.6	missense
RAD50	p.(E1101K)	c.3301G>A	.	chr5:131953898	21.97%	NM_005732.4	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	98.59%	NM_005514.8	missense, missense
MET	p.(R1319K)	c.3956G>A	.	chr7:116435812	35.85%	NM_001127500.3	missense
ANXA7	p.(Q176E)	c.526C>G	.	chr10:75148148	3.25%	NM_004034.4	missense
KMT2A	p.(L1380R)	c.4139T>G	.	chr11:118354950	2.39%	NM_001197104.2	missense
NOTCH3	p.(E229D)	c.687G>C	.	chr19:15302671	18.45%	NM_000435.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ATM	chr11:108098341	1	0.66
CHEK1	chr11:125496639	1	0.7
FANCA	chr16:89804984	1.07	0.65
ABRAXAS1	chr4:84383635	1.04	0.64
KMT2A	chr11:118307146	1.08	0.66
MLH3	chr14:75483761	1.16	0.68
MRE11	chr11:94153270	1.11	0.66
PPP2R2A	chr8:26149298	1.08	0.65
RAD51B	chr14:68290164	1	0.7
XRCC3	chr14:104165043	0.97	0.61
HLA-B	chr6:31322252	0.8	0.55
MEN1	chr11:64571785	1.04	0.64
DICER1	chr14:95556791	1.13	0.68
CYLD	chr16:50783549	1.13	0.67

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CBFB	chr16:67063242	1.04	0.64
CTCF	chr16:67644720	1.11	0.66
CDH1	chr16:68771249	1.09	0.66
ZFHX3	chr16:72820995	0.95	0.61
PRKACA	chr19:14204349	6.96	2.86
RUNX1	chr21:36164357	1.13	0.68
NRAS	chr1:115251152	0.95	0.61
FGFR1	chr8:38271452	0.89	0.59
PXDNL	chr8:52233342	0.69	0.51
FAM135B	chr8:139144776	1.12	0.67
CCND1	chr11:69455949	0.91	0.59
FGF19	chr11:69513948	0.81	0.55
FGF4	chr11:69588019	0.69	0.51
EMSY	chr11:76157926	0.83	0.56
YAP1	chr11:101981594	0.87	0.58
MAX	chr14:65472833	1.01	0.63
MAP2K7	chr19:7968792	7.17	2.94
KEAP1	chr19:10597314	9.84	3.94
SMARCA4	chr19:11094814	8.23	3.34
RNASEH2A	chr19:12917452	13.51	5.31
NOTCH3	chr19:15271451	4.75	2.03

Biomarker Descriptions

PIK3CA p.(E542K) c.1624G>A

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

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[200]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[201,202]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[201]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[203,204]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[203,204,205,206]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[207,208,209].

Alterations and prevalence: Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[29,210]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[211,212,213]. Somatic mutations in PIK3CA are observed in 50% of uterine corpus endometrial carcinoma, 35% of uterine carcinosarcoma, 32% of breast invasive carcinoma, 29% of cervical

Biomarker Descriptions (continued)

squamous cell carcinoma, 28% of colorectal adenocarcinoma, 22% of bladder urothelial carcinoma, 17% of head and neck squamous cell carcinoma, 16% of stomach adenocarcinoma, 11% of lung squamous cell carcinoma, 9% of esophageal adenocarcinoma, 8% of brain lower grade glioma, 6% of cholangiocarcinoma, 5% of skin cutaneous melanoma and lung adenocarcinoma, 4% of liver hepatocellular carcinoma, 3% of pancreatic adenocarcinoma and sarcoma, and 2% of mesothelioma, prostate adenocarcinoma, testicular germ cell tumors, and ovarian serous cystadenocarcinoma[8,9]. PIK3CA is amplified in 38% of lung squamous cell carcinoma, 20% of ovarian serous cystadenocarcinoma, 18% of esophageal adenocarcinoma, 16% of head and neck squamous cell carcinoma, 15% of cervical squamous cell carcinoma, 11% of uterine carcinosarcoma, 7% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma, 4% of bladder urothelial carcinoma, 3% of breast invasive carcinoma and pancreatic adenocarcinoma, and 2% of prostate adenocarcinoma, lung adenocarcinoma, and kidney renal clear cell carcinoma[8,9]. Alterations in PIK3CA are also observed in pediatric cancers[9]. Somatic mutations in PIK3CA are observed in 6% of non-Hodgkin Lymphoma (1 in 17 cases), 4% of glioma (11 in 297 cases), 3% of soft tissue sarcoma (1 in 38 patients), 2% of embryonal tumors (6 in 332 cases), 1% of leukemia (5 in 354 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), and peripheral nervous system tumors (1 in 1158 cases)[9].

Potential relevance: The PI3K inhibitor, alpelisib[214], is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations[215]. However, alpelisib did not improve response when administered with letrozole in patients with ER + early breast cancer with PIK3CA mutations[216]. The FDA also approved the kinase inhibitor, capivasertib (2023)[217] in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib[218], is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[219,220]. In colorectal cancers, PIK3CA mutations predict significantly improved survival and reduced disease recurrence with adjuvant aspirin therapy, compared to no benefit in wild-type PIK3CA tumors[185,194,221,222]. In 2025, the FDA granted fast track designation to the PI3Kα inhibitor and degrader, ETX-636[223], for the treatment of PIK3CA-mutant, HR-positive/HER-negative advanced breast cancer.

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)[151]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[152]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[152,153]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[154]. 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[61,62]. 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[155].

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[8,9].

Potential relevance: The PARP inhibitor, olaparib[129] 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[71] 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[61,156,157]. 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[158]. However, gene-level analyses from the phase III PROfound trial indicate that ATM-mutated tumors do not experience meaningful radiographic progression-free survival (rPFS) or overall survival (OS) benefit from olaparib, and that the observed survival advantage in the broader HRR-altered population is largely driven by BRCA1/2 alterations rather than ATM[159,160]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[48], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

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[15]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[124]. 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)[125,126]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[125]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[125,127].

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[8,128]. 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[8,128].

Potential relevance: The PARP inhibitor, olaparib[129] 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[48], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FANCA deletion

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, and FANCN (PALB2)[15]. 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[75,76]. 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[75]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[77,78]. 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[62,79]. 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[80,81]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[76,81,82,83,84].

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

Potential relevance: The PARP inhibitor, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes 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[85,86]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[84].

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit[15]. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36[50,166]. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks[50]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[50]. Together with the rest of the BRCA1-A complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer[50,167].

Alterations and prevalence: Somatic mutations in ABRAXAS1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, and 1% of stomach adenocarcinoma and lung squamous cell carcinoma[8,9].

Biomarker Descriptions (continued)

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

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes lysine methyltransferase 2A, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[15,93]. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily[93]. KMT2A influences the epigenetic regulation of several cellular functions, including neurogenesis, hematopoiesis, and osteogenesis[94]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes, including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[95]. These translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[95]. Loss of methyltransferase activity, along with gain-of-function partner gene activation, contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[95,96,97,98].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of adult AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[8,9,95,99]. 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[95]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations, which result in KMT2A truncation and loss of methyltransferase activity[8,100]. KMT2A alterations are also observed in pediatric cancers[8,9]. In infant acute leukemic cases, KMT2A rearrangement is reported in more than 70% of pediatric patients diagnosed with either AML or ALL and is observed in 5% of T-lymphoblastic leukemia/lymphoma[8,9,95,101,102].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[32,42]. 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[103,104,105]. 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[106]. KMT2A fusion is also associated with poor risk in adult and pediatric ALL[33,34,107]. Translocations in KMT2A are recognized by the World Health Organization (WHO) as a molecular subtype of B-lymphoblastic leukemia/lymphoma with KMT2A-rearrangement[108]. In 2024, the FDA approved the oral menin inhibitor, revumenib[109], 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 granted fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[110].

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[15]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[53]. MLH3 is considered a mismatch repair (MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[53,54,55]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[56].

Alterations and prevalence: Somatic mutations in MLH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, skin cutaneous melanoma, and stomach adenocarcinoma[8,9]. Biallelic deletions are observed in 2% of kidney chromophobe[8,9].

Potential relevance: Currently, no therapies are approved for MLH3 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[57]. 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)[58,59,60]. 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[57]. 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[61,62]. 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[63,64,65,66].

Biomarker Descriptions (continued)

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[8]. 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[67,68,69,70]

Potential relevance: The PARP inhibitor, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors[61,62]. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro[72,73,74].

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[178]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[179,180]. 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[181]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[182]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[182]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[183,184,185,186,187]. 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[180]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[179,180,184,188].

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[179,180,189,190]. 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[189,190].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[191] (2014) and nivolumab[192] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[191] 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[191]. Dostarlimab[193] (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[185,194]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[195] (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[185,196,197]. 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[197]. 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[198,199]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[198,199].

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[43,44]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[45]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[43].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[43,44,46,47]. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[8].

Biomarker Descriptions (continued)

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[48], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[43]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[49].

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[161]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[162]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[163]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[61,62]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[164]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[165].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[8,9]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[165].

Potential relevance: The PARP inhibitor, olaparib[129] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[48], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

STK11 c.735-1G>A

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression[1]. STK11 preserves hematopoietic stem cell homeostasis, and its loss drives metabolic dysfunction and promotes leukemic progression in myeloproliferative neoplasms via ROS and HIF-1α activation[2,3]. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development[4,5].

Alterations and prevalence: Somatic mutations in STK11 are observed in 13% of lung adenocarcinoma, 4% of cervical squamous cell carcinoma, 3% of cholangiocarcinoma and uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, pancreatic adenocarcinoma, adrenocortical carcinoma, and esophageal adenocarcinoma[6,7,8,9]. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer[8,9]. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others[4,7,8,9,10]. Biallelic loss of STK11 is observed in 3% of sarcoma, cervical squamous cell carcinoma, and ovarian serous cystadenocarcinoma[8,9]. Alterations in STK11 are also observed in pediatric cancers[11]. Biallelic loss of STK11 is observed in 6% of B-lymphoblastic leukemia/lymphoma (45 in 731 cases), 2% of leukemia (4 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases)[11]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and glioma (1 in 297 cases)[11].

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260[12] in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors[13]. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)[14].

Biomarker Descriptions (continued)

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[15,50]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[50,51]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[52].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[8,9]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[52].

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[15,117]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[117,118]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[119]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[119,120,121,122]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[123].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[15]. 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[130]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[131]. 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[132,133,134]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[135].

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[8,9]. Biallelic loss of HLA-B is observed in 5% of DLBCL[8,9].

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

MEN1 deletion

menin 1

Background: The MEN1 gene encodes the menin 1 protein[15]. 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[15,111]. MEN1 interacts with several proteins involved in transcription, signaling pathways, and cell division, including JUND, NF-κB, SMAD3, and estrogen receptor α[111,112,113]. MEN1 also interacts with the lysine methyltransferase 2A gene, KMT2A (MLL1), and UBTF to influence

Biomarker Descriptions (continued)

HOX expression, whose dysregulation plays a critical role in leukemic transformation[114,115]. 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[112,113].

Alterations and prevalence: Somatic mutations in MEN1 are observed in 8% of adrenocortical carcinoma, 5% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of uterine carcinosarcoma, pancreatic adenocarcinoma, and colorectal adenocarcinoma[8,9]. Biallelic deletion of MEN1 is observed in 1% of adrenocortical carcinoma and esophageal adenocarcinoma[8,9]. Alterations in MEN1 are also observed in pediatric cancers[9]. Somatic mutations in MEN1 are observed in 3% soft tissue sarcoma (1 in 38 cases) and less than 1% of bone cancer (3 in 327 cases), embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and leukemia (1 in 311 cases)[9]. Biallelic deletion of MEN1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases), leukemia (2 in 250 cases), and Wilms tumor (1 in 136 cases)[9].

Potential relevance: Although not approved for specific MEN1 alterations, the menin inhibitor revumenib[109] (2024) is approved for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older. However, somatic missense mutations in MEN1, including S155T, M327V, G331R, G331D, and T349M, are associated with acquired resistance to revumenib treatment in KMT2A-rearranged and NPM1-mutated acute leukemia[116].

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[15]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[87]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[87,88]. 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[87]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[87,88]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[88,89,90,91]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[92].

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[8,9], 3% of lung squamous cell carcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, and stomach adenocarcinoma, and 2% of head and neck squamous cell carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, kidney chromophobe, and glioblastoma multiforme[9]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% of kidney chromophobe[8,9]. Alterations in DICER1 are also observed in pediatric cancers[9]. 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)[9]. Biallelic deletion of DICER1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[9].

Potential relevance: Currently, no therapies are approved for DICER1 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[15,16]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[17]. 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[18,19]. 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[20]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[19,20]. 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[19].

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[8,9].

Biomarker Descriptions (continued)

Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[8,9].

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

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[15]. 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[38,39,40]. 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[39,40]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[40]

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[8]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[8]. 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[41]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[41].

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)[31,32,42].

CTCF deletion

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[15]. 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[141]. 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[141,142,143]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[141].

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[8,9].

Potential relevance: Currently, no therapies are approved for CTCF 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)[15,144]. 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[15]. 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[145]. 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[146,147]. 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[148].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[8,9,149,150]. 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[8,9]. Biallelic deletion of CDH1 is

Biomarker Descriptions (continued)

observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[8,9].

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

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[15,168,169]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[169,170]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[171,172,173,174,175]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[171,174,176,177].

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[8,9]. 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[8,9].

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

PRKACA amplification

protein kinase cAMP-activated catalytic subunit alpha

Background: The PRKACA gene encodes the protein kinase cAMP-activated catalytic subunit alpha (C-alpha) of protein kinase A (PKA), an inactive tetrameric holoenzyme with two regulatory (R) subunits and two catalytic (C) subunits (namely PRKACA and PRKACB)[15]. PKA is a cAMP-dependent protein kinase involved in the phosphorylation of several downstream targets and an essential regulator of several cell signaling pathways including differentiation, proliferation, and apoptosis[15,136,137]. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins[15,136]. Aberrations in PRKACA are oncogenic, as they are predicted to abolish the interaction with R subunits leading to cAMP-independent activation of PKA[138]. Germline amplification and somatic mutation of PRKACA are associated with the development and pathogenesis of benign adrenal tumors leading to Cushing syndrome, which is characterized by overproduction of cortisol resulting in metabolic abnormalities[138,139].

Alterations and prevalence: Somatic mutations in PRKACA are predominantly missense and occur in about 2-3% of melanoma, diffuse large B-cell lymphoma, and uterine cancer[8,9]. PRKACA fusions have also been observed in 2% of liver cancer[8,9]. Specifically, PRKACA fusion with DNAJB1 has been observed to be recurrent in fibrolamellar hepatocellular carcinoma, which results in the retention of a functional PRKACA catalytic domain and increased protein levels[136,140]. PRKACA amplification is observed in about 11% of ovarian cancer and 2-3% of adrenocortical carcinoma, sarcoma, and uterine cancer[136,140].

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

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[21]. 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[22]. Each of these proteins interacts with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex[22]. 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[23]. Specifically, CBFβ binds to the 'runt' domain of RUNX1, leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[24,25]. RUNX1 is frequently mutated in various hematological malignancies[25]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML)[26,27]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in

Biomarker Descriptions (continued)

myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[25].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[28]. RUNX1 translocations occur in 4% of all AML[8,9]. A recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[29]. The RUNX1::RUNX1T1 fusion, consists of the runt-homology domain (RHD) of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[25,29]. Another translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 2% of adult ALL[30]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[25]. RUNX1 somatic mutations are observed in approximately 10% of AML, 10-15% of MDS, 5% of uterine corpus endometrial carcinoma, 4% of breast invasive carcinoma, 3% of bladder urothelial carcinoma, and 2% of colorectal adenocarcinoma[8,9,25]. Biallelic deletion of RUNX1 is observed in 7% of esophageal adenocarcinoma and 2% of stomach adenocarcinoma[8,9]. Alterations in RUNX1 are common in pediatric cancers, particularly the ETV6::RUNX1 fusion, which is observed in 20-25% of childhood ALL[11,30]. Overall, RUNX1 fusions are observed in 12% of B-lymphoblastic leukemia/lymphoma[8,9]. Somatic mutations in RUNX1 are observed in 5% of T-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[8,9]. Biallelic deletion of RUNX1 is observed in 5% of leukemia and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[8,9].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[31]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1, is associated with favorable risk in AML[32]. The translocation t(12;21)(q34;q11) that results in ETV6::RUNX1 fusion is associated with standard risk in adult ALL and favorable risk in pediatric ALL[33,34,35]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[32,36,37].

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,

Genes Assayed (continued)

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

RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

PIK3CA p.(E542K) c.1624G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✖
capivasertib + fulvestrant	○	○	○	✖	✖
inavolisib + palbociclib + fulvestrant	○	○	○	✖	✖
aspirin	✖	○	✖	✖	✖
ETX-636	✖	✖	✖	✖	● (I/II)
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
RLY-2608	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (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

ATM deletion

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

* 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	***19.87%***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***
CHEK1	***CNV, CN:1.0***
CHEK1	***LOH, 11q24.2(125496639-125525271)x1***
RAD51B	***CNV, CN:1.0***
RAD51B	***LOH, 14q24.1(68290164-69061406)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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