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Patient Name: 손성자
Gender: Female
Sample ID: N26-11

Primary Tumor Site: ovary
Collection Date: 2025.12.16

Sample Cancer Type: Ovarian Cancer

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Report Highlights

6 Relevant Biomarkers
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Relevant Ovarian Cancer Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	***3.79 Mut/Mb measured***
Genomic Instability	***GIM 12 (Low)***

HRD Status: ***HR Proficient (HRD-)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	14
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	2

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*ARID1A p.(Q553*) c.1657C>T* AT-rich interaction domain 1A Allele Frequency: 50.78% Locus: chr1:27057949 Transcript: NM_006015.6	None*	None*	1
IIC	*DDR1 amplification* discoidin domain receptor tyrosine kinase 1 Locus: chr6:30852922	None*	None*	1
IIC	*TP53 p.(R248Q) c.743G>A* tumor protein p53 Allele Frequency: 72.69% Locus: chr17:7577538 Transcript: NM_000546.6	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

MDM2 amplification, Microsatellite stable, NRAS amplification, PIK3CA p.(V344G) c.1031T>G, PIK3CB amplification, PIK3R2 amplification, PPP2R1A p.(P179R) c.536C>G, GATA2 amplification, MECOM amplification, TPMT amplification, NQO1 p.(P187S) c.559C>T, PRKACA amplification, MEF2B amplification, Tumor Mutational Burden, Genomic Instability (Low)

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ARID1A	p.(Q553*)	c.1657C>T	.	chr1:27057949	50.78%	NM_006015.6	nonsense
TP53	p.(R248Q)	c.743G>A	COSM10662	chr17:7577538	72.69%	NM_000546.6	missense
PIK3CA	p.(V344G)	c.1031T>G	COSM22540	chr3:178921549	85.05%	NM_006218.4	missense
PPP2R1A	p.(P179R)	c.536C>G	COSM86034	chr19:52715971	35.87%	NM_014225.6	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	62.43%	NM_000903.3	missense
SOS1	p.(Q560R)	c.1679A>G	.	chr2:39249890	41.72%	NM_005633.4	missense
CNTNAP5	p.(D607N)	c.1819G>A	.	chr2:125367443	17.35%	NM_130773.4	missense
ASB18	p.(P103S)	c.307C>T	.	chr2:237149944	40.86%	NM_212556.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	1.11	0.67
CDKN2A	chr9:21968178	0.82	0.57
CDKN2B	chr9:22005728	0.95	0.61
DDR1	chr6:30852922	4.79	2.02

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
MDM2	chr12:69202958	12.97	5.0
NRAS	chr1:115251152	6.62	2.69
PIK3CB	chr3:138374221	4.86	2.05
PIK3R2	chr19:18266737	5.29	2.2
GATA2	chr3:128200046	7.03	2.83
MECOM	chr3:168802636	6.89	2.78
TPMT	chr6:18130879	5.3	2.21
PRKACA	chr19:14204349	5.04	2.11
MEF2B	chr19:19256562	5.26	2.19
ATR	chr3:142168234	4.47	1.9
NOTCH3	chr19:15271451	5.52	2.28
JAK3	chr19:17937461	5.08	2.12

Biomarker Descriptions

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[36,37]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[37].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[37,38]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[5,6]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[5,6].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[49]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[50,51,52]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[53]. 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[1,53,54]. CDKN2A aberrations commonly co-occur with CDKN2B[49]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways,

Biomarker Descriptions (continued)

leading to uncontrolled cell proliferation[55]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[56,57].

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[58]. 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[5,6]. 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[5,6]. Alterations in CDKN2A are also observed in pediatric cancers[6]. 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[6]. 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)[6].

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[23,59,60]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[61]. 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[62,63,64]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[65]. 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[66,67,68,69].

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,49]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[49]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[50,51,52]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[49]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,70,71].

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

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma[61].

ARID1A p.(Q553*) c.1657C>T

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,43]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[43,44]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[44]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[44,45]. ARID1A binds to transcription

Biomarker Descriptions (continued)

factors and coactivator/corepressor complexes to alter transcription[43]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[43].

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[45]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[43]. Somatic mutations in ARID1A have been identified in several cancers including 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[5,6,44]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[46]. Biallelic deletion of ARID1A is observed in 3% of cholangiocarcinoma and stomach adenocarcinoma, and 2% of pheochromocytoma and paraganglioma[5,6]. Alterations in ARID1A are also observed in pediatric cancers[6]. Somatic mutations in ARID1A are observed in 12% of non-Hodgkin lymphoma (2 in 17 cases), 8% of Hodgkin lymphoma (5 in 61 cases), 5% of T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of embryonal tumors (5 in 332 cases), 1% of glioma (4 in 297 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and peripheral nervous system tumors (2 in 1158 cases)[6]. Biallelic deletion of ARID1A is observed in 2% of peripheral nervous system cancers (2 in 91 cases), 1% of leukemia (3 in 250 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[47], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[48], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

DDR1 amplification

discoidin domain receptor tyrosine kinase 1

Background: DDR1 encodes discoidin domain receptor tyrosine kinase 1[1]. Unlike other receptor tyrosine kinases, including epidermal growth factor receptors (EGFRs) and fibroblast growth factor receptors (FGFRs), which exhibit rapid and transient activation, DDRs display delayed and prolonged activation following ligand binding[2]. DDR activation occurs through collagen binding, with DDR1 exhibiting the most specificity for type I and IV collagens[2]. Collagen mediated activation of DDR1 is observed to contribute to diverse cellular processes including proliferation, invasion, migration, differentiation, matrix remodeling, and embryonic development[3]. In cancer, aberrations in DDR1, including overexpression, have been associated with tumor progression[3,4].

Alterations and prevalence: Somatic mutations in DDR1 are observed in 7% of skin cutaneous melanoma, 4% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma and lung squamous cell carcinoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, and esophageal adenocarcinoma[5,6]. Amplification of DDR1 is observed in 6% of cholangiocarcinoma, 4% of uveal melanoma and ovarian serous cystadenocarcinoma, 3% of esophageal adenocarcinoma and skin cutaneous melanoma, and 2% of stomach adenocarcinoma, diffuse large B-cell lymphoma, liver hepatocellular, uterine carcinosarcoma, and pancreatic adenocarcinoma[5,6]. Biallelic deletion of DDR1 is observed in 6% of diffuse large B-cell lymphoma[5,6].

Potential relevance: Currently, no therapies are approved for DDR1 aberrations.

TP53 p.(R248Q) c.743G>A

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[89]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[90]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[91,92].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[5,6,93,94,95,96]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[97,98,99,100]. Alterations in TP53 are also observed in pediatric cancers[5,6]. 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)[5,6]. Biallelic loss

Biomarker Descriptions (continued)

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)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[101] (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[102,103]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[104]. 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)[15,17,30,105,106]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[88]. 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[107].

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene[1]. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING domain[18]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[18]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[19]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[19]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[19].

Alterations and prevalence: MDM2 is amplified in 19% of sarcoma, 9% of bladder urothelial carcinoma, 8% of glioblastoma multiforme, 7% of adrenocortical carcinoma, 5% of uterine carcinosarcoma, lung adenocarcinoma, esophageal adenocarcinoma, and stomach adenocarcinoma, 4% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and ovarian serous cystadenocarcinoma, 3% of breast invasive carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, testicular germ cell tumors, and lung squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma[5,6]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[20]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[21,22]. Somatic mutations in MDM2 are observed in 2% of uterine corpus endometrial carcinoma, adrenocortical carcinoma, and sarcoma[5,6]. Alterations in MDM2 are also observed in pediatric cancers[6]. Amplification of MDM2 is observed in 2% of bone cancer (1 in 42 cases), 1% of Wilms tumor (2 in 136 cases) and peripheral nervous system tumors (1 in 91 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[6]. Somatic mutations in MDM2 are observed in 2% of non-Hodgkin lymphoma (1 in 17 cases) and less than 1% of bone cancer (3 in 327 cases) and embryonal tumors (1 in 332 cases)[6].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[23].

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[108]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[109,110]. 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[111]. 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[112]. 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)[112]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[113,114,115,116,117]. 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[110]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[109,110,114,118].

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[109,110,119,120]. 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[119,120].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[121] (2014) and nivolumab[122] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[121] is also approved

Biomarker Descriptions (continued)

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[121]. Dostarlimab[123] (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[115,124]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[125] (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[115,126,127]. 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[127]. 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[128,129]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[128,129].

NRAS amplification

NRAS proto-oncogene, GTPase

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS[1]. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[157,158,159]. Recurrent mutations in RAS lead to several genetic disorders known as RASopathies, including Noonan syndrome, which results in heart and congenital defects, growth inhibition, and facial dysmorphic features[160]. Point mutations in NRAS are also observed in several cancers including melanoma, characterized thick tumors, increased tumor recurrence, treatment resistance, and increased mitosis[161].

Alterations and prevalence: NRAS mutations are observed in 29% of skin cutaneous melanoma, 8% of acute myeloid leukemia and thyroid carcinoma, 6% of colorectal adenocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of testicular germ cell tumors and cholangiocarcinoma, and 2% of thymoma, bladder urothelial carcinoma, uterine carcinosarcoma, and kidney chromophobe[5,6,162]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[5,6,163]. Mutations at A59, K117, and A146 have also been observed but are less frequent[6,164]. Alterations in NRAS are also observed in pediatric cancers[6]. Somatic mutation in NRAS are observed in 16% of leukemia (57 in 354 cases), 10% of B-lymphoblastic leukemia/lymphoma (24 in 252 cases), 8% of soft tissue sarcoma (3 in 38 cases), and less than 1% of glioma (2 in 297 cases), bone cancer (2 in 327 cases), and embryonal tumors (1 in 332 cases)[6].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[165] and panitumumab[166], are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[164]. In 2022, the FDA granted fast track designation to the pan-RAF inhibitor, KIN-2787[167], for the treatment of NRAS-mutant metastatic or unresectable melanoma. In 2023, the FDA granted fast track designation to the pan-RAF inhibitor, naporafenib, in combination with trametinib[168] for NRAS-mutated unresectable or metastatic melanoma. In 2024, the FDA granted fast track designation to the MAPK pathway inhibitor, IMM-1-104[169], for the treatment of NRAS-mutant metastatic or unresectable melanoma. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[15] as well as melanoma[170]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[171].

PIK3CA p.(V344G) c.1031T>G

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[133]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[72,73]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[72]. 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[41,42]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[41,42,74,75]. 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[134,135,136].

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)[137,138]. 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[139,140,141]. Somatic mutations in PIK3CA are observed

Biomarker Descriptions (continued)

in 50% of uterine corpus endometrial carcinoma, 35% of uterine carcinosarcoma, 32% of breast invasive carcinoma, 29% of cervical squamous cell carcinoma, 28% of colorectal adenocarcinoma, 22% of bladder urothelial carcinoma, 17% of head and neck squamous cell carcinoma, 16% of stomach adenocarcinoma, 11% of lung squamous cell carcinoma, 9% of esophageal adenocarcinoma, 8% of brain lower grade glioma, 6% of cholangiocarcinoma, 5% of skin cutaneous melanoma and lung adenocarcinoma, 4% of liver hepatocellular carcinoma, 3% of pancreatic adenocarcinoma and sarcoma, and 2% of mesothelioma, prostate adenocarcinoma, testicular germ cell tumors, and ovarian serous cystadenocarcinoma[5,6]. 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[5,6]. Alterations in PIK3CA are also observed in pediatric cancers[6]. 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)[6].

Potential relevance: The PI3K inhibitor, alpelisib[142], 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[143]. However, alpelisib did not improve response when administered with letrozole in patients with ER + early breast cancer with PIK3CA mutations[144]. The FDA also approved the kinase inhibitor, capivasertib (2023)[145] 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[146], 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[147,148]. 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[115,124,149,150]. In 2025, the FDA granted fast track designation to the PI3Kα inhibitor and degrader, ETX-636[151], for the treatment of PIK3CA-mutant, HR-positive/HER-negative advanced breast cancer.

PIK3CB amplification

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

Background: The PIK3CB gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[72]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[72,73]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[72]. 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[41,42]. The reversible phosphorylation of inositol lipids regulate diverse aspects of cell growth and metabolism[41,42,74,75]. Aberrations in PIK3CB that lead to activation of the PI3K/AKT/MTOR pathway have been observed to promote tumor formation, suggesting an oncogenic role for PIK3CB[72,76,77].

Alterations and prevalence: Somatic mutations in PIK3CB are predominantly missense with amino acid substitutions at D1067 being the most recurrent and observed to lead to hyperactivation of the PI3K pathway[5,6,78]. PIK3CB mutations are observed in about 9% of uterine cancer and 2-3% of melanoma, glioblastoma, cholangiocarcinoma, colorectal, bladder, stomach, esophageal, and squamous lung cancers[5,6]. Amplification of PIK3CB is also observed in 9% of squamous lung cancer, 7% of cervical cancer, and 5-6% of head and neck, ovarian, and esophageal cancers[5,6].

Potential relevance: Currently, no therapies are approved for PIK3CB aberrations.

PIK3R2 amplification

phosphoinositide-3-kinase regulatory subunit 2

Background: The PIK3R2 gene encodes the phosphoinositide-3-kinase regulatory subunit 2 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1,39]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[39]. PIK3R2 encodes the p85β protein, one of five p85 isoforms[39]. p85β is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[40]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3)[41,42]. Increased PIK3R2 expression has been observed to correlate with elevated AKT activation and tumor stage, supporting an oncogenic role for PIK3R2[40].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in PIK3R2 are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and colorectal adenocarcinoma[5,6]. Amplification of PIK3R2 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, mesothelioma, and liver hepatocellular carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for PIK3R2 aberrations.

PPP2R1A p.(P179R) c.536C>G

protein phosphatase 2 scaffold subunit Aalpha

Background: The PPP2R1A gene encodes the protein phosphatase 2 regulatory subunit A alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family[1,152]. 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 (includes PPPP2CA and PPP2CB)[152,153]. Specifically, the A subunit is composed of 15 tandem HEAT repeats, consisting of approximately 40 amino acid residues organized into two anti-parallel alpha-helices which are responsible for binding both the regulatory B and catalytic C subunits[154]. Recurrent mutations in PPP2R1A have been observed to promote malignant growth in uterine cancer[155].

Alterations and prevalence: Somatic mutations in PPP2R1A are predominantly missense and are observed in 28% of uterine carcinosarcoma and 17% of uterine cancer[5]. Recurrent mutations are observed at codons P179, R183, and S256 within HEAT repeats 1-8 which are involved in interactions with the regulatory B subunit[5,155]. PPP2R1A mutations are also observed at lesser frequency in other cancer types including 2-3% of melanoma, uveal melanoma, lung adenocarcinoma, esophageal, squamous lung, stomach, cervical, and colorectal cancers[5]. PPP2R1A amplification is found to occur in about 4% of uterine cancer as well as 2% of diffuse large B-cell lymphoma (DLBCL), low grade glioma, adrenocortical carcinoma, and bladder cancer[5].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[156], in combination with camonsertib for the treatment of adult patients with PPP2R1A mutated endometrial cancer and platinum resistant ovarian cancer.

GATA2 amplification

GATA binding protein 2

Background: The GATA2 gene encodes GATA binding protein 2, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1 and GATA3-6[1,7,8]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[8]. GATA2 is highly expressed in hematopoietic cells and is a critical component for the proliferation and maintenance of stem cells[9]. Germline mutations are spontaneous and are inherited in an autosomal dominant pattern[10,11]. Germline mutations predispose patients to myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML)[10,11]. GATA2 deficiency is recognized as a MDS predisposition syndrome[9].

Alterations and prevalence: GATA2 somatic mutations cause loss of function in the mutated allele, which leads to haploinsufficiency[12]. Hemizygous mutations in GATA2 frequently co-occur with the inv(3)/t(3;3) aberration that involves the fusion of RPN1/MECOM[13]. Up to 10% of intermediate-risk karyotype AML with CEBPA mutations also harbor GATA2 somatic mutations[9]. The gain-of-function mutation GATA2 L359V has been identified in 10% of chronic myeloid leukemia during blast phase[14]. Somatic mutations in GATA2 are also observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma and AML, and 2% of colorectal adenocarcinoma[5,6]. Amplifications in GATA2 are observed in up to 6% of lung squamous cell carcinoma and cervical squamous cell carcinoma, and up to 3% of ovarian serous cystadenocarcinoma, esophageal adenocarcinoma, and head and neck squamous cell carcinoma[5,6]. Alterations in GATA2 are also observed in the pediatric population[6]. Somatic mutations are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of Hodgkin lymphoma (1 in 61 cases) and leukemia (5 in 311 cases), and less than 1% of embryonal tumor (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and bone cancer (1 in 327 cases)[6].

Potential relevance: GATA2 nonsense, frameshift, or splice site missense mutations in codons 349-398 confer poor prognosis in MDS[15]. GATA2::MECOM fusion is associated with adverse risk in acute myeloid leukemia (AML)[16,17]. GATA2::MECOM fusion with FLT3 ITD or FLT3 TKD mutation are indicated for combination therapy with midostaurin, cytarabine, and daunorubicin in acute myeloid leukemia[16].

MECOM amplification

MDS1 and EVI1 complex locus

Background: The MECOM gene encodes the MDS1 and EVI1 complex locus (MECOM), a zinc-finger transcriptional factor that regulates hematopoietic cell differentiation[24]. The MECOM locus encodes multiple alternative splice variants that result in MDS1-EVI1, MDS1,

Biomarker Descriptions (continued)

and EVI1 protein isoforms[25]. The EVI1 isoform is the most abundant and oncogenic form of MECOM that is expressed in various cancers including acute myeloid leukemia (AML)[25,26]. MECOM is a frequent target of chromosomal translocation which can lead to MECOM overexpression and leukemogenesis[27].

Alterations and prevalence: Somatic mutations MECOM are observed in up to 22% of malignant melanoma; 75% of these mutations are missense and the remaining 25% are truncating mutations[5,6,28]. MECOM amplifications are observed in up to 35% of lung squamous cell carcinoma, 30% of ovarian serous cystadenocarcinoma, and 20% of esophageal adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[5,6]. MECOM rearrangements occur with various partner genes including ETV6, RUNX1, and H2AFY[29]. The t(3;21)(q26;q22) translocation that results in the MECOM::RUNX1 fusion is most commonly observed in chronic myeloid leukemia (CML) in blast crisis. The t(3;3)(q21.3;q26.2)/ inv(3)(q21.3;q26.3) translocation, also referred to as inv(3)/t(3;3), results in a GATA2::MECOM fusion and is observed in AML, primary myelofibrosis (PMF), and myelodysplastic syndrome (MDS)[15,16,30]. The inv(3)/ t(3;3) translocation repositions the distal GATA enhancer element and activates MECOM expression while simultaneously causing GATA2 haploinsufficiency[31].

Potential relevance: AML with MECOM rearrangement is considered a distinct molecular subtype of AML as defined by the World Health Organization (WHO)[32]. MECOM rearrangements, including GATA2::MECOM fusions, are associated with poor/adverse risk in AML[16,17]. Inv(3) is associated with poor cytogenetic risk in MDS as defined by the revised international prognostic scoring system (IPSS-R) scoring system[15]. In PMF, inv(3) is considered an unfavorable karyotype associated with intermediate risk as defined by the dynamic international prognostic scoring system (DIPSS)-Plus scoring system[30]. MECOM overexpression is observed in 10% of de novo AML associated with poor prognosis, and is commonly found in MLL-rearranged cases[33,34]. Amplification of MECOM is associated with favorable prognosis in ovarian cancer[35].

TPMT amplification

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,130,131]. 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[130,131,132]. 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[130,132].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[5,6]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[5,6]. 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[5,6]. Alterations in TPMT are also observed in pediatric cancers[6]. Somatic mutations are observed in less than 1% of peripheral nervous system tumors (1 in 1158 cases)[6]. Amplification of TPMT is observed in 1% of peripheral nervous system tumors (1 in 91 cases)[6].

Potential relevance: Currently, no therapies are approved for TPMT 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)[1]. 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[1,79,80]. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins[1,79]. Aberrations in PRKACA are oncogenic, as they are predicted to abolish the interaction with R subunits leading to cAMP-independent activation of PKA[81]. 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[81,82].

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[5,6]. PRKACA fusions have also been observed in 2% of liver cancer[5,6]. Specifically, PRKACA fusion with DNAJB1 has been observed to be recurrent in fibrolamellar hepatocellular carcinoma, which results in the retention of

Biomarker Descriptions (continued)

a functional PRKACA catalytic domain and increased protein levels[79,83]. PRKACA amplification is observed in about 11% of ovarian cancer and 2-3% of adrenocortical carcinoma, sarcoma, and uterine cancer[79,83].

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

MEF2B amplification

myocyte enhancer factor 2B

Background: The MEF2B gene encodes myocyte enhancer factor 2B, a member of the MADS/MEF2 family of DNA binding proteins, which also includes MEF2A, MEF2C, and MEF2D[1,84]. MEF2B is a transcription factor that regulates cell development, including lymphocyte, neuron, muscle and endothelial cells[84]. MEF2B transcriptional targets include BCL6, SMHC, BZLF1, and SOST[84]. Mutations in MEF2B have been observed to promote increased transcription of BCL6[85]. Aberrations in BCL6 often lead to altered target gene transcription, including those involved in cell cycle arrest, differentiation, and apoptosis[86,87].

Alterations and prevalence: Somatic mutations in MEF2B are observed in 2% of uterine corpus endometrial carcinoma and diffuse large B-cell lymphoma (DLBCL), and 1% of skin cutaneous melanoma[5,6]. MEF2B amplification is observed in 6% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, esophageal adenocarcinoma, and uterine corpus endometrial carcinoma, 2% of adrenocortical carcinoma, and 1% of liver hepatocellular carcinoma, uveal melanoma, and sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for MEF2B aberrations. In diffuse large B-cell lymphoma, MEF2B mutations are associated with diagnostic significance[88].

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,

Genes Assayed (continued)

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

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
CTS-3497	✖	✖	✖	✖	● (I/II)
IDE397	✖	✖	✖	✖	● (I/II)
PH020-803	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462, pembrolizumab	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)
GH-56	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
HSK-41959	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

MTAP deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)
S-095035, TNG-462	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

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

CDKN2B deletion

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

ARID1A p.(Q553*) c.1657C>T

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

DDR1 amplification

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

TP53 p.(R248Q) c.743G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (I)

* 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	***30.72%***
BRCA1	***LOH, 17q21.31(41197602-41276231)x2***
BRIP1	***LOH, 17q23.2(59760627-59938976)x2***
CDK12	***LOH, 17q12(37618286-37687611)x2***
RAD51C	***LOH, 17q22(56769933-56811619)x2***
RAD51D	***LOH, 17q12(33427950-33446720)x2***

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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