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Patient Name: 오선희
Gender: F
Sample ID: N25-314

Primary Tumor Site:
Collection Date: 2025.11.11

Sample Cancer Type: Endometrial Carcinoma

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Relevant Endometrial Carcinoma Findings

Gene	Finding
BRAF	None detected
ERBB2	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***17.96 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*ARID1A p.(P1115Qfs*46) c.3344delC* AT-rich interaction domain 1A Allele Frequency: 15.03% Locus: chr1:27097750 Transcript: NM_006015.6	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

*CREBBP p.(R1446C) c.4336C>T, KMT2B p.(R2057Afs*34) c.6169delC, KMT2D p.(E1241Gfs*9) c.3721_3722insG, MSH2 p.(R383*) c.1147C>T, MYC p.(A59V) c.176C>T, PIK3CA p.(R108H) c.323G>A, PIK3R1 p.(R631*) c.1891C>T, PIK3R2 p.(G373R) c.1117G>A, TP53 p.(R273C) c.817C>T, NOTCH4 p.(L6Tfs*54) c.15_18delACTGinsCA, TAP2 p.(A328Gfs*52) c.983delC, MGA p.(R2435Q) c.7304G>A, B2M p.(L15Ffs*41) c.43_44delCT, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ARID1A	p.(P1115Qfs*46)	c.3344delC	.	chr1:27097750	15.03%	NM_006015.6	frameshift Deletion
CREBBP	p.(R1446C)	c.4336C>T	COSM88749	chr16:3788618	14.18%	NM_004380.3	missense
KMT2B	p.(R2057Afs*34)	c.6169delC	.	chr19:36223613	16.65%	NM_014727.3	frameshift Deletion
KMT2D	p.(E1241Gfs*9)	c.3721_3722insG	.	chr12:49443649	97.19%	NM_003482.4	frameshift Insertion
MSH2	p.(R383*)	c.1147C>T	.	chr2:47656951	19.37%	NM_000251.3	nonsense
MYC	p.(A59V)	c.176C>T	.	chr8:128750639	9.97%	NM_002467.6	missense
PIK3CA	p.(R108H)	c.323G>A	COSM27497	chr3:178916936	5.45%	NM_006218.4	missense
PIK3R1	p.(R631*)	c.1891C>T	.	chr5:67592075	13.10%	NM_181523.3	nonsense
PIK3R2	p.(G373R)	c.1117G>A	COSM993028	chr19:18273784	5.16%	NM_005027.4	missense
TP53	p.(R273C)	c.817C>T	COSM10659	chr17:7577121	5.45%	NM_000546.6	missense
NOTCH4	p.(L6Tfs*54)	c.15_18delACTGinsCA	.	chr6:32191688	97.83%	NM_004557.4	frameshift Block Substitution
TAP2	p.(A328Gfs*52)	c.983delC	.	chr6:32800563	14.69%	NM_018833.2	frameshift Deletion
MGA	p.(R2435Q)	c.7304G>A	COSM71633	chr15:42052633	5.75%	NM_001164273.1	missense
B2M	p.(L15Ffs*41)	c.43_44delCT	COSM144579	chr15:45003780	16.37%	NM_004048.4	frameshift Deletion
EPHA2	p.(L582P)	c.1745T>C	.	chr1:16460095	17.43%	NM_004431.5	missense
ACVR2A	p.(M482I)	c.1446G>A	.	chr2:148684747	4.75%	NM_001616.5	missense
SETD2	p.(T2304I)	c.6911C>T	.	chr3:47098363	4.20%	NM_014159.7	missense
CFAP20DC	p.(I135V)	c.403A>G	.	chr3:58855973	3.20%	NM_198463.4	missense
ZBTB20	p.(P31L)	c.92C>T	.	chr3:114099171	18.30%	NM_001164342.2	missense
RAC1	p.(R121W)	c.361C>T	.	chr7:6441514	5.00%	NM_018890.4	missense
NOTCH1	p.(R2111M)	c.6332G>T	.	chr9:139391859	12.71%	NM_017617.5	missense
NOTCH1	p.(E493K)	c.1477G>A	.	chr9:139411802	5.45%	NM_017617.5	missense
MEN1	p.(R610W)	c.1828C>T	.	chr11:64571826	19.56%	NM_000244.3	missense
ATM	p.(A2454V)	c.7361C>T	.	chr11:108200994	9.70%	NM_000051.4	missense
CHD4	p.(R1095C)	c.3283C>T	.	chr12:6700689	4.26%	NM_001273.5	missense
KMT2D	p.(K1753del)	c.5257_5259delAAG	.	chr12:49437710	4.34%	NM_003482.4	nonframeshift Deletion
KMT2D	p.(E1241G)	c.3722A>G	.	chr12:49443649	2.81%	NM_003482.4	missense
ACVR1B	p.(T405I)	c.1214C>T	.	chr12:52379087	4.40%	NM_020328.4	missense
ERBB3	p.(A90V)	c.269C>T	.	chr12:56478813	14.12%	NM_001982.4	missense
STAT6	p.(R370W)	c.1108C>T	.	chr12:57498351	13.66%	NM_003153.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TPP2	p.(D1016E)	c.3048T>A	.	chr13:103309501	5.78%	NM_003291.4	missense
IGF1R	p.(R210C)	c.628C>T	.	chr15:99251324	13.70%	NM_000875.5	missense
CNTNAP4	p.(A113T)	c.337G>A	.	chr16:76461370	5.38%	NM_138994.5	missense
CNTNAP4	p.(R768W)	c.2302C>T	.	chr16:76555192	2.97%	NM_138994.5	missense
NF1	p.(?)	c.3709-1G>T	.	chr17:29562628	4.41%	NM_001042492.3	unknown
SOX9	p.(N184S)	c.551A>G	.	chr17:70118979	4.00%	NM_000346.4	missense
CCNE1	p.(P396L)	c.1187C>T	.	chr19:30314638	5.65%	NM_001238.4	missense
KMT2B	p.(P714S)	c.2140C>T	.	chr19:36212389	2.15%	NM_014727.3	missense
ASXL1	p.(L212M)	c.634C>A	.	chr20:31017772	3.60%	NM_015338.6	missense
PLCG1	p.(R694Q)	c.2081G>A	.	chr20:39795196	18.04%	NM_002660.3	missense
EP300	p.(G211V)	c.632G>T	.	chr22:41513728	4.30%	NM_001429.4	missense
ZMYM3	p.(R828H)	c.2483G>A	.	chrX:70466292	54.05%	NM_201599.3	missense
RPA4	p.(D29Cfs*6)	c.85_86delGA	.	chrX:96139387	11.13%	NM_013347.4	frameshift Deletion

Biomarker Descriptions

ARID1A p.(P1115Qfs*46) c.3344delC

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[22]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[22,52]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[52,53]. 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[53]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[53,54]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[52]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[52].

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[54]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[52]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[9,10,53]. 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[55].

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[56], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[57], 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.

Biomarker Descriptions (continued)

CREBBP p.(R1446C) c.4336C>T

CREB binding protein

Background: The CREBBP gene encodes the CREB binding protein (also known as CBP), a highly conserved and ubiquitously expressed tumor suppressor. CREBBP is a member of the KAT3 family of lysine acetyl transferases, which, along with EP300, interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[34,35]. CREBBP functions as a global transcriptional coactivator through the modification of lysines on nuclear proteins[34]. CREBBP binds to cAMP-response element binding protein (CREB) and is known to play a role in embryonic development, growth, and chromatin remodeling[34]. Upon disruption of normal CREBBP functions through genomic alterations, cells become susceptible to defects in differentiation and malignant transformation[36]. Inherited CREBBP mutations and deletions result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[37].

Alterations and prevalence: Mutations in CREBBP are observed in up to 12% of bladder urothelial carcinoma, uterine corpus endometrial carcinoma, and skin cutaneous melanoma, and in 5-10% of stomach adenocarcinoma, lung squamous cell carcinoma, and cervical squamous cell carcinoma[9,10]. CREBBP is frequently mutated in 15-17% of small cell lung cancer (SCLC)[38]. Inactivating mutations and deletions of CREBBP account for over 70% of all B-cell non-Hodgkin lymphoma diagnoses including 60% of follicular lymphoma and 30% of diffuse large-B-cell lymphoma (DLBCL)[34]. The rare t(11;16)(q23;p13) translocation fuses CREBBP with the partner gene KMT2A/MLL, in 0.2% secondary AML and 0.1% myelodysplastic syndrome (MDS)[39,40,41]. Elevated expression of CBP was detected in lung cancer cells and tumor tissue as compared to normal lung cells in one study[42].

Potential relevance: The t(8;16)(p11.2;p13.3) translocation resulting in KAT6A::CREBBP fusion is associated with poor/adverse risk in AML[43,44]. A mutation in CREBBP is a diagnostic marker of diffuse large B-cell lymphoma[13]. SCLC patients with CREBBP-positive tumors demonstrate lower overall survival (OS) and disease-free survival (DFS) compared to those with CREBBP-negative tumors[45].

KMT2B p.(R2057Afs*34) c.6169delC

lysine methyltransferase 2B

Background: The KMT2B gene encodes the lysine methyltransferase 2B protein, a transcriptional coactivator and histone H3 lysine K (H3K4) methyltransferase[22]. KMT2B belongs to the SET domain protein methyltransferase superfamily[46]. Specifically, KMT2B along with KDM6A promotes the transcription of the oncogene MYC by H3K4 methylation[47].

Alterations and prevalence: Somatic mutations in KMT2B are observed in 22% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 11% colorectal adenocarcinoma, 10% of stomach adenocarcinoma, 7% of adrenocortical carcinoma, and 5% of bladder urothelial carcinoma and lung squamous cell carcinoma[9,10].

Potential relevance: Currently, no therapies are approved for KMT2B aberrations.

KMT2D p.(E1241Gfs*9) c.3721_3722insG

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[22]. KMT2D belongs to the SET domain protein methyltransferase superfamily[46]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[46]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[46].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[9,10].

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

MSH2 p.(R383*) c.1147C>T

mutS homolog 2

Background: The MSH2 gene encodes the mutS homolog 2 protein[22]. MSH2 is a tumor suppressor gene that heterodimerizes with MSH6 to form the MutSα complex or with MSH3 to form the MutSβ complex[63]. Both MutS complexes function in DNA damage recognition of base-base mismatches or insertion/deletion (indels) mispairs[63]. Specifically, the MutSα complex recognizes 1-2 nucleotide indels while MutSβ recognizes longer indel mispairs[63]. DNA damage recognition initiates the mismatch repair (MMR)

Biomarker Descriptions (continued)

process that repairs mismatch errors which typically occur during DNA replication[63]. Mutations in MSH2 result in the degradation of MSH6[64]. Loss of MSH2 protein expression correlates with mutations in the genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[65]. MSH2, along with MLH1, MSH6, and PMS2, form the core components of the MMR pathway[66]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[67]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[66,68,69]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[66,70]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer.[68,70,71,72]. Specifically, MSH2 mutations are associated with an increased risk of ovarian and pancreatic cancer[73,74,75,76].

Alterations and prevalence: Somatic mutations in MSH2 are observed in 8% of uterine corpus endometrial carcinoma, as well as 2-3% of bladder urothelial carcinoma, melanoma, and colorectal adenocarcinoma[9,10]. Alterations in MSH2 are observed in pediatric cancers[9,10]. Somatic mutations are observed in 3% of soft tissue sarcoma, 1% of embryonal tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), and peripheral nervous system tumors (1 in 1158 cases)[9,10].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[77]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[78,79]. MSH2 mutations are consistent with high grade in pediatric diffuse gliomas[80,81].

MYC p.(A59V) c.176C>T

MYC proto-oncogene, bHLH transcription factor

Background: The MYC gene encodes the MYC proto-oncogene, bHLH transcription factor (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[1,2,3,4]. MYC is part of the MYC oncogene family, which includes the related transcription factors, MYCN and MYCL, and regulates transcription in 10-15% of promoter regions[5]. MYC functions as a heterodimer in complex with the transcription factor MAX[2,6].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including those at codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[7,8]. Amplification of the MYC gene is observed in 15-30% of ovarian serous cystadenocarcinoma, esophageal adenocarcinoma, uterine carcinosarcoma, and breast invasive carcinoma, 10-15% of pancreatic adenocarcinoma, stomach adenocarcinoma, and liver hepatocellular carcinoma, 5-10% of head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, prostate adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, and 2-5% of skin cutaneous melanoma, brain lower grade glioma, sarcoma, cervical squamous cell carcinoma, uveal melanoma, diffuse B-cell lymphoma, glioblastoma, and kidney chromophobe[9,10]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, resulting in increased MYC expression[11,12]. Overall, MYC translocations are observed in 2% of diffuse large B-cell lymphoma[9,10]. Somatic mutations in MYC are observed in 7% of diffuse large B-cell lymphoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and stomach adenocarcinoma[9,10]. Alterations in MYC are also observed in pediatric cancers[10]. Somatic mutations in MYC have been observed in 59% of non-Hodgkin lymphoma, 2% of leukemia, and less than 1% of bone cancer (2 in 327 cases) and B-lymphoblastic leukemia/lymphoma (1 in 252 cases)[10]. Amplification of MYC is observed in 6% of embryonal tumor, 5% of bone cancer, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and MYC translocations are observed in 5% of T-lymphoblastic leukemia/lymphoma[10].

Potential relevance: B-cell lymphoma with MYC translocations that co-occur with BCL2 or BCL6 are referred to as double hit lymphoma, while co-occurrence with BCL2 and BCL6 rearrangements is referred to as triple-hit lymphoma[13,14]. MYC translocations are a diagnostic marker of Burkitt Lymphoma[15,16]. MYC translocations are also indicative of high risk for multiple myeloma and are associated with poor risk in acute lymphoblastic leukemia[17,18]. Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression[1,19,20,21].

PIK3CA p.(R108H) c.323G>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[109]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of

Biomarker Descriptions (continued)

four p110 catalytic subunits to activated tyrosine protein kinases[110,111]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[110]. 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[50,51]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[50,51,86,87]. 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[112,113,114].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[9,10]. 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)[115,116]. 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[117,118,119]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[9,10].

Potential relevance: The PI3K inhibitor, alpelisib[120], 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. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[121]. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations[121]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[122]. The FDA also approved the kinase inhibitor, capivasertib (2023)[123] 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[124], 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[125,126]. 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[127,128,129,130].

PIK3R1 p.(R631*) c.1891C>T

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[22]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[48]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[48]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[48]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[50,51]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[50,51,86,87]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[88]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[48].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[9]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[9].

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

PIK3R2 p.(G373R) c.1117G>A

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[22,48]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[48]. PIK3R2 encodes the p85β protein, one of five p85 isoforms[48]. p85β is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[49]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3)[50,51]. Increased PIK3R2 expression has been observed to correlate with elevated AKT activation and tumor stage, supporting an oncogenic role for PIK3R2[49].

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[9,10]. 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[9,10].

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

TP53 p.(R273C) c.817C>T

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[22]. 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%)[9,10,93,94,95,96]. 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[9,10]. 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[9,10]. 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)[9,10]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[9,10].

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 mutation 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)[18,44,105,106,107]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[13]. 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[108].

NOTCH4 p.(L6Tfs*54) c.15_18delACTGinsCA

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[27]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[28,29]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[30,31,32,33].

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

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

TAP2 p.(A328Gfs*52) c.983delC

transporter 2, ATP binding cassette subfamily B member

Background: The TAP2 gene encodes the transporter 2, ATP binding cassette subfamily B member protein[22]. Along with TAP1, TAP2 is a member of the superfamily of ATP-binding cassette (ABC) transporters[22]. Together, TAP1 and TAP2 are capable of ATP controlled

Biomarker Descriptions (continued)

dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules[23,24]. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression[25,26].

Alterations and prevalence: Somatic mutations in TAP2 are predominantly missense or truncating and have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and stomach adenocarcinoma, and 2% of lung adenocarcinoma[9,10]. Biallelic deletion of TAP2 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)[9,10].

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

MGA p.(R2435Q) c.7304G>A

MGA, MAX dimerization protein

Background: The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily[22,82]. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT[83]. MGA is capable of heterodimerization with the MAX bHLHZ transcription factor, which results in DNA recognition and transcriptional regulation of target genes involved in cell growth and proliferation[82]. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation[84]. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair[85].

Alterations and prevalence: Somatic mutations in MGA are predominantly missense or truncating and are observed in 16% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 8% of stomach adenocarcinoma and lung adenocarcinoma, and 6% of colorectal adenocarcinoma and bladder urothelial carcinoma[9,10]. MGA biallelic deletion is observed in 6% of diffuse large B-cell lymphoma (DLBCL), 3% of mesothelioma, and 2% of ovarian serous cystadenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma[9,10].

Potential relevance: Currently, no therapies are approved for MGA aberrations. However, MGA mutation has been observed to be enriched in non-small cell lung cancer (NSCLC) patients with higher objective response rates to immune checkpoint inhibitor (ICI) therapy[85].

B2M p.(L15Ffs*41) c.43_44delCT

beta-2-microglobulin

Background: The B2M gene encodes the beta-2-microglobulin protein[22]. B2M is an extracellular component of the major histocompatibility class (MHC) class I and is important for proper folding and transport of MHC class I to the cell surface of nucleated cells[58]. MHC class I molecules are located on the cell surface and present antigens from within the cell for recognition by cytotoxic T cells[59]. Peptide antigen presentation by MHC class I requires B2M, and mutation or loss of B2M prevents presentation and results in escape from immune recognition[60]. In cancer, mutations or loss of B2M allows for immune evasion by tumor cells, thereby preventing their destruction and supporting a tumor suppressor role for B2M[60].

Alterations and prevalence: Somatic mutations in B2M are observed in 22% of diffuse large B-cell lymphoma (DLBCL), 5% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of cervical squamous cell carcinoma and skin cutaneous melanoma[9,10]. Biallelic loss of B2M is observed in 8% of DLBCL 5% of mesothelioma, and 2% of lung adenocarcinoma and skin cutaneous melanoma[9,10].

Potential relevance: Currently, no therapies are approved for B2M aberrations. Loss of B2M has been implicated in resistance to immunotherapy in melanoma[60,61]. However, B2M mutations in microsatellite instability-high colorectal carcinomas show response to immune checkpoint inhibitors[62].

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,

Genes Assayed (continued)

Genes Assayed for the Detection of DNA Sequence Variants (continued)

IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed 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

ARID1A p.(P1115Qfs*46) c.3344delC

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

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

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

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