

Patient Name: 김선보
Gender: M
Sample ID: N25-172

Primary Tumor Site: skin
Collection Date: 2025.07.15

Sample Cancer Type: Unknown Primary Origin

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	BRCA2 c.7977-1G>A BRCA2, DNA repair associated Allele Frequency: 25.44% Locus: chr13:32937315 Transcript: NM_000059.4	None*	abiraterone + niraparib ^{1, 2 / II+} bevacizumab + olaparib ^{1, 2 / II+} olaparib ^{1, 2 / II+} rucaparib ^{1 / II+} talazoparib + hormone therapy ^{1 / II+} bevacizumab + niraparib ^{II+} niraparib ^{II+} olaparib + hormone therapy ^{II+} talazoparib ^{II+}	42
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	13
IIC	CCND1 amplification cyclin D1 Locus: chr11:69455949	None*	None*	7
IIC	PIK3CA amplification phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Locus: chr3:178916680	None*	None*	4
IIC	MYCL amplification MYCL proto-oncogene, bHLH transcription factor Locus: chr1:40362966	None*	None*	2
IIC	FANCF deletion Fanconi anemia complementation group F Locus: chr11:22646196	None*	None*	1

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², 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	<i>FGF19 amplification</i> fibroblast growth factor 19 Locus: chr11:69513948	None*	None*	1
IIC	<i>MDM2 amplification</i> MDM2 proto-oncogene Locus: chr12:69202958	None*	None*	2
IIC	<i>TP53 c.96+1G>A</i> tumor protein p53 Allele Frequency: 76.25% Locus: chr17:7579699 Transcript: NM_000546.6	None*	None*	1

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

*ABRAXAS1 deletion, BCL6 amplification, FGF3 amplification, FGF4 amplification, Microsatellite stable, PIK3R2 amplification, MECOM amplification, HLA-A deletion, HLA-B deletion, TAP2 deletion, CYP2C9 deletion, NQO1 p.(P187S) c.559C>T, ZFH3 p.(Q3197Sfs*45) c.9588_9589insAG, PRKACA amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA2	p.(?)	c.7977-1G>A	.	chr13:32937315	25.44%	NM_000059.4	unknown
TP53	p.(?)	c.96+1G>A	.	chr17:7579699	76.25%	NM_000546.6	unknown
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	34.92%	NM_000903.3	missense
ZFH3	p.(Q3197Sfs*45)	c.9588_9589insAG	.	chr16:72822586	11.48%	NM_006885.4	frameshift Insertion
ERBB4	p.(E740*)	c.2218G>T	.	chr2:212483985	74.97%	NM_005235.3	nonsense
CTNNB1	p.(G455D)	c.1364G>A	.	chr3:41275198	46.67%	NM_001904.4	missense
APC	p.(R399G)	c.1195A>G	.	chr5:112154924	2.65%	NM_000038.6	missense
POT1	p.(P593A)	c.1777C>G	.	chr7:124465321	38.15%	NM_015450.3	missense
POT1	p.(V529E)	c.1586T>A	.	chr7:124469316	52.05%	NM_015450.3	missense
CDKN2A	p.(?)	c.150+2T>G	.	chr9:21974675	75.11%	NM_001195132.2	unknown
CDH1	p.(I505T)	c.1514T>C	.	chr16:68849611	62.88%	NM_004360.5	missense
NOTCH3	p.(A399S)	c.1195G>T	.	chr19:15299983	71.49%	NM_000435.3	missense

Variant Details (continued)

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0.8	0.64
CCND1	chr11:69455949	34.07	10.62
PIK3CA	chr3:178916680	8.43	2.93
MYCL	chr1:40362966	18.58	5.98
FANCF	chr11:22646196	0.8	0.64
FGF19	chr11:69513948	37.2	11.56
MDM2	chr12:69202958	6.72	2.41
ABRAXAS1	chr4:84383635	0.45	0.54
BCL6	chr3:187440209	7.6	2.68
FGF3	chr11:69625020	40.6	12.58
FGF4	chr11:69588019	37.33	11.6
PIK3R2	chr19:18266737	5.55	2.07
MECOM	chr3:168802636	8.1	2.83
HLA-A	chr6:29910229	0	0.34
HLA-B	chr6:31322252	0.77	0.63
TAP2	chr6:32796585	0.6	0.58
CYP2C9	chr10:96698378	0.98	0.69
PRKACA	chr19:14204349	7.2	2.56
MUTYH	chr1:45794962	8.05	2.82
RAD54L	chr1:46714017	7.77	2.73
TP63	chr3:189456442	6.08	2.23
CTNND2	chr5:10988230	0.93	0.68
PRDM9	chr5:23509577	0.67	0.6
ARID2	chr12:46123536	7.42	2.63
ACVR1B	chr12:52345528	5.65	2.1
NOTCH3	chr19:15271451	8.33	2.9
JAK3	chr19:17937461	4.83	1.85
ZNF217	chr20:52188253	0.82	0.65

Biomarker Descriptions

BRCA2 c.7977-1G>A

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function

Biomarker Descriptions (continued)

and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{18,19}. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{18,19}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{20,21,22}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{20,23}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{24,25,26,27,28,29,30,31}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme^{6,7}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)³². Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{33,34}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib³⁵ (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib³⁵ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib³⁶ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib³⁷ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib³⁷ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib³⁸ (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate³⁹ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁴⁰. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁴¹. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁴², for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348⁴³, a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹. 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)⁷¹. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{72,73,74}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions⁷⁵. 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^{1,75,76}. CDKN2A aberrations commonly co-occur with CDKN2B⁷¹. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation⁷⁷. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{78,79}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations⁸⁰. 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^{6,7}. 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

Biomarker Descriptions (continued)

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^{6,7}. Alterations in CDKN2A are also observed in pediatric cancers⁷. 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 tumors⁷. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)⁷.

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^{17,81,82}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma⁸³. 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^{84,85,86}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁸⁷. 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^{88,89,90,91}.

CCND1 amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3^{210,211,212}. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein^{210,211}. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis^{210,211,213}. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1^{212,214}.

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)^{6,7,215,216}. These mutations block phosphorylation-dependent nuclear export and proteolysis^{217,218,219,220}. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers^{6,7,134}. MCL is genetically characterized by the t(11;14) (q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis^{221,222}.

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma¹⁴⁹.

PIK3CA amplification

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) enzyme¹⁹⁰. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases^{191,192}. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively¹⁹¹. 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^{69,70}. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism^{69,70,193,194}. 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^{195,196,197}.

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^{6,7}. 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)^{198,199}. 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^{200,201,202}. 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^{6,7}.

Biomarker Descriptions (continued)

Potential relevance: The PI3K inhibitor, alpelisib²⁰³, 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 tumors²⁰⁴. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations²⁰⁴. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations²⁰⁵. The FDA also approved the kinase inhibitor, capivasertib (2023)²⁰⁶ 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, inavolisib²⁰⁷, 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^{208,209}.

MYCL amplification

MYCL proto-oncogene, bHLH transcription factor

Background: The MYCL gene encodes MYCL proto-oncogene, a basic helix-loop-helix transcription factor¹. MYCL is a member of MYC oncogene family that includes related transcription factors, MYC and MYCN which regulate transcription in 10-15% of promoter regions^{1,114}. MYCL, along with MYC and MYCN, control cell proliferation, replication, evasion of growth suppression and cell death¹¹⁵.

Alterations and prevalence: Amplification of MYCL was first discovered in small cell lung cancer (SCLC) cell lines and is observed in 8% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma and esophageal squamous cell carcinoma, as well as 3% uterine corpus endometrial carcinoma^{6,7,116}.

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

FANCF deletion

Fanconi anemia complementation group F

Background: The FANCF gene encodes the FA complementation group F protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCG, FANCI, FANCI (BRIP1), FANCL, FANCM and FANCN (PALB2)¹. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway^{59,60}. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex⁵⁹. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair^{61,62}. Loss of function mutations in the FA family and HRR pathway, including FANCF, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{63,64}. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition^{65,66}.

Alterations and prevalence: Somatic mutations in FANCF are observed in 2% of uterine corpus endometrial carcinoma, and 1% of lung squamous cell carcinoma, adrenocortical carcinoma, and bladder urothelial carcinoma^{6,7}.

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

FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members^{117,118}. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases^{117,118}. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival^{119,120,121}. FGF19 is specifically observed to bind FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation^{151,152}. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma^{151,153}.

Alterations and prevalence: FGF19 amplification is observed in about 35% of esophageal cancer, 23% of head and neck cancer, 10-15% of invasive breast carcinoma, cholangiocarcinoma, squamous lung, and bladder cancers as well as 5-7% of melanoma, liver,

Biomarker Descriptions (continued)

ovarian, and stomach cancers⁶. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma¹⁵⁴.

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. Selective, irreversible FGFR4 inhibitors, including fisogatinib (BLU-554), are under current clinical trial evaluation. In a phase-I clinical study of fisogatinib in patients with advanced hepatocellular carcinoma, 63% of the 115 patients enrolled were FGF19-positive by IHC¹⁵⁵. Additionally, in 53 patients with tissue available for evaluation, 96% also exhibited mRNA-expression of FGFR4 and KLB. The total overall response rate observed for fisogatinib in FGF19-positive patients evaluable for response was 17% (11/66)¹⁵⁵.

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene. 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 domain¹². 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 domains¹². 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 levels¹³. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53¹³. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2¹³.

Alterations and prevalence: MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma^{6,7}. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers¹⁴. The most common co-occurring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation^{15,16}.

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 liposarcoma¹⁷.

TP53 c.96+1G>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 repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis¹²⁹. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential¹³⁰. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{131,132}.

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%)^{6,7,133,134,135,136}. 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^{6,7}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{137,138,139,140}. Alterations in TP53 are also observed in pediatric cancers^{6,7}. 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)^{6,7}. 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)^{6,7}.

Potential relevance: The small molecule p53 reactivator, PC14586¹⁴¹ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprentapopt¹⁴², (2019) and breakthrough designation¹⁴³ (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{144,145}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma¹⁴⁶. 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)^{50,51,52,55,147,148}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant¹⁴⁹. 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 system¹⁵⁰.

Biomarker Descriptions (continued)

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit¹. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36^{126,127}. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks¹²⁶. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair¹²⁶. Together with the rest of the BRCA1-A complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer^{126,128}.

Alterations and prevalence: Somatic mutations in ABRAXAS1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, and 1% of stomach adenocarcinoma and lung squamous cell carcinoma^{6,7}.

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

BCL6 amplification

B-cell CLL/lymphoma 6

Background: The BCL6 gene encodes the B-cell lymphoma 6 (BCL6) transcription repressor, a protein that is responsible for inhibiting the expression of several genes including those involved in the DNA damage response, cell cycle checkpoints, and modulating BCL2 expression^{103,104,105}. BCL6 is most commonly expressed in germinal center B-cells and is required for germinal cell formation and affinity maturation during T-cell dependent antibody responses¹⁰⁴. BCL6 is observed to competitively bind DNA motifs recognized by the oncogenic transcription factor STAT6, thereby repressing STAT6 mediated gene transcription^{106,107}. Aberrations in BCL6 often lead to altered target gene transcription, including those involved in cell cycle arrest, differentiation, and apoptosis^{103,104}.

Alterations and prevalence: BCL6 rearrangement most commonly occurs with immunoglobulin H (IGH) partners and results in the truncation or removal the BCL6 promoter region and juxtaposition of BCL6 downstream of the partner gene promoter¹⁰⁸. Replacement of the BCL6 promoter resulting from such translocations has been observed to lead to aberrant BCL6 expression¹⁰⁹. BCL6 rearrangement is a common event in lymphoma and has been observed in up to 40% of diffuse large B-cell lymphoma (DLBCL) and 15% of follicle center lymphomas^{104,108}. Somatic mutations in BCL6 are observed in 7% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma, and 2% of uterine carcinosarcoma, lung adenocarcinoma, and sarcoma^{6,7}. Mutations in the 5' regulatory sequences of BCL6 are observed in 30-40% of germinal center B-cells and are believed to disrupt BCL6 negative autoregulation¹⁰⁴. Amplifications are observed in 31% of lung squamous cell carcinoma, 16% of esophageal adenocarcinoma and ovarian serous cystadenocarcinoma, and 14% of head and neck and cervical squamous cell carcinoma, 9% of uterine carcinosarcoma, 6% of uterine corpus endometrial carcinoma, and 2-4% of stomach adenocarcinoma, diffuse large B-cell lymphoma, bladder urothelial carcinoma, breast invasive carcinoma, testicular germ cell tumors, liver hepatocellular carcinoma, and pancreatic adenocarcinoma^{6,7}. Alterations in BCL6 are rare in pediatric cancers^{6,7}. Somatic mutations in BCL6 are observed in 3% of soft tissue sarcoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumors (2 in 332 cases), and glioma (1 in 297 cases)^{6,7}. Amplification of BCL6 is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)^{6,7}.

Potential relevance: B-cell lymphoma with BCL6 translocations that co-occur with MYC are referred to as double-hit lymphoma (DHL), while co-occurrence with MYC and BCL2 rearrangements is referred to as triple-hit lymphoma¹¹⁰. Such concomitant rearrangements are recognized by the World Health Organization (WHO) as diagnostic entity of diffuse large B-cell lymphoma/high grade B-cell lymphoma (HGBL) with MYC and BCL2 rearrangements¹¹¹. DHL expressing BCL6 rearrangements are most often aggressive with poor prognosis, involve extra nodal sites, and have a germinal center phenotype^{112,113}.

FGF3 amplification

fibroblast growth factor 3

Background: The FGF3 gene encodes the fibroblast growth factor 3 protein, a member of the FGF protein family composed of twenty-two members^{117,118}. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases^{117,118}. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival^{119,120,121}. Specifically, FGF3 has been shown to bind to both FGFR1 and FGFR2^{122,123}. Overexpression of FGF3 has been associated with certain tumor types including lung and liver cancers^{124,125}. Additionally, constitutive ectopic expression has been suggested to promote tumorigenesis in vitro, supporting an oncogenic role for FGF3¹²³.

Biomarker Descriptions (continued)

Alterations and prevalence: FGF3 amplification is observed in about 35% of esophageal cancer, 24% of head and neck cancer, 10-15% of invasive breast carcinoma, squamous lung, and bladder cancers as well as 5-10% of cholangiocarcinoma, melanoma, liver, ovarian and stomach cancers⁶. FGF3 overexpression is correlated with non-small cell lung cancer (NSCLC) development as well as tumor metastasis and recurrence in hepatocellular carcinoma^{124,125}.

Potential relevance: Currently, no therapies are approved for FGF3 aberrations.

FGF4 amplification

fibroblast growth factor 4

Background: The FGF4 gene encodes the fibroblast growth factor 4 protein, a member of the FGF protein family, which is composed of 22 members^{11,118}. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases^{117,118}. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways, thereby influencing cell proliferation, migration, and survival^{119,120,121}.

Alterations and prevalence: Amplifications in FGF4 are observed in various tumor types, but most frequently are found in up to 35% of esophageal adenocarcinoma, 24% of head and neck squamous cell carcinoma, 14% of breast invasive carcinoma, 12% of lung squamous cell carcinoma, 11% of cholangiocarcinoma, 10% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, and 5% of liver hepatocellular carcinoma^{6,7}. FGF4 overexpression has been associated with Kaposi sarcoma lesions as well as testicular cancer^{156,157}.

Potential relevance: Currently, no therapies are approved for FGF4 aberrations.

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 genome¹⁶⁸. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{169,170}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2¹⁷¹. 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 D17S250¹⁷². 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)¹⁷². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{173,174,175,176,177}. 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 genes¹⁷⁰. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{169,170,174,178}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endometrial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{169,170,179,180}. 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^{179,180}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹⁸¹ (2014) and nivolumab¹⁸² (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹⁸¹ is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication¹⁸¹. Dostarlimab¹⁸³ (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^{175,184}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹⁸⁵ (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^{175,186,187}. 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 patients¹⁸⁷. 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^{188,189}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{188,189}.

Biomarker Descriptions (continued)

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^{1,67}. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit⁶⁷. PIK3R2 encodes the p85 β protein, one of five p85 isoforms⁶⁷. p85 β is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity⁶⁸. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3)^{69,70}. Increased PIK3R2 expression has been observed to correlate with elevated AKT activation and tumor stage, supporting an oncogenic role for PIK3R2⁶⁸.

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^{6,7}. 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^{6,7}.

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

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 differentiation⁴⁴. The MECOM locus encodes multiple alternative splice variants that result in MDS1-EVI1, MDS1, and EVI1 protein isoforms⁴⁵. The EVI1 isoform is the most abundant and oncogenic form of MECOM that is expressed in various cancers including acute myeloid leukemia (AML)^{45,46}. MECOM is a frequent target of chromosomal translocation which can lead to MECOM overexpression and leukemogenesis⁴⁷.

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^{6,7,48}. 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^{6,7}. MECOM rearrangements occur with various partner genes including ETV6, RUNX1, and H2AFY⁴⁹. 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)^{50,51,52}. The inv(3)/t(3;3) translocation repositions the distal GATA enhancer element and activates MECOM expression while simultaneously causing GATA2 haploinsufficiency⁵³.

Potential relevance: AML with MECOM rearrangement is considered a distinct molecular subtype of AML as defined by the World Health Organization (WHO)⁵⁴. MECOM rearrangements, including GATA2::MECOM fusions, are associated with poor/adverse risk in AML^{50,55}. Inv(3) is associated with poor cytogenetic risk in MDS as defined by the revised international prognostic scoring system (IPSS-R) scoring system⁵². 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 system⁵¹. MECOM overexpression is observed in 10% of de novo AML associated with poor prognosis, and is commonly found in MLL-rearranged cases^{56,57}. Amplification of MECOM is associated with favorable prognosis in ovarian cancer⁵⁸.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A¹. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells⁹². MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁹³. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{94,95,96}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁹⁷.

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

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

Biomarker Descriptions (continued)

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B¹. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells⁹². MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁹³. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{94,95,96}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B⁹⁷.

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma^{6,7}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{6,7}.

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

TAP2 deletion

transporter 2, ATP binding cassette subfamily B member

Background: The TAP2 gene encodes the transporter 2, ATP binding cassette subfamily B member protein¹. Along with TAP1, TAP2 is a member of the superfamily of ATP-binding cassette (ABC) transporters¹. Together, TAP1 and TAP2 are capable of ATP controlled dimerization and make up the ABC transporter associated with antigen processing (TAP), which plays a role in adaptive immunity by transporting peptides across the ER membrane for the loading of major histocompatibility (MHC) class I molecules^{2,3}. TAP2 deregulation, including altered expression, has been observed in several tumor types, which may impact tumor progression^{4,5}.

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^{6,7}. Biallelic deletion of TAP2 is observed in 6% of diffuse large B-cell lymphoma (DLBCL)^{6,7}.

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

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins¹. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids^{1,8}. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents^{9,10}. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro^{9,10,11}. CYP2C9 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis^{8,9,10,11}. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors⁹. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease⁹.

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe^{6,7}. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma^{6,7}. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma^{6,7}.

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

ZFXH3 p.(Q3197Sfs*45) c.9588_9589insAG

zinc finger homeobox 3

Background: ZFXH3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains^{1,158,159}. Functionally, ZFXH3 is found to be necessary for neuronal and myogenic differentiation^{159,160}. ZFXH3 is capable of binding and repressing transcription of α -fetoprotein (AFP), thereby negatively

Biomarker Descriptions (continued)

regulating the expression of MYB and cancer cell growth^{161,162,163,164,165}. In addition, ZFH3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFH3^{161,164,166,167}.

Alterations and prevalence: Somatic mutations in ZFH3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia^{6,7}. Biallelic loss of ZFH3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for ZFH3 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^{1,98,99}. 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^{1,98}. Aberrations in PRKACA are oncogenic, as they are predicted to abolish the interaction with R subunits leading to cAMP-independent activation of PKA¹⁰⁰. 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^{100,101}.

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^{6,7}. PRKACA fusions have also been observed in 2% of liver cancer^{6,7}. Specifically, PRKACA fusion with DNAJB1 has been observed to be recurrent in fibrolamellar hepatocellular carcinoma, which results in the retention of a functional PRKACA catalytic domain and increased protein levels^{98,102}. PRKACA amplification is observed in about 11% of ovarian cancer and 2-3% of adrenocortical carcinoma, sarcoma, and uterine cancer^{98,102}.

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO1D, 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, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, 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,

Genes Assayed (continued)

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

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, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, 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, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

Relevant Therapy Summary

☒ In this cancer type ☐ In other cancer type ☒ In this cancer type and other cancer types ☒ No evidence

BRCA2 c.7977-1G>A


















































































































































Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/> (II)
bevacizumab + olaparib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="checkbox"/>
abiraterone + niraparib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

* 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

BRCA2 c.7977-1G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
rucaparib					
talazoparib + enzalutamide					
niraparib					 (II)
bevacizumab + niraparib					
olaparib + abiraterone acetate					
talazoparib					 (II)
niraparib, dostarlimab					 (II)
olaparib, talazoparib, atezolizumab + talazoparib					 (II)
pamiparib, tislelizumab					 (II)
ZEN-3694, talazoparib					 (II)
AMXI-5001					 (I/II)
sacituzumab govitecan, berzosertib					 (I/II)
HS-10502					 (I)
niraparib, chemotherapy					 (I)
novobiocin					 (I)
olaparib, chemotherapy					 (I)
GEN-1, chemotherapy, olaparib, niraparib					 (III)
saruparib, hormone therapy					 (III)
abiraterone + niraparib, hormone therapy, radiation therapy, steroid					 (II)
camrelizumab, fluzoparib					 (II)
camrelizumab, fluzoparib, chemotherapy					 (II)
fluzoparib					 (II)
olaparib + hormone therapy					 (II)
olaparib, durvalumab					 (II)
olaparib, durvalumab, chemotherapy					 (II)
olaparib, pembrolizumab					 (II)
pamiparib					 (II)
pembrolizumab, olaparib, chemotherapy					 (II)
tuvusertib, lartisertib, niraparib					 (II)

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

Relevant Therapy Summary (continued)

● In this cancer type
 ○ In other cancer type
 ⓘ In this cancer type and other cancer types
 ✕ No evidence

BRCA2 c.7977-1G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AZD-9574	✕	✕	✕	✕	○ (I/II)
IDB-476	✕	✕	✕	✕	○ (I/II)
ATX-559	✕	✕	✕	✕	○ (I)
axatilimab, olaparib	✕	✕	✕	✕	○ (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
AMG 193	✕	✕	✕	✕	● (I/II)
ficlatuzumab, cetuximab	✕	✕	✕	✕	○ (III)
palbociclib, cetuximab	✕	✕	✕	✕	○ (III)
chemotherapy, cetuximab, radiation therapy	✕	✕	✕	✕	○ (II/III)
abemaciclib	✕	✕	✕	✕	○ (II)
niraparib, dostarlimab	✕	✕	✕	✕	○ (II)
ribociclib, everolimus	✕	✕	✕	✕	○ (II)
tiragolumab, atezolizumab	✕	✕	✕	✕	○ (II)
tislelizumab, palbociclib	✕	✕	✕	✕	○ (I/II)
ipatasertib, chemotherapy, radiation therapy	✕	✕	✕	✕	○ (I)

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✕	✕	✕	✕	ⓘ (II)
palbociclib	✕	✕	✕	✕	● (II)
PF-07220060, midazolam	✕	✕	✕	✕	● (I/II)
ribociclib, everolimus	✕	✕	✕	✕	○ (II)
zotatifin, hormone therapy	✕	✕	✕	✕	○ (I/II)

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

Relevant Therapy Summary (continued)

● In this cancer type
 ○ In other cancer type
 ① In this cancer type and other cancer types
 ✕ No evidence

PIK3CA amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, gedatolisib	✕	✕	✕	✕	● (I)
pembrolizumab, chemotherapy	✕	✕	✕	✕	○ (IV)
ribociclib, everolimus	✕	✕	✕	✕	○ (II)
TOS-358	✕	✕	✕	✕	○ (I)

MYCL amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
MRT-2359	✕	✕	✕	✕	● (I/II)
dinutuximab beta, chemotherapy, radiation therapy	✕	✕	✕	✕	○ (III)

FANCF deletion

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

FGF19 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TYRA-430	✕	✕	✕	✕	● (I)

MDM2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
retifanlimab, pemigatinib	✕	✕	✕	✕	○ (II)
BTX-A51	✕	✕	✕	✕	○ (I)

TP53 c.96+1G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab, chemotherapy	✕	✕	✕	✕	○ (IV)

* 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
Not Detected	Not Applicable

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 OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.06(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 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. 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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