

Patient Name: 문은비

Gender: F

Sample ID: N25-170

Primary Tumor Site: ovary

Collection Date: 2025.07.30

Sample Cancer Type: Ovarian Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	6 Relevant Biomarkers
Biomarker Descriptions	3	0 Therapies Available
Relevant Therapy Summary	15	17 Clinical Trials

Relevant Ovarian Cancer Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	3.79 Mut/Mb measured
Genomic Instability	GIM 6 (Low)

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

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	MTAP deletion methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	9
IIC	KRAS amplification KRAS proto-oncogene, GTPase Locus: chr12:25362709	None*	None*	4
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	CCND2 amplification cyclin D2 Locus: chr12:4383227	None*	None*	2

* 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	ARID1A p.(Q1342Rfs*139) c.4025delA	None*	None*	1
	AT-rich interaction domain 1A			
	Allele Frequency: 73.04%			
	Locus: chr1:27100312			
	Transcript: NM_006015.6			
IIC	CDKN2B deletion	None*	None*	1
	cyclin dependent kinase inhibitor 2B			
	Locus: chr9:22005728			

* 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

ARID2 deletion, CDKN1B deletion, FANCC deletion, FANCG deletion, FGF23 amplification, Microsatellite stable, PPP2R2A deletion, RPA1 deletion, TP53 p.(V203L) c.607G>T, TSC1 deletion, JAK1 deletion, FUBP1 deletion, JAK2 deletion, PTCH1 deletion, PPP6C deletion, NOTCH1 deletion, SLC01B3 amplification, KMT2D deletion, ACVR1B deletion, GPS2 deletion, NCOR1 deletion, Tumor Mutational Burden, Genomic Instability (Low)

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ARID1A	p.(Q1342Rfs*139)	c.4025delA	.	chr1:27100312	73.04%	NM_006015.6	frameshift Deletion
TP53	p.(V203L)	c.607G>T	.	chr17:7578242	54.70%	NM_000546.6	missense
CTNND2	p.(R774Q)	c.2321G>A	.	chr5:11111112	30.33%	NM_001332.4	missense
DICER1	p.(L978R)	c.2933T>G	.	chr14:95572432	35.62%	NM_030621.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	0.13	0.34
KRAS	chr12:25362709	4.89	2.03
CDKN2A	chr9:21968178	0	0.27
CCND2	chr12:4383227	10.52	4.02
CDKN2B	chr9:22005728	0.1	0.32
ARID2	chr12:46123536	0.96	0.63
CDKN1B	chr12:12870763	0.9	0.61
FANCC	chr9:97863909	1.15	0.7
FANCG	chr9:35074046	1.11	0.68

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
FGF23	chr12:4479456	11.01	4.2
PPP2R2A	chr8:26149298	0.63	0.51
RPA1	chr17:1733385	1.11	0.69
TSC1	chr9:135771600	1	0.65
JAK1	chr1:65300225	1	0.65
FUBP1	chr1:78414385	0.83	0.59
JAK2	chr9:5021954	0.97	0.63
PTCH1	chr9:98209140	1.04	0.66
PPP6C	chr9:127911878	0.85	0.59
NOTCH1	chr9:139390441	0.97	0.64
SLCO1B3	chr12:21007974	6.44	2.57
KMT2D	chr12:49415529	0.92	0.61
ACVR1B	chr12:52345528	1.04	0.66
GPS2	chr17:7216071	1.08	0.68
NCOR1	chr17:15935586	0.99	0.64
TNFRSF14	chr1:2488070	4.62	1.93
EPHA2	chr1:16451707	4.51	1.89
MAGOH	chr1:53692690	1.03	0.65
FGFR1	chr8:38271452	1.04	0.66
IKBKB	chr8:42129602	0.9	0.61
CD274	chr9:5456050	0.87	0.6
PDCD1LG2	chr9:5522530	1.1	0.68
NTRK2	chr9:87549097	1.11	0.68
ABL1	chr9:133738250	0.87	0.6
RAD52	chr12:1022494	5.04	2.08

Biomarker Descriptions

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase¹. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate^{36,37}. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation³⁷.

Biomarker Descriptions (continued)

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers^{37,38}. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma^{18,19}. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma^{18,19}.

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

KRAS amplification

KRAS proto-oncogene, GTPase

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival^{91,92,93}.

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer¹⁸. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61^{18,94,95}. Mutations at A59, K117, and A146 have also been observed but are less frequent^{19,96}.

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib⁹⁷ (2021) and adagrasib⁹⁸ (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma⁹⁹. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036¹⁰⁰, for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398¹⁰¹ was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avotemetinib¹⁰² was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520¹⁰³, was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001¹⁰⁴, was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib¹⁰⁵, was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab¹⁰⁶ and panitumumab¹⁰⁷, are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)⁹⁶. Additionally, KRAS mutations are associated with poor prognosis in NSCLC¹⁰⁸.

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)¹³⁰. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{131,132,133}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions¹³⁴. 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^{1,134,135}. CDKN2A aberrations commonly co-occur with CDKN2B¹³⁰. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation¹³⁶. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{137,138}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations¹³⁹. 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^{18,19}. 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

Biomarker Descriptions (continued)

adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{18,19}. Alterations in CDKN2A are also observed in pediatric cancers¹⁹. 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 tumors¹⁹. 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)¹⁹.

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^{140,141,142}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma¹⁴³. 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^{144,145,146}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme¹⁴⁷. 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^{148,149,150,151}.

CCND2 amplification

cyclin D2

Background: The CCND2 gene encodes the cyclin D2 protein, a member of the highly conserved D-cyclin family that also includes CCND1 and CCND3^{160,161,162}. 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^{160,161}. 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^{160,161,163}. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND2^{162,164}.

Alterations and prevalence: Somatic mutations in CCND2 are observed in 2-3% of melanoma, diffuse large B-cell lymphoma (DLBCL), and uterine cancer¹⁸. Additionally, amplification of CCND2 is observed in 6-7% of ovarian and uterine carcinosarcoma, 4-5% of low grade gliomas and testicular cancer, and 2-3% of sarcomas, glioblastoma, squamous lung, colorectal, pancreatic, and head and neck cancers¹⁸.

Potential relevance: Currently, no therapies are approved for CCND2 aberrations.

ARID1A p.(Q1342Rfs*139) c.4025delA

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein¹. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes ARID1B^{1,42}. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex^{42,43}. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B⁴³. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{43,44}. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription⁴². Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function⁴².

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 tumors⁴⁴. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations⁴². 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^{18,19,43}. 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 response⁴⁵.

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800⁴⁶, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulumimostat⁴⁷, 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)

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression^{1,130}. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)¹³⁰. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{131,132,133}. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A¹³⁰. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma^{1,158,159}.

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B-cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{18,19}. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma^{18,19}. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers^{18,19}. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)^{18,19}.

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma¹⁴³.

ARID2 deletion

AT-rich interaction domain 2

Background: The ARID2 gene encodes the AT-rich interaction domain 2 protein¹. ARID2, also known as BAF200, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID5B⁴⁹. ARID2 is an essential member of the PBAF complex, a SWI/SNF chromatin-remodeling complex^{49,50}. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57^{43,50}. ARID2 may alter the expression of IFN responsive genes, which suppress cell proliferation⁴⁹. Loss of function mutations in ARID2 may promote cell proliferation, suggesting a tumor suppressor role of ARID2⁴⁹.

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 tumors⁴⁴. Somatic mutations in ARID2 are observed in 17% of skin cutaneous melanoma, 11% of uterine corpus endometrial carcinoma, 8% of bladder urothelial carcinoma and stomach adenocarcinoma, 7% of colorectal adenocarcinoma, and 5% of liver hepatocellular carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma^{18,19}. ARID2 biallelic deletions are observed in 2% of mesothelioma^{18,19}.

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

CDKN1B deletion

cyclin dependent kinase inhibitor 1B

Background: The CDKN1B gene encodes the cyclin-dependent kinase inhibitor 1B protein and is also known as p27 or KIP1. CDKN1B belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1A (also known as WAF1/p21) and CDKN2C (also known as KIP2/p57)^{125,126}. CDKN1B is involved in controlling G1/S cell cycle progression, cell proliferation, and apoptosis^{1,125,126}. Specifically, in the nucleus, CDKN1B acts as a tumor suppressor by binding with the cyclin E-CDK2 and cyclin D-CDK4 complexes¹²⁷. However, cytoplasmic localization of the CDKN1B/p27 is associated with invasiveness and metastasis in melanoma thereby giving it potential oncogenic function¹²⁸. Germline mutations of CDKN1B are commonly associated with multiple endocrine neoplasia type 4 (MEN4), a hereditary disease characterized by parathyroid, anterior pituitary, or neuroendocrine tumors^{126,129}.

Alterations and prevalence: Somatic aberrations commonly observed in CDKN1B are mutations, copy number loss and amplification. Mutations that lead to a truncated form of CDKN1B are observed in 2% of endometrial carcinoma^{18,19,126}. CDKN1B copy number loss is observed in 4% of prostate adenocarcinoma, and 2% of mature B-cell neoplasm^{18,19}. Amplifications of CDKN1B are observed in 4% of ovarian epithelial tumors, 5% of seminoma, and 3% of non-seminomatous germ cell tumor^{18,19}.

Potential relevance: Currently, no targeted therapies are approved for CDKN1B aberrations.

Biomarker Descriptions (continued)

FANCC deletion

Fanconi anemia complementation group C

Background: The FANCC gene encodes the FA complementation group C protein, a member of the Fanconi anemia (FA) family, which also includes FANCA, FANCB, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, 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^{115,116}. 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) complex¹¹⁵. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair^{117,118}. Loss of function mutations in the FA family and HRR pathway, including FANCC, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{119,120}. 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^{121,122}.

Alterations and prevalence: Somatic mutations in FANCC are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, 2% of colorectal adenocarcinoma, stomach adenocarcinoma and uterine carcinosarcoma, and 1% of bladder urothelial carcinoma and lung squamous cell carcinoma^{18,19}.

Potential relevance: Currently, no therapies are approved for FANCC aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCC are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib¹²³.

FANCG deletion

Fanconi anemia complementation group G

Background: The FANCG gene encodes the FA complementation group G protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, 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^{115,116}. 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) complex¹¹⁵. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair^{117,118}. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss^{119,120}. 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^{121,122}.

Alterations and prevalence: Somatic mutations in FANCG are observed in 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma^{18,19}.

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

FGF23 amplification

fibroblast growth factor 23

Background: The FGF23 gene encodes the fibroblast growth factor 23 protein, a member of the FGF protein family, which is composed of 22 members^{1,53}. 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^{53,54}. 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^{55,56,57}. Normally expressed in osteoclasts, FGF23 is known to function as an endocrine FGF and promotes the regulation of vitamin D levels and phosphate homeostasis^{54,58}.

Alterations and prevalence: Amplifications in FGF23 are observed in up to 7% of uterine carcinosarcoma, 6% of ovarian serous cystadenocarcinoma, and 5% of testicular germ cell tumors and brain lower grade glioma^{18,19}. Somatic mutations are observed in up to 4% of skin cutaneous melanoma and 2% of uterine corpus endometrial carcinoma and adrenocortical carcinoma^{18,19}. Expression of FGF23 has been observed in prostate cancer cells and has been shown to promote growth and invasion in vitro⁵⁸.

Potential relevance: Currently, no therapies are approved for FGF23 aberrations.

Biomarker Descriptions (continued)

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 genome⁵⁹. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{60,61}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁶². 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 D17S250⁶³. 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)⁶³. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{64,65,66,67,68}. 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 genes⁶¹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{60,61,65,69}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{60,61,70,71}. 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^{70,71}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁷² (2014) and nivolumab⁷³ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁷² 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 indication⁷². Dostarlimab⁷⁴ (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^{66,75}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁷⁶ (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^{66,77,78}. 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 patients⁷⁸. 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^{79,80}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{79,80}.

PPP2R2A deletion

protein phosphatase 2 regulatory subunit B alpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)^{29,30}. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway³¹. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway²⁹.

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer^{29,30,32,33}. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma¹⁸.

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex³⁴, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib²⁹. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit³⁵.

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1¹. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)¹¹⁴. RPA is involved in multiple DNA repair processes including base excision repair

Biomarker Descriptions (continued)

(BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)¹¹⁴. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair¹¹⁴.

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma^{18,19}. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma^{18,19}.

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

TP53 p.(V203L) c.607G>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 repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis¹⁶⁸. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential¹⁶⁹. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{170,171}.

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%)^{18,19,88,172,173,174}. 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^{18,19}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{175,176,177,178}. Alterations in TP53 are also observed in pediatric cancers^{18,19}. 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)^{18,19}. 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)^{18,19}.

Potential relevance: The small molecule p53 reactivator, PC14586¹⁷⁹ (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, eprenetapopt¹⁸⁰, (2019) and breakthrough designation¹⁸¹ (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^{182,183}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma¹⁸⁴. 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)^{20,23,185,186,187,188}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant¹⁸⁹. 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 system¹⁹⁰.

TSC1 deletion

tuberous sclerosis 1

Background: The TSC1 gene encodes the hamartin protein. TSC1 and TSC2 (also known as tuberlin) form a complex through their respective coiled-coil domains³⁹. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis⁴⁰. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway^{39,41}. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs³⁹.

Alterations and prevalence: Somatic mutations are observed in up to 8.5% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, and up to 6% of skin cutaneous melanoma^{18,19}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for TSC1 aberrations.

JAK1 deletion

Janus kinase 1

Background: The JAK1 gene encodes Janus kinase 1, a non-receptor protein tyrosine kinase (PTK)^{1,2}. JAK1 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2³. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain³. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling^{3,4,5}. Since JAK1 mediates interferon-γ regulated tumor surveillance, inactivation of JAK1 is believed to inhibit the presentation of tumor antigens and contribute to immune evasion^{5,191,192}.

Alterations and prevalence: Activating missense mutations in JAK1 that result in constitutive signal transduction are observed in both pediatric and adult T-cell lymphoblastic leukemia^{193,194,195}. The recurrent somatic mutation V658F observed in JAK1 is homologous to the V617F mutation in JAK2 and is a known driver mutation in myeloproliferative disease¹⁹⁴. Recurrent activating mutations in JAK1 are infrequently observed in solid cancers, although two variants, S703I and S729C, were reported in hepatocellular carcinomas^{196,197,198}. In addition, V658F and R724H were infrequently observed in diverse cancer types^{18,19}. Truncating mutations in JAK1, resulting from dispersed or recurrent frameshift mutations, are common in solid cancers and particularly enriched in uterine cancers^{5,18,19}. Recurrent truncating mutations in JAK1 are also associated with high tumor mutation burden (TMB) and microsatellite instability (MSI)^{191,192}. JAK1 alterations are rare in pediatric cancers^{18,19}. Somatic mutations are observed in 12% of T-lymphoblastic leukemia/lymphoma, 2% of B-lymphoblastic leukemia/lymphoma (4 in 252 cases), and less than 1% of bone cancer (3 in 327 cases) and glioma (1 in 297 cases)^{18,19}. JAK1 is amplified in less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)^{18,19}.

Potential relevance: Currently, no therapies are approved for JAK1 aberrations. However, ruxolitinib²² is a JAK1/2 inhibitor that is FDA approved (2011) for primary myelofibrosis and polycythemia vera. Other JAK inhibitors, including tofacitinib (2012) and baricitinib (2018), are approved for rheumatoid arthritis. JAK1 mutations and fusions confer poor risk in B-cell ALL²³. Clinical cases associated with high TMB but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2²⁴.

FUBP1 deletion

far upstream element binding protein 1

Background: The FUBP1 gene encodes the far upstream element binding protein 1, a DNA/RNA binding protein implicated in a variety of cellular functions^{1,124}. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of transcription, translation, and splicing¹²⁴. FUBP1 activates the transcription of targets including the oncogene MYC which functions in cell cycle regulation, metabolism, and apoptosis¹²⁴. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation¹²⁴.

Alterations and prevalence: Somatic mutations in FUBP1 are observed in 9% of brain lower grade glioma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of colorectal adenocarcinoma^{18,19}. Mutations typically result in inactivation of FUBP1 through alteration of splicing sites, introduction of stop codons, or out-of-frame insertions or deletions¹²⁴. Biallelic loss of FUBP1 is observed in 3% of pheochromocytoma and paraganglioma^{18,19}. Co-deletion of 1p and 19q is frequently observed in oligodendrogliomas, which results in the monoallelic loss of FUBP1 and CIC on 19q¹²⁴.

Potential relevance: Currently, no therapies are approved for FUBP1 aberrations.

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)^{1,2}. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2². Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain³. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling^{3,4,5}. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion^{6,7}.

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2^{8,9}. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)^{10,11}. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL^{12,13}. JAK2 fusions are observed in myeloid

Biomarker Descriptions (continued)

and lymphoid leukemias with partner genes including TEL, PCM1, and BCR^{14,15,16,17}. JAK2 fusions are infrequently observed in solid tumors¹⁸. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers¹⁸. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma^{18,19}. Alterations in JAK2 are also observed in pediatric cancers^{18,19}. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)^{18,19}. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)^{18,19}. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)^{18,19}.

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)^{20,21}. Ruxolitinib²² (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia²³. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2²⁴. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited^{14,15,16,17}.

PTCH1 deletion

patched 1

Background: The PTCH1 gene encodes the patched 1 protein, a transmembrane protein that along with PTCH2, belongs to the patched gene family¹. PTCH1 is involved in the Hedgehog (Hh) signaling pathway that plays a significant role in embryonic development, cell proliferation, and cell differentiation^{165,166}. PTCH1 is a tumor suppressor gene that inhibits the transmembrane receptor Smoothened (SMO) and prevents downstream Hh signaling pathway activation^{165,166}. The Hh pathway is activated when one of the Hh ligands including Sonic hedgehog (SHh), Indian hedgehog (IHh), or Desert Hedgehog (DHh) bind to PTCH1 and disrupt SMO inhibition¹⁶⁶. Inactivating mutations in PTCH1 lead to ligand-independent signaling of Hh, as PTCH1 no longer prevents SMO activity¹⁶⁶. Germline mutations in PTCH1 are associated with basal cell nevus syndrome (BCNS) or Gorlin Syndrome with a predisposition to non-cancerous and cancerous tumors including basal cell carcinoma^{166,167}.

Alterations and prevalence: Inactivating mutations in PTCH1 are observed in 85% of sporadic basal cell carcinomas¹⁶⁷. Somatic mutations in PTCH1 are also observed in 11% of uterine corpus endometrial carcinoma and 4-5% of stomach adenocarcinoma, skin cutaneous melanoma, cholangiocarcinoma, esophagus adenocarcinoma, colorectal adenocarcinoma, and mesothelioma^{18,19}.

Potential relevance: Currently, no therapies are approved for PTCH1 aberrations.

PPP6C deletion

protein phosphatase 6 catalytic subunit

Background: PPP6C encodes protein phosphatase 6 catalytic subunit and is a member of the serine/threonine protein phosphatase family^{1,199}. As the catalytic subunit of the heterotrimeric phosphoprotein phosphatase 6 (PP6) holoenzyme, PPP6C is involved in diverse processes such as cell cycle regulation, DNA damage response, autophagy, miRNA processing, inflammatory signaling, and lymphocyte development^{199,200}. Loss of PPP6C results in hyperphosphorylation of Aurora A kinase, which results in defects in mitotic spindle assembly and subsequent genomic instability²⁰⁰. Overexpression of PPP6C has been observed to result in decreased colony formation of human endometrial carcinoma cells in vitro, supporting a possible tumor suppressor role for PPP6C²⁰¹.

Alterations and prevalence: Somatic mutations in PPP6C are observed in 7% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma^{18,19}. Biallelic loss of PPP6C is observed in 1% of thyroid carcinoma, pancreatic adenocarcinoma, and skin cutaneous melanoma^{18,19}. Amplification of PPP6C is observed in 2% kidney chromophobe^{18,19}.

Potential relevance: Currently, no therapies are approved for PPP6C aberrations.

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting

Biomarker Descriptions (continued)

NOTCH signaling⁸¹. 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^{82,83}. 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^{84,85,86,87}.

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers^{18,19,88}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{89,90}.

Potential relevance: Currently, no therapies are approved for NOTCH1 aberrations.

SLC01B3 amplification

solute carrier organic anion transporter family member 1B3

Background: The SLC01B3 gene encodes the solute carrier organic anion transporter family member 1B3 protein that functions as a transmembrane receptor involved in sodium-independent uptake of various molecules including bilirubin glucuronide, bile acids, steroid and thyroid hormones, as well as, numerous drugs, toxins, and their conjugates^{1,51}. SLC01B3 is observed as a key transport receptor for a variety of antitumor therapies. In cancer, variations in the expression patterns of SLC01B3 have been demonstrated to confer therapeutic resistance to taxanes, camptothecin, and Androgen Deprivation Therapy (ADT)⁵².

Alterations and prevalence: Somatic mutations of SLC01B3 are observed in 14% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 4% of esophageal adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma, 3% of bladder urothelial carcinoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma, lung adenocarcinoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, and uterine carcinosarcoma^{18,19}. Amplification of SLC01B3 is observed in 7% of testicular germ cell tumors, 6% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, 3% of lung adenocarcinoma, esophageal adenocarcinoma, and lung squamous cell carcinoma, and 2% of sarcoma, stomach adenocarcinoma, pancreatic adenocarcinoma, brain lower grade glioma, and bladder urothelial carcinoma^{18,19}.

Potential relevance: Currently, no therapies are approved for SLC01B3 aberrations.

KMT2D deletion

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase¹. KMT2D belongs to the SET domain protein methyltransferase superfamily⁴⁸. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity⁴⁸. 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 expression⁴⁸.

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^{18,19}.

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

ACVR1B deletion

activin A receptor type 1B

Background: The ACVR1B gene encodes the activin A type 1B receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family^{1,25}. ACVR1B is a type I receptor that forms a heterotetrameric complex with at least two type I receptors (including ACVR1) and two type II receptors (including BMPR2, ACVR2A, and ACVR2B)^{25,26}. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrameric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream signaling^{25,26}. Loss of function mutations and homozygous deletion in ACVR1B has been observed in pancreatic cancer and is associated with increased cell growth, colony formation, and tumorigenicity^{27,28}.

Alterations and prevalence: Somatic mutations of ACVR1B are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, 3% of stomach adenocarcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and kidney chromophobe, and 1% of head and neck

Biomarker Descriptions (continued)

squamous cell carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, brain lower grade glioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma, and acute myeloid leukemia^{18,19}. Biallelic deletion of ACRV1B is observed in 1% of stomach adenocarcinoma, brain lower grade glioma, and pancreatic adenocarcinoma^{18,19}.

Potential relevance: Currently, no therapies are approved for ACRV1B aberrations.

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2¹. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling¹⁵². GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development^{152,153}. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2^{154,155,156}.

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma^{18,19}. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma^{18,19}. Isolated GPS2 fusions have been reported in cancer with various fusion partners^{18,19,157}. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma¹⁵⁷.

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

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)^{1,109,110}. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability^{109,110,111,112}. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models¹¹⁰. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer^{110,113}.

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma^{18,19}. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma^{18,19}. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma^{18,19}.

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNA1, 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, MYO10, 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,

Genes Assayed (continued)

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

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, TGFBF1, 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, ERFFI1, 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, TGFBF2, 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, ERFFI1, 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, TGFBF2, 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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✕	✕	✕	✕	● (I/II)
TNG-456, abemaciclib	✕	✕	✕	✕	● (I/II)
TNG-462	✕	✕	✕	✕	● (I/II)
GTA-182	✕	✕	✕	✕	● (I)
ISM-3412	✕	✕	✕	✕	● (I)
MRTX-1719	✕	✕	✕	✕	● (I)
PH020-803	✕	✕	✕	✕	● (I)
S-095035	✕	✕	✕	✕	● (I)
SYH-2039	✕	✕	✕	✕	● (I)

KRAS amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
regorafenib	✕	✕	✕	✕	● (II)
BBO-11818, pembrolizumab, cetuximab, chemotherapy	✕	✕	✕	✕	● (I)
BGB-53038	✕	✕	✕	✕	● (I)
HMPL-415	✕	✕	✕	✕	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
AMG 193	✕	✕	✕	✕	● (I/II)

CCND2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✕	✕	✕	✕	● (II)
palbociclib	✕	✕	✕	✕	● (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

ARID1A p.(Q1342Rfs*139) c.4025delA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	×	×	×	×	<div></div> (II)

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	×	×	×	×	<div></div> (II)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	14.03%
RAD54L	LOH, 1p34.1(46714017-46743978)x2

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

Thermo Fisher Scientific's Ion Torrent 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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