

Patient Name: 정영자

Gender: F

Sample ID: N25-307

Primary Tumor Site:

Collection Date: 2024.09.10

Sample Cancer Type: Cholangiocarcinoma

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Relevant Cholangiocarcinoma Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR2	None detected	NTRK3	None detected
IDH1	None detected	RET	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	3.79 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	BRCA2 p.(L1103*) c.3308delT BRCA2, DNA repair associated Allele Frequency: 32.66% Locus: chr13:32911797 Transcript: NM_000059.4	olaparib II+ rucaparib II+	abiraterone + niraparib 1, 2 / II+ bevacizumab + olaparib 1, 2 / II+ niraparib 1 / II+ olaparib 1, 2 / II+ rucaparib 1 / II+ talazoparib + hormone therapy 1 / II+ bevacizumab + niraparib II+ talazoparib II+ olaparib + hormone therapy	13
IIC	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	4

* 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>BAP1 deletion</i> BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	<i>BARD1 deletion</i> BRCA1 associated RING domain 1 Locus: chr2:215593375	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

*ERBB3 p.(G284R) c.850G>C, KMT2C deletion, MAP2K7 deletion, PARP3 deletion, RAD51B deletion, RB1 p.(Y225Sfs*9) c.674_693delATTTTATTAACTCTCACCT, UGT1A1 p.(G71R) c.211G>A, KMT2D deletion, PDIA3 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA2	p.(L1103*)	c.3308delT	.	chr13:32911797	32.66%	NM_000059.4	nonsense
ERBB3	p.(G284R)	c.850G>C	COSM5413554	chr12:56481922	38.78%	NM_001982.4	missense
RB1	p.(Y225Sfs*9)	c.674_693delATTTTAT . TAACTCTCACCT	.	chr13:48934217	45.89%	NM_000321.3	frameshift Deletion
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	33.35%	NM_000463.3	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT . CA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
EGFR	p.(M111I)	c.333G>A	.	chr7:55211090	27.22%	NM_005228.5	missense
RAB11FIP1	p.([A651V;L652=])	c.1952_1954delCCCins . TCT	.	chr8:37730366	70.40%	NM_001002814.3	missense, synonymous
KMT2D	p.(E685K)	c.2053G>A	.	chr12:49445413	34.11%	NM_003482.4	missense

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.74
CDKN2A	chr9:21968178	0.74	0.66
BAP1	chr3:52436290	0.41	0.57
BARD1	chr2:215593375	1	0.79
KMT2C	chr7:151833866	0.83	0.68
MAP2K7	chr19:7968792	0.87	0.69
PARP3	chr3:51976651	0.87	0.7

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RAD51B	chr14:68290164	1	0.73
KMT2D	chr12:49415529	0.89	0.7
PDIA3	chr15:44038719	0.89	0.7
BARD1	chr2:215593375	1	0.79
BRCA2	chr13:32890491	1	0.74
RAD51B	chr14:68290164	1	0.73
NFE2L2	chr2:178095457	0.8	0.67
FGF9	chr13:22245989	0.74	0.66

Biomarker Descriptions

BRCA2 deletion, BRCA2 p.(L1103*) c.3308delT

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 and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{27,28}. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{27,28}. 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^{29,30,31}. 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%^{29,32}.

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^{33,34,35,36,37,38,39,40}. 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^{8,9}.

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)⁴¹. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{42,43}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁴⁴ (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, olaparib⁴⁴ 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. Rucaparib⁴⁵ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib⁴⁶ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib⁴⁶ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib⁴⁷ (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 acetate⁴⁸ 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 reported⁴⁹. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁵⁰. 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, pidnarulex⁵¹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but

Biomarker Descriptions (continued)

through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹⁸. 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)⁵⁸. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{59,60,61}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions⁶². 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^{18,62,63}. CDKN2A aberrations commonly co-occur with CDKN2B⁵⁸. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation⁶⁴. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{65,66}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations⁶⁷. 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^{8,9}. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{8,9}. Alterations in CDKN2A are also observed in pediatric cancers⁹. 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 tumors⁹. 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)⁹.

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^{68,69,70}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma⁷¹. 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^{72,73,74}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁷⁵. 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^{76,77,78,79}.

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes¹⁸. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation⁹⁹. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure⁹⁹. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma^{100,101,102,103,104,105}.

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma^{8,9}. BAP1 biallelic deletions are observed in 11% of mesothelioma^{8,9}.

Potential relevance: Currently, no therapies are approved for BAP1 aberrations.

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the *in vitro* E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene^{18,113}. The cysteine-rich N-terminal

Biomarker Descriptions (continued)

RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage^{18,113,114,115}. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction^{18,114,116,117}. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{117,118}. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility¹¹⁶. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53¹¹⁹. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer^{119,120}.

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma^{8,9}. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer^{8,9}.

Potential relevance: The PARP inhibitor, olaparib⁴⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁵¹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

ERBB3 p.(G284R) c.850G>C

erb-b2 receptor tyrosine kinase 3

Background: The ERBB3 gene encodes the erb-b2 receptor tyrosine kinase 3, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB3/HER3, EGFR/ERBB1/HER1, ERBB2/HER2, and ERBB4/HER4 make up the HER protein family¹. ERBB3/HER3 binds to extracellular factors, such as neuregulins, but has an impaired kinase domain². Upon ligand binding, ERBB3 forms hetero-dimers with other ERBB/HER family members, including ERBB2/HER2 resulting in activation of tyrosine kinase activity primarily through its dimerization partner.

Alterations and prevalence: ERBB3 gene amplification leading to an increase in expression occurs at low frequency (1-5%) in several cancer types including bladder, esophagus, lung adenocarcinoma, ovarian, pancreas, sarcoma, stomach, and uterine cancers^{3,4,5,6,7,8,9}. ERBB3 is also the target of relatively frequent (5-10%) and recurrent somatic mutations in diverse cancer types including bladder, cervical, colorectal, and stomach cancers^{3,6,8,9,10}. Recurrent ERBB3 mutations such as V104L/M, occur primarily in the extracellular domain.

Potential relevance: Currently, no therapies are approved for ERBB3 aberrations. Overexpression and activation of ERBB3/HER3 is one mechanism of acquired resistance to therapies targeting EGFR and ERBB2/HER2^{11,12}. Preclinical and translational research studies have characterized the oncogenic potential of recurrent ERBB3 mutations and their sensitivity to anti-ERBB antibodies and small molecule inhibitors^{13,14,15,16}. A phase I study exhibited progression-free survival (PFS) of 2.5 months and overall survival (OS) of 9 months in 25 patients with ERBB3 mutations treated by anti-ERBB antibodies or molecular-targeted agents¹⁷.

KMT2C deletion

lysine methyltransferase 2C

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase¹⁸. KMT2C belongs to the SET domain protein methyltransferase superfamily⁸⁰. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type⁸¹. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes^{82,83}. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes^{82,83}. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation⁸¹.

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma^{8,9}. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma^{8,9}.

Potential relevance: Currently, no therapies are approved for KMT2C aberrations.

Biomarker Descriptions (continued)

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7¹⁸. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10^{23,24,25}. Activation of MAPK proteins occurs through a kinase signaling cascade^{23,24,26}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{23,24,26}. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation^{23,24,26}.

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma^{8,9}. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma^{8,9}.

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein¹⁸. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4⁵². PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARYlation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure^{52,53}. PARP enzymes are involved in several DNA repair pathways^{52,53}. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)^{54,55}. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs⁵⁴.

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma^{8,9}. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma^{8,9}.

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death^{56,57}. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib⁴⁴ (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, olaparib⁴⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib⁴⁵ (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib⁴⁶ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib⁴⁷ (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.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)¹⁰⁶. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex¹⁰⁷. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP¹⁰⁸. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{109,110}. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents¹¹¹. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk¹¹².

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer^{8,9}. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk¹¹².

Potential relevance: The PARP inhibitor, olaparib⁴⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁵¹, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RB1 p.(Y225Sfs*9) c.674_693delATTTTATTAACCTCTCACCT

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation^{84,85}. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase⁸⁶. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation^{84,85,87}. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma⁸⁸.

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)⁹. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)⁹. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)^{89,90,91}.

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily^{18,92}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{92,93}. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance⁹⁴. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation^{94,95,96,97}. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38⁹⁸.

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

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

KMT2D deletion

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase¹⁸. KMT2D belongs to the SET domain protein methyltransferase superfamily⁸⁰. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity⁸⁰. 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 expression⁸⁰.

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^{8,9}.

Biomarker Descriptions (continued)

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

PDIA3 deletion

protein disulfide isomerase family A member 3

Background: The PDIA3 gene encodes the protein disulfide isomerase family A member 3¹⁸. PDIA3 is a member of the protein disulfide isomerase (PDI) gene family, and acts as an enzymatic chaperone for reconstructing misfolded proteins¹⁹. PDIA3 has also been identified as being involved EGFR regulation, mTOR signaling, and associated with the major histocompatibility complex (MHC) protein loading complex (PLC)²⁰. Deregulation of PDIA3, including both overexpression and loss, has been observed in several cancer types, suggesting that PDIA3 may exhibit differing roles depending on the tumor type^{20,21,22}.

Alterations and prevalence: Somatic mutations in PDIA3 are observed in 5% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, skin cutaneous melanoma, and 1% of stomach adenocarcinoma, bladder urothelial carcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, and glioblastoma multiforme^{8,9}. Deletions in PDIA3 are observed in 6% of diffuse large B-cell lymphoma 5% of mesothelioma, and 2% of lung adenocarcinoma, and ovarian serous cystadenocarcinoma^{8,9}.

Potential relevance: Currently, no therapies are approved for PDIA3 aberrations. Overexpression of PDIA3 in hepatocellular carcinoma and colon cancer is associated with advanced disease and poor prognosis¹⁹. Conversely, PDIA3 loss is correlated with aggressive disease and poor survival in gastric cancer and head and neck cancer^{21,22}.

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, 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, AURKB, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBF, 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, ERFF1, 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, PDGFRB, 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,

Genes Assayed (continued)

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

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, RSP02, RSP03, 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, CBF3, 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, ERFF1, 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 p.(L1103*) c.3308delT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" 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"/>
rucaparib	<input type="radio"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>
niraparib	<input type="radio"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input type="radio"/>	<input checked="" type="checkbox"/>
talazoparib + enzalutamide	<input type="radio"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
bevacizumab + niraparib	<input checked="" type="checkbox"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
olaparib + abiraterone acetate	<input checked="" type="checkbox"/>	<input type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
talazoparib	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="radio"/>	<input checked="" type="radio"/> (II)
niraparib, dostarlimab	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (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 p.(L1103*) c.3308delT (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, durvalumab	✕	✕	✕	✕	● (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)

BRCA2 deletion

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

CDKN2A deletion

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

BAP1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✕	✕	✕	✕	● (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

BARD1 deletion

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

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

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

References

1. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985 Sep 6;229(4717):974-6. PMID: 2992089
2. Knighton et al. Structural features that specify tyrosine kinase activity deduced from homology modeling of the epidermal growth factor receptor. *Proc. Natl. Acad. Sci. U.S.A.* 1993 Jun 1;90(11):5001-5. PMID: 8389462
3. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
4. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
5. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011 Jun 29;474(7353):609-15. PMID: 21720365
6. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
7. Cancer et al. Integrated genomic characterization of endometrial carcinoma. *Nature*. 2013 May 2;497(7447):67-73. PMID: 23636398
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
10. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012 Jul 18;487(7407):330-7. PMID: 22810696
11. Mujoo et al. Regulation of ERBB3/HER3 signaling in cancer. *Oncotarget*. 2014 Nov 15;5(21):10222-36. PMID: 25400118
12. Gaborit et al. Emerging anti-cancer antibodies and combination therapies targeting HER3/ERBB3. *Hum Vaccin Immunother.* 2016 Mar 3;12(3):576-92. PMID: 26529100
13. Mishra et al. Genomic alterations of ERBB receptors in cancer: clinical implications. *Oncotarget*. 2017 Dec 26;8(69):114371-114392. PMID: 29371993
14. Jaiswal et al. Oncogenic ERBB3 mutations in human cancers. *Cancer Cell*. 2013 May 13;23(5):603-17. PMID: 23680147
15. Zhang et al. HER3/ErbB3, an emerging cancer therapeutic target. *Acta Biochim. Biophys. Sin. (Shanghai)*. 2016 Jan;48(1):39-48. PMID: 26496898
16. Ross et al. Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in ERBB2 and ERBB3. *Cancer*. 2018 Apr 1;124(7):1358-1373. PMID: 29338072
17. Verlingue et al. Human epidermal receptor family inhibitors in patients with ERBB3 mutated cancers: Entering the back door. *Eur. J. Cancer*. 2018 Mar;92:1-10. PMID: 29413684
18. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
19. Zou et al. P4HB and PDIA3 are associated with tumor progression and therapeutic outcome of diffuse gliomas. *Oncol Rep.* 2018 Feb;39(2):501-510. PMID: 29207176
20. Zhang et al. PDIA3 correlates with clinical malignant features and immune signature in human gliomas. *Aging (Albany NY)*. 2020 Aug 29;12(15):15392-15413. PMID: 32687065
21. Chung et al. Downregulation of ERp57 expression is associated with poor prognosis in early-stage cervical cancer. *Biomarkers*. 2013 Nov;18(7):573-9. PMID: 23957851
22. Leys et al. Expression and prognostic significance of prothymosin-alpha and ERp57 in human gastric cancer. *Surgery*. 2007 Jan;141(1):41-50. PMID: 17188166
23. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. *Clin. Cancer Res.* 2013 May 1;19(9):2301-9. PMID: 23406774
24. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. *Br J Pharmacol.* 2014 Jan;171(1):24-37. PMID: 24117156
25. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev.* 2011 Mar;75(1):50-83. PMID: 21372320
26. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *Int J Mol Sci.* 2020 Feb 7;21(3). PMID: 32046099
27. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. *Breast Cancer Res.* 2002;4(1):9-13. PMID: 11879553

References (continued)

28. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene*. 2002 Dec 16;21(58):8981-93. PMID: 12483514
29. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017 Jun 20;317(23):2402-2416. PMID: 28632866
30. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J. Natl. Cancer Inst.* 2007 Dec 5;99(23):1811-4. PMID: 18042939
31. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br. J. Cancer*. 2007 Jan 15;96(1):11-5. PMID: 17213823
32. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. *JNCI Cancer Spectr.* 2020 Aug;4(4):pkaa029. PMID: 32676552
33. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. *GeneReviews® [Internet]*. PMID: 20301425
34. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin. Proc.* 2010 Dec;85(12):1111-20. PMID: 21123638
35. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc. Natl. Acad. Sci. U.S.A.* 2011 Nov 1;108(44):18032-7. PMID: 22006311
36. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J. Clin. Oncol.* 2012 Jul 20;30(21):2654-63. PMID: 22711857
37. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiol. Biomarkers Prev.* 2004 Dec;13(12):2078-83. PMID: 15598764
38. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003 Oct 24;302(5645):643-6. PMID: 14576434
39. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br. J. Cancer*. 2000 Nov;83(10):1301-8. PMID: 11044354
40. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. *Environ Mol Mutagen.* 2022 Jul;63(6):308-316. PMID: 36054589
41. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. *Br. J. Cancer*. 2018 Nov;119(11):1401-1409. PMID: 30353044
42. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005 Apr 14;434(7035):913-7. PMID: 15829966
43. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005 Apr 14;434(7035):917-21. PMID: 15829967
44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf
48. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
49. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. *J. Pathol.* 2013 Feb;229(3):422-9. PMID: 23165508
50. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst.)*. 2018 Nov;71:172-176. PMID: 30177437
51. <https://www.senhwabio.com/en/news/20220125>
52. Amé et al. The PARP superfamily. *Bioessays*. 2004 Aug;26(8):882-93. PMID: 15273990
53. Morales et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. *Crit Rev Eukaryot Gene Expr.* 2014;24(1):15-28. PMID: 24579667
54. Rulten et al. PARP-3 and APLF function together to accelerate nonhomologous end-joining. *Mol Cell*. 2011 Jan 7;41(1):33-45. PMID: 21211721
55. Beck et al. PARP3 affects the relative contribution of homologous recombination and nonhomologous end-joining pathways. *Nucleic Acids Res.* 2014 May;42(9):5616-32. PMID: 24598253
56. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. *Clin Cancer Res.* 2019 Jul 1;25(13):3759-3771. PMID: 30760478
57. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. *Science*. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823

References (continued)

58. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. *Nat Commun.* 2021 Apr 6;12(1):2047. PMID: 33824349
59. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. *Am. J. Respir. Cell Mol. Biol.* 2018 Aug;59(2):200-214. PMID: 29420051
60. Roussel. The INK4 family of cell cycle inhibitors in cancer. *Oncogene.* 1999 Sep 20;18(38):5311-7. PMID: 10498883
61. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). *Biochem. Biophys. Res. Commun.* 1999 Aug 27;262(2):534-8. PMID: 10462509
62. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet.* 2013;14:257-79. PMID: 23875803
63. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell.* 2006 Oct 20;127(2):265-75. PMID: 17055429
64. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
65. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
66. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
67. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. *Clin Cancer Res.* 2021 Jul 15;27(14):4025-4035. PMID: 34074656
68. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2025]
69. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2025]
70. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
71. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol.* 2020 Jul;30(4):844-856. PMID: 32307792
72. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med.* 2019 Jul 29;17(1):245. PMID: 31358010
73. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. *Anticancer Res.* 2013 Aug;33(8):2997-3004. PMID: 23898052
74. von et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway. *Cancer Res.* 2015 Sep 15;75(18):3823-31. PMID: 26183925
75. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. *Neuro-oncology.* 2012 Jul;14(7):870-81. PMID: 22711607
76. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. *Oncotarget.* 2018 Sep 7;9(70):33247-33248. PMID: 30279955
77. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J. Clin. Oncol.* 2014 Dec 10;32(35):3930-8. PMID: 25267748
78. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. *J. Natl. Cancer Inst.* 2018 Dec 1;110(12):1393-1399. PMID: 29878161
79. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. *Cancer Clin Oncol.* 2013;2(1):51-61. PMID: 23935769
80. Froimchuk et al. Histone H3 lysine 4 methyltransferase KMT2D. *Gene.* 2017 Sep 5;627:337-342. PMID: 28669924
81. Fagan et al. COMPASS Ascending: Emerging clues regarding the roles of MLL3/KMT2C and MLL2/KMT2D proteins in cancer. *Cancer Lett.* 2019 Aug 28;458:56-65. PMID: 31128216
82. Wang et al. Resetting the epigenetic balance of Polycomb and COMPASS function at enhancers for cancer therapy. *Nat Med.* 2018 Jun;24(6):758-769. PMID: 29785026
83. Masclef et al. Roles and mechanisms of BAP1 deubiquitinase in tumor suppression. *Cell Death Differ.* 2021 Feb;28(2):606-625. PMID: 33462414
84. Korenjak et al. E2F-Rb complexes regulating transcription of genes important for differentiation and development. *Curr Opin Genet Dev.* 2005 Oct;15(5):520-7. doi: 10.1016/j.gde.2005.07.001. PMID: 16081278
85. Sachdeva et al. Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma. *J. Clin. Invest.* 2012 Feb;122(2):425-34. PMID: 22293180
86. Dyson. RB1: a prototype tumor suppressor and an enigma. *Genes Dev.* 2016 Jul 1;30(13):1492-502. PMID: 27401552
87. Cobrinik. Pocket proteins and cell cycle control. *Oncogene.* 2005 Apr 18;24(17):2796-809. PMID: 15838516

References (continued)

88. Dommering et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. *Fam. Cancer*. 2012 Jun;11(2):225-33. PMID: 22205104
89. Anasua et al. Acute lymphoblastic leukemia as second primary tumor in a patient with retinoblastoma. *Oman J Ophthalmol*. May-Aug 2016;9(2):116-8. PMID: 27433042
90. Tanaka et al. Frequent allelic loss of the RB, D13S319 and D13S25 locus in myeloid malignancies with deletion/translocation at 13q14 of chromosome 13, but not in lymphoid malignancies. *Leukemia*. 1999 Sep;13(9):1367-73. PMID: 10482987
91. Gombos et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor?. *Ophthalmology*. 2007 Jul;114(7):1378-83. PMID: 17613328
92. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. *Front Cell Neurosci*. 2014;8:349. PMID: 25389387
93. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene*. 2006 Mar 13;25(11):1659-72. PMID: 16550166
94. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. *Br J Cancer*. 2020 Apr;122(9):1277-1287. PMID: 32047295
95. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. *Mol Carcinog*. 2014 Apr;53(4):314-24. PMID: 23143693
96. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. *Oncotarget*. 2017 Jan 10;8(2):3640-3648. PMID: 27690298
97. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. *PLoS One*. 2015;10(5):e0127524. PMID: 26010150
98. Karas et al. *JCO Oncol Pract*. 2021 Dec 3;OP2100624. PMID: 34860573
99. Murali et al. Tumours associated with BAP1 mutations. *Pathology*. 2013 Feb;45(2):116-26. PMID: 23277170
100. Wiesner et al. Germline mutations in BAP1 predispose to melanocytic tumors. *Nat. Genet*. 2011 Aug 28;43(10):1018-21. PMID: 21874003
101. Wadt et al. A cryptic BAP1 splice mutation in a family with uveal and cutaneous melanoma, and paraganglioma. *Pigment Cell Melanoma Res*. 2012 Nov;25(6):815-8. PMID: 22889334
102. Cheung et al. Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma. *Cancer Genet*. 2013 May;206(5):206-10. PMID: 23849051
103. Njauw et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. *PLoS ONE*. 2012;7(4):e35295. PMID: 22545102
104. Pilarski et al. Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases. *Genes Chromosomes Cancer*. 2014 Feb;53(2):177-82. PMID: 24243779
105. Popova et al. Germline BAP1 mutations predispose to renal cell carcinomas. *Am. J. Hum. Genet*. 2013 Jun 6;92(6):974-80. PMID: 23684012
106. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. *Genes (Basel)*. 2018 Dec 13;9(12). PMID: 30551670
107. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. *Semin. Cell Dev. Biol*. 2011 Oct;22(8):898-905. PMID: 21821141
108. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. *Mol. Cell. Biol*. 2013 Jan;33(2):387-95. PMID: 23149936
109. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. *Endocr. Relat. Cancer*. 2016 Jun;23(6):R267-85. PMID: 27226207
110. Lord et al. BRCAness revisited. *Nat. Rev. Cancer*. 2016 Feb;16(2):110-20. PMID: 26775620
111. Date et al. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. *Cancer Res*. 2006 Jun 15;66(12):6018-24. PMID: 16778173
112. Pelttari et al. RAD51B in Familial Breast Cancer. *PLoS ONE*. 2016;11(5):e0153788. PMID: 27149063
113. Morris et al. BRCA1 : BARD1 induces the formation of conjugated ubiquitin structures, dependent on K6 of ubiquitin, in cells during DNA replication and repair. *Hum. Mol. Genet*. 2004 Apr 15;13(8):807-17. PMID: 14976165
114. Baer et al. The BRCA1/BARD1 heterodimer, a tumor suppressor complex with ubiquitin E3 ligase activity. *Curr. Opin. Genet. Dev*. 2002 Feb;12(1):86-91. PMID: 11790560
115. Zhao et al. BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing. *Nature*. 2017 Oct 19;550(7676):360-365. PMID: 28976962

References (continued)

116. Cimmino et al. Dualistic Role of BARD1 in Cancer. *Genes (Basel)*. 2017 Dec 8;8(12). PMID: 29292755
117. De et al. BRCAness: a deeper insight into basal-like breast tumors. *Ann. Oncol.* 2013 Nov;24 Suppl 8:viii13-viii21. PMID: 24131964
118. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. *Cold Spring Harb Perspect Biol.* 2015 Apr 1;7(4):a016600. PMID: 25833843
119. Irminger-Finger et al. Identification of BARD1 as mediator between proapoptotic stress and p53-dependent apoptosis. *Mol. Cell.* 2001 Dec;8(6):1255-66. PMID: 11779501
120. Thai et al. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers. *Hum. Mol. Genet.* 1998 Feb;7(2):195-202. PMID: 9425226