

Patient Name: 이영희
Gender: F
Sample ID: N26-61

Primary Tumor Site: ovary
Collection Date: 2026.01.21

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
BRCA1	BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA	NTRK2	None detected
BRCA2	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	6.63 Mut/Mb measured
Genomic Instability	GIM 36 (High)

HRD Status: **HR Deficient (HRD+)**

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA BRCA1, DNA repair associated Allele Frequency: 78.07% Locus: chr17:41243479 Transcript: NM_007294.4	bevacizumab + olaparib ^{1, 2 / II+} niraparib ^{1 / II+} olaparib ^{1, 2 / II+} rucaparib ^{1 / II+} bevacizumab + niraparib ^{II+}	abiraterone + niraparib ^{1, 2 / II+} olaparib ^{1, 2 / II+} rucaparib ^{1 / II+} talazoparib + hormone therapy ^{1 / II+} talazoparib ^{II+} olaparib + hormone therapy	28
IA	Genomic Instability GIM 36 (High)	bevacizumab + olaparib ^{1, 2 / II+} niraparib ^{1 / II+}	None*	15

* 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>ESR1</i> p.(H488Y) c.1462C>T estrogen receptor 1 Allele Frequency: 28.45% Locus: chr6:152415612 Transcript: NM_001122740.2	None*	elacestrant ^{1, 2 / I, II+}	0
IIC	<i>CCNE1</i> amplification cyclin E1 Locus: chr19:30303647	None*	None*	11
IIC	<i>ATM</i> deletion ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	3

* 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.

Alerts informed by public data sources: Contraindicated, Resistance, Breakthrough, Fast Track

BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA pidnarulex¹

Genomic Instability pidnarulex¹

CCNE1 amplification camonsertib + lunresertib¹

Public data sources included in alerts: FDA¹, NCCN, EMA², ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

MRE11 deletion, *MSH6* p.(K537Ifs*33) c.1610_1613delAGTA, Microsatellite stable, *PPP2R2A* deletion, *TP53* p.(C238R) c.712T>C, *MECOM* amplification, *FAT1* deletion, *FAT1* p.(T2369Rfs*2) c.7105delA, *HLA-A* deletion, *HLA-B* deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA1	p.(N1355Kfs*10)	c.4065_4068delTCAA	.	chr17:41243479	78.07%	NM_007294.4	frameshift Deletion
ESR1	p.(H488Y)	c.1462C>T	.	chr6:152415612	28.45%	NM_001122740.2	missense
MSH6	p.(K537Ifs*33)	c.1610_1613delAGTA	.	chr2:48026728	10.89%	NM_000179.3	frameshift Deletion
TP53	p.(C238R)	c.712T>C	COSM44321	chr17:7577569	67.15%	NM_000546.6	missense
FAT1	p.(T2369Rfs*2)	c.7105delA	.	chr4:187540634	39.42%	NM_005245.4	frameshift Deletion
PIK3CD	p.(P8L)	c.23C>T	.	chr1:9770536	56.83%	NM_005026.5	missense
ARID1A	p.(P223H)	c.668C>A	.	chr1:27023562	41.39%	NM_006015.6	missense
MECOM	p.(S1235P)	c.3703T>C	.	chr3:168802714	6.57%	NM_004991.4	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
DAXX	p.(S130C)	c.388A>T	.	chr6:33289200	10.83%	NM_001141970.2	missense
PGM3	p.(D486N)	c.1456G>A	.	chr6:83880191	5.25%	NM_001199917.2	missense
NF1	p.(A3V)	c.8C>T	.	chr17:29422335	18.35%	NM_001042492.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CCNE1	chr19:30303647	10.23	3.88
ATM	chr11:108098341	1.04	0.66
MRE11	chr11:94153270	1	0.65
PPP2R2A	chr8:26149298	1	0.65
MECOM	chr3:168802636	6	2.4
FAT1	chr4:187509708	1.04	0.67
HLA-A	chr6:29910229	0.93	0.63
HLA-B	chr6:31322252	1.09	0.68
FGFR3	chr4:1801456	0.77	0.57
YAP1	chr11:101981594	0.9	0.62

Biomarker Descriptions

BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA, Genomic Instability

BRCA1, DNA repair associated

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA¹⁵⁵. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs^{155,156}. HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2^{157,158,159,160}. A consequence of HRD due to the failure to repair DSBs is genomic instability^{161,162}. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division^{163,164,165,166,167,168}. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)^{164,169,170}. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability¹⁶³. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible^{171,172,173}. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars^{174,175}. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)^{155,176}. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type¹⁵⁵. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)^{155,161,177,178}.

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation¹⁷⁹. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon

Biomarker Descriptions (continued)

adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma¹⁷⁹. 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^{180,181,182,183,184,185,186,187}. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme^{6,29}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme^{6,29}.

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies^{188,189,190}. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality^{155,191,192,193}. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib⁸⁴ was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer⁸⁴. In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L^{84,158,194}. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers⁸⁴. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib¹⁹⁵ (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib¹⁹⁶ (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib²³ (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability¹⁹⁷. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁷, for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex⁷ causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported¹⁹⁸. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality¹⁹⁹. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations^{199,200,201,202}.

ESR1 p.(H488Y) c.1462C>T

estrogen receptor 1

Background: The ESR1 gene encodes estrogen receptor 1 (ER α), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses²⁷. A related gene, ESR2, encodes the cognate ER β protein²⁷. ER α is a ligand-activated transcription factor regulated by the hormone estrogen^{110,111}. Estrogen binding to ER α results in receptor dimerization, nuclear translocation, and target gene transcription. In addition, estrogen binding to the ER α results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival¹¹². In neuroblastoma, MYCN-driven miR-17~92 cluster expression suppresses ESR1 to block differentiation, whereas estrogen-activated ESR1 cooperates with ETS-1 to promote MMP1/9 expression and tumor proliferation, migration, and invasion^{113,114}.

Alterations and prevalence: Approximately 70% of breast cancers express ER α and ER β positivity. Mutations in the ER α ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance^{115,116,117,118}. Somatic mutations in ESR1 are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of stomach adenocarcinoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, and esophageal adenocarcinoma^{6,29}. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease^{119,120,121,122,123}. Amplification of ESR1 is observed in 5% of uterine carcinosarcoma, 4% of sarcoma, 3% of uterine corpus endometrial carcinoma, and 2% of ovarian serous cystadenocarcinoma, adrenocortical carcinoma, and breast invasive carcinoma^{6,29}. Alterations in ESR1 are also observed in pediatric cancers¹²⁴. Somatic mutations in ESR1 are observed in 5% of T-lymphoblastic leukemia/lymphoma (2 in 41 cases), 1% of glioma (3 in 297 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), leukemia (1 in 311 cases), and peripheral nervous system cancers (1 in 1158 cases)¹²⁴. Amplification of ESR1 is observed in less than 1% of leukemia (1 in 250 cases)¹²⁴.

Biomarker Descriptions (continued)

Potential relevance: The FDA has approved elacestrant¹²⁵ (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer¹²⁶. The FDA also approved imlunestrant¹²⁷ (2025) for the treatment of adults with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. The FDA has also granted fast track designations to the following therapies: AC-699¹²⁸ (2024) and lasofoxifene¹²⁹ (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizestrant¹³⁰ for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel¹³¹ (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen¹³² (1977), fulvestrant¹³³ (2002), letrozole¹³⁴ (1995), and exemestane¹³⁵ (2005) are FDA approved for ER-positive metastatic breast cancers^{136,137}. Although ER α and ER β positivity predicts response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance^{138,139,140}.

CCNE1 amplification

cyclin E1

Background: The CCNE1 gene encodes the cyclin E1 protein, a member of the highly conserved E-cyclin family which also includes CCNE2⁴⁵. CCNE1 facilitates progression from G1 to the S phase of the cell cycle by binding to cyclin dependent kinase 2 (CDK2) which results in phosphorylation and inactivation of the retinoblastoma (RB1) protein⁴⁵. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition resulting in cell cycle progression, a common event observed in tumorigenesis^{46,47,48}. Additionally, CCNE1 is often deregulated in a variety of cancer types supporting an oncogenic role for CCNE1^{45,49}.

Alterations and prevalence: CCNE1 amplification is observed in about 40% of uterine carcinosarcoma, 20% of ovarian cancer, 11% of stomach cancer, 7-8% sarcoma, uterine, and esophageal cancers, 5-6%, adrenocortical carcinoma, squamous lung, and bladder cancers⁶. Additionally, CCNE1 overexpression has been observed in many different tumor types including in 70-80% of Hodgkin's lymphoma.^{45,49,50}

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib⁵¹, in combination with camonsertib for the treatment of adult patients with CCNE1 amplified endometrial cancer and platinum resistant ovarian cancer. CCNE1 amplification and overexpression has been associated with poor prognosis in certain cancer types including lung and breast cancers^{52,53,54}.

ATM deletion

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)⁷⁹. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair⁸⁰. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB^{80,81}. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins⁸². ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss^{13,14}. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability⁸³.

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer^{6,29}.

Potential relevance: The PARP inhibitor, olaparib⁸⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib²³ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors^{13,85,86}. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib⁸⁷. However, gene-level analyses from the phase III PROfound trial indicate that ATM-mutated tumors do not experience meaningful radiographic progression-free survival (rPFS) or overall survival (OS) benefit from olaparib, and that the observed survival advantage in the broader HRR-altered population is largely driven by BRCA1/2 alterations rather than ATM^{88,89}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

MRE11 deletion

MRE11 homolog, double strand break repair nuclease

Background: The MRE11 gene encodes the meiotic recombination 11 protein, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) complex, which is necessary for the maintenance of genomic stability⁹. The MRN complex is involved in the repair of double-stranded breaks (DSB) through two mechanisms namely homologous recombination repair (HRR) and non-homologous end joining (NHEJ)^{10,11,12}. Dimerization of MRE11 is required for DNA binding of the MRN complex, and it acts as a 3'-5' exonuclease and ssDNA endonuclease upon binding DNA⁹. MRE11 is a tumor suppressor gene and loss of function mutations are implicated in the BRCAness phenotype, characterized by a defect in the HRR pathway mimicking BRCA1 or BRCA2 loss^{13,14}. Germline mutations in MRE11 have been identified as candidate susceptibility aberrations in colorectal cancer and a hallmark of ataxia-telangiectasia-like disorder (ALTD), a heritable disease resulting in progressive cerebellar degeneration and cancer predisposition^{15,16,17,18}.

Alterations and prevalence: Somatic mutations in MRE11 are observed in 6-7% of uterine cancer as well as 2-3% of lung adenocarcinoma and melanoma⁶. Mutations in the T11 polypyrimidine tract of MRE11 intron 5 are associated with aberrant splicing and reduced MRE11 protein expression. The presence of MRE11 splice variants is frequently observed in mismatch repair deficient (dMMR)/microsatellite instability (MSI-H) colorectal and endometrial cancers^{19,20,21,22}.

Potential relevance: The PARP inhibitor, talazoparib²³ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors^{13,14}. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro^{24,25,26}.

MSH6 p.(K537ifs*33) c.1610_1613delAGTA

mutS homolog 6

Background: The MSH6 gene encodes the mutS homolog 6 protein²⁷. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSa complex⁶¹. The MutSa complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides⁶¹. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication⁶¹. Mutations in MSH2 result in the degradation of MSH6⁶². MSH6, along with MLH1, MSH2, and PMS2, form the core components of the MMR pathway⁶¹. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication⁶¹. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes⁶³. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{64,65,66}. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes^{64,67}. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{65,67,68,69}. Specifically, MSH6 mutations are associated with an increased risk of ovarian and pancreatic cancer^{70,71,72,73}.

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma^{6,29}. Alterations in MSH6 are observed in pediatric cancers^{6,29}. Somatic mutations are observed in 9% of hepatobiliary cancer, 2% of T-lymphoblastic leukemia/lymphoma, 1% of B-lymphoblastic leukemia/lymphoma, and less than 1% of glioma (2 in 297 cases) and bone cancer (2 in 327 cases)^{6,29}.

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies⁷⁴. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment^{75,76}. MSH6 mutations are consistent with high grade in pediatric diffuse gliomas^{77,78}.

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 genome¹⁴¹. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{65,67}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁶⁶. 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 D17S250¹⁴². 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)¹⁴². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{68,143,144,145,146}. 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 genes⁶⁷.

Biomarker Descriptions (continued)

LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{65,67,68,69}.

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^{65,67,147,148}. 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^{147,148}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁷⁴ (2014) and nivolumab⁷⁵ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁷⁴ 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 indication⁷⁴. Dostarlimab¹⁴⁹ (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^{144,150}. 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^{144,151,152}. 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 patients¹⁵². 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^{153,154}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{153,154}.

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)^{1,2}. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway³. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway¹.

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^{1,2,4,5}. 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 lymphoma⁶.

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁷, 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 veliparib¹. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit⁸.

TP53 p.(C238R) c.712T>C

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 repair²⁷. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis⁹⁰. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential⁹¹. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{92,93}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{6,29,94,95,96,97}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282^{6,29}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{98,99,100,101}. Alterations in TP53 are also observed in pediatric cancers^{6,29}. 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,

Biomarker Descriptions (continued)

2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)^{6,29}. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)^{6,29}.

Potential relevance: The small molecule p53 reactivator, PC14586¹⁰² (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{103,104}. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma¹⁰⁵. 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)^{37,38,41,106,107}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant¹⁰⁸. 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 system¹⁰⁹.

MECOM amplification

MDS1 and EVI1 complex locus

Background: The MECOM gene encodes the MDS1 and EVI1 complex locus (MECOM), a zinc-finger transcriptional factor that regulates hematopoietic cell differentiation³⁰. The MECOM locus encodes multiple alternative splice variants that result in MDS1-EVI1, MDS1, and EVI1 protein isoforms³¹. The EVI1 isoform is the most abundant and oncogenic form of MECOM that is expressed in various cancers including acute myeloid leukemia (AML)^{31,32}. MECOM is a frequent target of chromosomal translocation which can lead to MECOM overexpression and leukemogenesis³³.

Alterations and prevalence: Somatic mutations MECOM are observed in up to 22% of malignant melanoma; 75% of these mutations are missense and the remaining 25% are truncating mutations^{6,29,34}. MECOM amplifications are observed in up to 35% of lung squamous cell carcinoma, 30% of ovarian serous cystadenocarcinoma, and 20% of esophageal adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma^{6,29}. MECOM rearrangements occur with various partner genes including ETV6, RUNX1, and H2AFY³⁵. The t(3;21)(q26;q22) translocation that results in the MECOM::RUNX1 fusion is most commonly observed in chronic myeloid leukemia (CML) in blast crisis. The t(3;3)(q21.3;q26.2)/inv(3)(q21.3;q26.3) translocation, also referred to as inv(3)/t(3;3), results in a GATA2::MECOM fusion and is observed in AML, primary myelofibrosis (PMF), and myelodysplastic syndrome (MDS)^{36,37,38}. The inv(3)/t(3;3) translocation repositions the distal GATA enhancer element and activates MECOM expression while simultaneously causing GATA2 haploinsufficiency³⁹.

Potential relevance: AML with MECOM rearrangement is considered a distinct molecular subtype of AML as defined by the World Health Organization (WHO)⁴⁰. MECOM rearrangements, including GATA2::MECOM fusions, are associated with poor/adverse risk in AML^{36,41}. Inv(3) is associated with poor cytogenetic risk in MDS as defined by the revised international prognostic scoring system (IPSS-R) scoring system³⁸. In PMF, inv(3) is considered an unfavorable karyotype associated with intermediate risk as defined by the dynamic international prognostic scoring system (DIPSS)-Plus scoring system³⁷. MECOM overexpression is observed in 10% of de novo AML associated with poor prognosis, and is commonly found in MLL-rearranged cases^{42,43}. Amplification of MECOM is associated with favorable prognosis in ovarian cancer⁴⁴.

FAT1 deletion, FAT1 p.(T2369Rfs*2) c.7105delA

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats^{27,28}. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions²⁸. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion²⁸. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/ β -catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition²⁸. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1²⁸.

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot^{6,29}. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma^{6,29}. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma^{6,29}.

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

Biomarker Descriptions (continued)

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A²⁷. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells⁵⁵. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁵⁶. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{57,58,59}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁶⁰.

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma^{6,29}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{6,29}.

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B²⁷. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells⁵⁵. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁵⁶. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{57,58,59}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B⁶⁰.

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma^{6,29}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{6,29}.

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

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer

Variant class: HR Deficient

Supporting Statement:

The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

<https://www.senhwabio.com/en/news/20220125>

Genomic Instability

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer

Variant class: HR Deficient

Supporting Statement:

The FDA has granted Fast Track designation to the small molecule inhibitor, pidnarulex, for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

<https://www.senhwabio.com/en/news/20220125>

CCNE1 amplification

camonsertib + lunresertib

Cancer type: Endometrial Carcinoma, Ovarian Cancer

Variant class: CCNE1 amplification

Supporting Statement:

- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated platinum resistant ovarian cancer.
- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated endometrial cancer.

Reference:

<https://ir.reparerx.com/news-releases/news-release-details/repere-therapeutics-announces-fast-track-designation-granted-fda>

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, PDXNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABC1, 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, 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, ERF1, 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, PDXNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, 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, CBF, 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, ERF1, 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

BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	●	●	●	●	● (IV)
rucaparib	●	●	✕	●	✕
bevacizumab + olaparib	●	●	●	●	✕
niraparib	●	●	✕	●	● (II)
abiraterone + niraparib	○	○	○	✕	✕
talazoparib + enzalutamide	○	○	✕	✕	✕
bevacizumab + niraparib	✕	●	✕	✕	✕
olaparib + abiraterone acetate	✕	○	✕	✕	✕
talazoparib	✕	✕	✕	○	● (II)
fluzoparib, bevacizumab	✕	✕	✕	✕	● (III)
IMNN-001, chemotherapy, olaparib, niraparib	✕	✕	✕	✕	● (III)
olaparib, bevacizumab	✕	✕	✕	✕	● (III)
fluzoparib	✕	✕	✕	✕	● (II)
niraparib, dostarlimab	✕	✕	✕	✕	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✕	✕	✕	✕	● (II)
ZEN-3694, talazoparib	✕	✕	✕	✕	● (II)
AMXI-5001	✕	✕	✕	✕	● (I/II)
AZD-9574	✕	✕	✕	✕	● (I/II)
IDB-476	✕	✕	✕	✕	● (I/II)
sacituzumab govitecan, berzosertib	✕	✕	✕	✕	● (I/II)
ATX-559	✕	✕	✕	✕	● (I)
cirtuvivint, olaparib	✕	✕	✕	✕	● (I)
HS-10502	✕	✕	✕	✕	● (I)
MOMA-313, olaparib	✕	✕	✕	✕	● (I)
niraparib, chemotherapy	✕	✕	✕	✕	● (I)
novobiocin	✕	✕	✕	✕	● (I)
olaparib, chemotherapy	✕	✕	✕	✕	● (I)
pidnarulex	✕	✕	✕	✕	● (I)

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

Relevant Therapy Summary (continued)

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

BRCA1 p.(N1355Kfs*10) c.4065_4068delTCAA (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
SIM-0501	✕	✕	✕	✕	● (I)
SNV-1521, trastuzumab deruxtecan	✕	✕	✕	✕	● (I)
XL-309, olaparib	✕	✕	✕	✕	● (I)

Genomic Instability

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	●	●	✕	●	● (II)
bevacizumab + olaparib	●	✕	●	●	✕
olaparib	✕	✕	✕	✕	● (IV)
fluzoparib, bevacizumab	✕	✕	✕	✕	● (III)
IMNN-001, chemotherapy, olaparib, niraparib	✕	✕	✕	✕	● (III)
atezolizumab + talazoparib	✕	✕	✕	✕	● (II)
fluzoparib	✕	✕	✕	✕	● (II)
AMXI-5001	✕	✕	✕	✕	● (I/II)
sacituzumab govitecan, berzosertib	✕	✕	✕	✕	● (I/II)
cirtuvivint, olaparib	✕	✕	✕	✕	● (I)
HS-10502	✕	✕	✕	✕	● (I)
MOMA-313, olaparib	✕	✕	✕	✕	● (I)
pidnarulex	✕	✕	✕	✕	● (I)
SIM-0501	✕	✕	✕	✕	● (I)
XL-309, olaparib	✕	✕	✕	✕	● (I)

ESR1 p.(H488Y) c.1462C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
elacestrant	○	○	○	✕	✕

CCNE1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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 ① In this cancer type and other cancer types ✕ No evidence

CCNE1 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
APR-1051	✕	✕	✕	✕	● (I/II)
ARTS-021, chemotherapy	✕	✕	✕	✕	● (I/II)
ECI-830, hormone therapy, ribociclib	✕	✕	✕	✕	● (I/II)
INX-315, hormone therapy	✕	✕	✕	✕	● (I/II)
WJB-001	✕	✕	✕	✕	● (I/II)
ETX-197, hormone therapy	✕	✕	✕	✕	● (I)
lunresertib, camonsertib, Debio-0123	✕	✕	✕	✕	● (I)
nedisertib, tuvusertib	✕	✕	✕	✕	● (I)
NKT-3964	✕	✕	✕	✕	● (I)
NKT-5097	✕	✕	✕	✕	● (I)

ATM deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✕	✕	✕	✕	● (II)
senaparib, IMP-9064	✕	✕	✕	✕	● (I/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
ATM	CNV, CN:1.04

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 (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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