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Patient Name: 황상호
Gender: M
Sample ID: N25-18

Primary Tumor Site: unknown
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Sample Cancer Type: Unknown Primary Origin

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*RAD50 deletion* RAD50 double strand break repair protein Locus: chr5:131892978	None*	None*	3
IIC	*TP53 p.(R273L) c.818G>T* tumor protein p53 Allele Frequency: 61.60% Locus: chr17:7577120 Transcript: NM_000546.6	None*	None*	3
IIC	*TMPRSS2::ERG fusion* transmembrane protease, serine 2 - ERG, ETS transcription factor Locus: chr21:42870046 - chr21:39817544	None*	None*	2
IIC	*PIK3R1 c.502+1G>T* phosphoinositide-3-kinase regulatory subunit 1 Allele Frequency: 20.37% Locus: chr5:67569842 Transcript: NM_181523.3	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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

*APC p.(L93Hfs*46) c.277_278insA, FAT1 p.(Q16*) c.46C>T, Microsatellite stable, NOTCH4 p.(L8Afs*52) c.21_23delGCTinsC, DICER1 p.(Q941Afs*8) c.2821_2822delCA, NQO1 p.(P187S) c.559C>T, PPM1D p.(S85*) c.254C>A, DSC3 p.(Y319*) c.957C>A, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FAT1	p.(Q16*)	c.46C>T	.	chr4:187630936	11.35%	NM_005245.4	nonsense
PIK3R1	p.(?)	c.502+1G>T	.	chr5:67569842	20.37%	NM_181523.3	unknown
APC	p.(L93Hfs*46)	c.277_278insA	.	chr5:112102942	19.43%	NM_000038.6	frameshift Insertion
NOTCH4	p.(L8Afs*52)	c.21_23delGCTinsC	.	chr6:32191683	100.00%	NM_004557.4	frameshift Block Substitution
DICER1	p.(Q941Afs*8)	c.2821_2822delCA	.	chr14:95572542	25.62%	NM_030621.4	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	44.72%	NM_000903.3	missense
TP53	p.(R273L)	c.818G>T	COSM10779	chr17:7577120	61.60%	NM_000546.6	missense
PPM1D	p.(S85*)	c.254C>A	.	chr17:58678029	11.80%	NM_003620.4	nonsense
DSC3	p.(Y319*)	c.957C>A	.	chr18:28598752	3.14%	NM_001941.5	nonsense
BRINP3	p.(E322K)	c.964G>A	.	chr1:190130018	28.97%	NM_199051.3	missense
PARP1	p.(Q40H)	c.120G>T	.	chr1:226595511	27.61%	NM_001618.4	missense
OR2L8	p.(H158Q)	c.474C>A	.	chr1:248112633	25.29%	NM_001001963.1	missense
MYCN	p.(L440Ifs*16)	c.1318_1319delCTinsA	.	chr2:16086142	9.87%	NM_005378.6	frameshift Block Substitution
RAF1	p.(I551M)	c.1653C>G	.	chr3:12626636	22.01%	NM_002880.4	missense
PROS1	p.(R69W)	c.205A>T	.	chr3:93646123	35.14%	NM_000313.4	missense
HCN1	p.(S811C)	c.2432C>G	.	chr5:45262264	40.00%	NM_021072.4	missense
NMUR2	p.(Q381K)	c.1141C>A	.	chr5:151771859	14.35%	NM_020167.5	missense
TNFAIP3	p.(E193K)	c.577G>A	.	chr6:138196915	18.10%	NM_001270507.2	missense
CSMD3	p.(P3680L)	c.11039C>T	.	chr8:113237085	21.65%	NM_198123.2	missense
CSMD3	p.(T2639K)	c.7916C>A	.	chr8:113318391	32.54%	NM_198123.2	missense
PTCH1	p.(E534Q)	c.1600G>C	.	chr9:98239043	14.66%	NM_000264.5	missense
SYT10	p.(T493S)	c.1477A>T	.	chr12:33532790	35.81%	NM_198992.4	missense
TMEM132D	p.(Q363H)	c.1089G>T	.	chr12:130015630	47.42%	NM_133448.3	missense
BRCA1	p.(E649Q)	c.1945G>C	.	chr17:41245603	13.85%	NM_007294.4	missense
SPOP	p.(E304K)	c.910G>A	.	chr17:47679297	10.18%	NM_001007228.2	missense
KEAP1	p.(G332C)	c.994G>T	.	chr19:10602584	61.24%	NM_203500.2	missense
KMT2B	p.(M1354I)	c.4062G>T	.	chr19:36218115	3.70%	NM_014727.3	missense
KIR3DL1	p.(G379W)	c.1135G>T	.	chr19:55341412	78.20%	NM_001322168.1	missense
EP300	p.(D1384N)	c.4150G>A	.	chr22:41564849	30.90%	NM_001429.4	missense
COL4A6	p.(G1147C)	c.3439G>T	.	chrX:107413893	62.17%	NM_033641.4	missense
STAG2	p.(L203F)	c.607C>T	.	chrX:123179158	54.92%	NM_001042749.2	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NSDHL	p.(G44R)	c.130_132delGGTinsCGG	.	chrX:152018830	65.21%	NM_015922.3	missense

Gene Fusions

Genes	Variant ID	Locus
TMPRSS2::ERG	TMPRSS2-ERG.T2E4.COSF28	chr21:42870046 - chr21:39817544
TMPRSS2::ERG	TMPRSS2-ERG.T1E4.COSF25	chr21:42880008 - chr21:39817544

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
RAD50	chr5:131892978	0.87	0.69
PXDNL	chr8:52233342	0.65	0.63
RB1	chr13:48877953	4.37	1.64
RNASEH2B	chr13:51484145	5.56	1.96

Biomarker Descriptions

PIK3R1 c.502+1G>T

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[2]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[2]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[2]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[3,4]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[3,4,5,6]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[7]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[2].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[8]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[8].

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

TP53 p.(R273L) c.818G>T

tumor protein p53

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[9]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[10,11].

Biomarker Descriptions (continued)

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%)[8,12,13,14,15,16]. 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[8,12]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[17,18,19,20].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[21]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[22] and breakthrough designation[23] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[24,25]. 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)[26,27,28,29,30,31]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[32]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[33].

DSC3 p.(Y319*) c.957C>A

desmocollin 3

Background: The DSC3 gene encodes desmocollin 3, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC1 and DSC2[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[34]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[35]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC3 in tumorigenesis[34,36,37,38].

Alterations and prevalence: Somatic mutations in DSC3 are observed in 19% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, and 3% of bladder urothelial carcinoma[8,12]. Biallelic deletion of DSC3 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[8,12].

Potential relevance: Currently, no therapies are approved for DSC3 aberrations.

NOTCH4 p.(L8Afs*52) c.21_23delGCTinsC

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[39]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[40,41]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[42,43,44,45].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[8].

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

FAT1 p.(Q16*) c.46C>T

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[1,46]. 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 functions[46]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[46]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-

Biomarker Descriptions (continued)

catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[46]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[46].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[8,12]. 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[8,12]. 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[8,12].

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

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[47]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[48,49]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[50]. 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 D17S250[51]. 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)[51]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[52,53,54,55,56]. 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 genes[49]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[48,49,53,57].

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[48,49,58,59]. 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[58,59].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[60] (2014) and nivolumab[61] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[60] 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 indication[60]. Dostarlimab[62] (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[54,63]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[64] (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[54,65,66]. 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 patients[66]. 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[67,68]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[67,68].

APC p.(L93Hfs*46) c.277_278insA

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[69]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[70,71]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[69,72]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[73].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[8,12,74]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[75,76].

Biomarker Descriptions (continued)

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

TMPRSS2::ERG fusion

ERG, ETS transcription factor, transmembrane protease, serine 2

Background: The ERG gene encodes the erythroblast transformation-specific (ETS) transcription factor ERG, which belongs to the ETS family of transcriptional regulators that are involved in embryonic development, cell proliferation, differentiation, angiogenesis, inflammation, and apoptosis[1].

Alterations and prevalence: ERG gene fusions are the most common molecular subtype of prostate cancer and are present in over 30% of cases[12,77,78]. ERG fusions to the androgen-regulated TMPRSS2 promoter occur in over 90% of prostate cancer with ERG rearrangements. The fusion of ERG to EWSR1 is a common abnormality in Ewing sarcoma and is observed in 5% of cases[79].

Potential relevance: Currently, no therapies are approved for ERG aberrations. The t(21;22)(q22;q12) and t(16;21)(p11;q22) translocations resulting in EWSR1::ERG and FUS::ERG fusions, respectively, are useful as ancillary diagnostic markers in Ewing sarcoma/peripheral neuroectodermal tumors[80,81]. TMPRSS2::ERG fusions overexpress ERG and are associated with poor prognosis as well as tumor aggressiveness in prostate cancer[77,82]. Because TMPRSS2 is involved in androgen regulation, TMPRSS2::ERG expression in prostate cancer tends to be positively correlated with androgen receptor (AR) overexpression[83]. Therapies for treating advanced prostate cancer often involve androgen deprivation, which in turn leads to a reduction of TMPRSS2::ERG expression. However, acquired resistance to these therapies restores androgen signaling and TMPRSS2::ERG expression[84].

DICER1 p.(Q941Afs*8) c.2821_2822delCA

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[85]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[85,86]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[85]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[85,86]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[86,87,88,89]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[90].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, and 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[8,12]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% kidney chromophobe[8,12].

Potential relevance: Currently, no therapies are approved for DICER1 aberrations.

PPM1D p.(S85*) c.254C>A

protein phosphatase, Mg2+/Mn2+ dependent 1D

Background: The PPM1D gene encodes the protein phosphatase, Mg2+/Mn2+ dependent 1D, which is a member of the PP2C family of Ser/Thr protein phosphatases[1]. Upon cellular stress, p53-induced PPM1D dephosphorylates and downregulates target CHK1 and P53, which are involved in DNA repair pathways and cell cycle checkpoints[91,92]. PPM1D function leads to the inhibition of apoptosis, cancer cell proliferation, migration, and invasion[91,92]. Mutations of PPM1D are associated with a predisposition to breast and ovarian cancer[91].

Alterations and prevalence: Somatic mutations in PPM1D are predominantly truncating or missense and are observed in 6% of uterine corpus endometrial carcinoma, 2% of stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[8,12]. Amplification of PPM1D is observed in 8% of breast invasive carcinoma, 5% of mesothelioma, 4% of liver hepatocellular carcinoma, and 3% of bladder urothelial carcinoma and stomach adenocarcinoma[8,12]. Biallelic deletion of PPM1D is observed in 2% of ovarian serous cystadenocarcinoma and less than 1% of cervical squamous cell carcinoma, lung squamous cell carcinoma, glioblastoma multiforme, brain lower grade glioma, uterine corpus endometrial carcinoma, and colorectal adenocarcinoma[8,12].

Potential relevance: Currently, no therapies are approved for PPM1D aberrations.

Biomarker Descriptions (continued)

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases[93,94]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[94,95]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[95,96]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[95,96]. RAD50 contains long coiled-coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response[95,97]. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[98,99]. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer[100].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[8,12]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[101].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[102]. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression[102]. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype[103].

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, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D,

Genes Assayed (continued)

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

RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

RAD50 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
niraparib + hormone therapy	✖	✖	✖	✖	○ (II)
olaparib, pembrolizumab	✖	✖	✖	✖	○ (II)

TP53 p.(R273L) c.818G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
hormone therapy, chemotherapy	✖	✖	✖	✖	○ (III)
hormone therapy, hormone therapy + chemotherapy	✖	✖	✖	✖	○ (II)
olaparib, pembrolizumab	✖	✖	✖	✖	○ (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

TMPRSS2::ERG fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
hormone therapy, chemotherapy	✖	✖	✖	✖	○ (III)
hormone therapy	✖	✖	✖	✖	○ (II)

PIK3R1 c.502+1G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
chemotherapy, capivasertib	✖	✖	✖	✖	○ (III)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***47.31%***
BRCA1	***SNV, E649Q, AF:0.14***
BRCA2	***LOH, 13q13.1(32890491-32972932)x2***
ATM	***LOH, 11q22.3(108098341-108236285)x3***
CHEK1	***LOH, 11q24.2(125496639-125525271)x3***

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 Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.0.2 data version 2025.04(004)). 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 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. 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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