

Patient Name: 이소안  
Gender: F  
Sample ID: N25-206

Primary Tumor Site: ovary  
Collection Date: 2025.08.22

## Sample Cancer Type: Endometrial Carcinoma

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

## Relevant Endometrial Carcinoma Findings

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

Genomic Alteration	Finding
Microsatellite Status	<b>Microsatellite stable</b>
Tumor Mutational Burden	<b>6.64 Mut/Mb measured</b>

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<b>PIK3CA p.(Q546K) c.1636C&gt;A</b> phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 33.93% Locus: chr3:178936094 Transcript: NM_006218.4	None*	<b>inavolisib + palbociclib + hormone therapy<sup>1 / I</sup></b> <b>capivasertib + hormone therapy<sup>1, 2 / II</sup></b> +	5
IIC	<b>CTNNB1 p.(D32Y) c.94G&gt;T</b> catenin beta 1 Allele Frequency: 33.10% Locus: chr3:41266097 Transcript: NM_001904.4	None*	None*	1

\* Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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**  
*Microsatellite stable, PARP4 p.(Q535Tfs\*10) c.1602\_1602delGinsAA, HLA-B deletion, NQ01 p.(P187S) c.559C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(Q546K)	c.1636C>A	COSM766	chr3:178936094	33.93%	NM_006218.4	missense
CTNNB1	p.(D32Y)	c.94G>T	COSM5661	chr3:41266097	33.10%	NM_001904.4	missense
PARP4	p.(Q535Tfs*10)	c.1602_1602delGinsAA	.	chr13:25052261	1.82%	NM_006437.4	frameshift Block Substitution
NQ01	p.(P187S)	c.559C>T	.	chr16:69745145	49.47%	NM_000903.3	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGC GGCCGCAGCGGC	.	chr5:79950707	53.20%	NM_002439.5	nonframeshift Deletion
NBN	p.(P306T)	c.916C>A	.	chr8:90976716	52.73%	NM_002485.5	missense
PTEN	p.(D52del)	c.155_157delATG	.	chr10:89653851	73.88%	NM_000314.8	nonframeshift Deletion
CLEC2A	p.(T133I)	c.398C>T	.	chr12:10069311	44.84%	NM_001130711.2	missense
PARP4	p.(?)	c.3285_3285+5delinsA GT	.	chr13:25021149	100.00%	NM_006437.4	unknown
CBFB	p.(I114V)	c.340A>G	.	chr16:67100642	49.00%	NM_022845.3	missense

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0.2	0.61

Biomarker Descriptions

PIK3CA p.(Q546K) c.1636C>A

*phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme<sup>59</sup>. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases<sup>60,61</sup>. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively<sup>60</sup>. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction<sup>62,63</sup>. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism<sup>62,63,64,65</sup>. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability<sup>66,67,68</sup>.

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers<sup>8,9</sup>. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)<sup>69,70</sup>. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation<sup>71,72,73</sup>. PIK3CA resides in the 3q26 cytoband, a region frequently amplified

## Biomarker Descriptions (continued)

(10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers<sup>8,9</sup>.

**Potential relevance:** The PI3K inhibitor, alpelisib<sup>74</sup>, is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression  $\geq$  6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors<sup>75</sup>. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations<sup>75</sup>. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations<sup>76</sup>. The FDA also approved the kinase inhibitor, capivasertib (2023)<sup>77</sup> in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib<sup>78</sup>, is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers<sup>79,80</sup>.

### CTNNB1 p.(D32Y) c.94G>T

*catenin beta 1*

**Background:** The CTNNB1 gene encodes catenin beta-1 ( $\beta$ -catenin), an integral component of cadherin-based adherens junctions, which are involved in maintaining adhesion and regulating the growth of epithelial cell layers<sup>10</sup>. CTNNB1 binds to the APC protein in the cytoplasm and interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling<sup>11</sup>. Steady-state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis<sup>12,13,14</sup>. CTNNB1 exon 3 mutations can lead to persistent activation of the WNT/ $\beta$ -catenin pathway and alter downstream nuclear transcription<sup>15</sup>.

**Alterations and prevalence:** Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-3 $\beta$  and inhibit CTNNB1 degradation<sup>15,16,17,18</sup>. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% in uterine carcinoma, and 15% in adrenocortical carcinoma<sup>8,9,19,20,21,22,23</sup>. Alterations in CTNNB1 are also observed in pediatric cancers<sup>8,9</sup>. Somatic mutations are observed in 36% of hepatobiliary cancer (4 in 11 cases), 6% of embryonal tumor (21 in 332 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of Wilms tumor (11 in 710 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and bone cancer (1 in 327 cases)<sup>8,9</sup>.

**Potential relevance:** Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer<sup>24</sup>. Mutation of CTNNB1 is considered an ancillary diagnostic biomarker for desmoid fibromatosis and WNT-activated medulloblastoma<sup>25,26,27</sup>.

### 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<sup>37</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>38,39</sup>. 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<sup>40</sup>. 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<sup>41</sup>. 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)<sup>41</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>42,43,44,45,46</sup>. 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<sup>39</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>38,39,43,47</sup>.

**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<sup>38,39,48,49</sup>. 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<sup>48,49</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>50</sup> (2014) and nivolumab<sup>51</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>50</sup> 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

## Biomarker Descriptions (continued)

approved with a tumor agnostic indication<sup>50</sup>. Dostarlimab<sup>52</sup> (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<sup>44,53</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>54</sup> (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<sup>44,55,56</sup>. 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<sup>56</sup>. 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<sup>57,58</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>57,58</sup>.

### PARP4 p.(Q535Tfs\*10) c.1602\_1602delGinsAA

*poly(ADP-ribose) polymerase family member 4*

**Background:** The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein<sup>1</sup>. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3<sup>28</sup>. 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<sup>28,29</sup>. PARP enzymes are involved in several DNA repair pathways<sup>28,29</sup>. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins<sup>30</sup>.

**Alterations and prevalence:** Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma<sup>8,9</sup>. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)<sup>8,9</sup>.

**Potential relevance:** Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (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<sup>31,32</sup>. Although not indicated for specific alterations in PARP4, several PARPi including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib<sup>33</sup> (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, olaparib<sup>33</sup> 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. Rucaparib<sup>34</sup> (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. Talazoparib<sup>35</sup> (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib<sup>36</sup> (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.

### HLA-B deletion

*major histocompatibility complex, class I, B*

**Background:** The HLA-B gene encodes the major histocompatibility complex, class I, B<sup>1</sup>. 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 cells<sup>2</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>3</sup>. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the  $\alpha$  polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self<sup>4,5,6</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B<sup>7</sup>.

**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<sup>8,9</sup>. Biallelic loss of HLA-B is observed in 5% of DLBCL<sup>8,9</sup>.

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

## Genes Assayed

### Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO1D, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

### Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, 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, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

### Genes Assayed for the Detection of Fusions

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

PIK3CA p.(Q546K) c.1636C>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capivasertib + fulvestrant	<div></div>	<div></div>	<div></div>	<div></div>	<div></div>
inavolisib + palbociclib + fulvestrant	<div></div>	<div></div>	<div></div>	<div></div>	<div></div>
HTL-0039732, atezolizumab	<div></div>	<div></div>	<div></div>	<div></div>	<div></div> (I/II)
inavolisib, hormone therapy	<div></div>	<div></div>	<div></div>	<div></div>	<div></div> (I/II)
JS-105, chemotherapy	<div></div>	<div></div>	<div></div>	<div></div>	<div></div> (I/II)
JS-105	<div></div>	<div></div>	<div></div>	<div></div>	<div></div> (I)
SNV-4818, hormone therapy	<div></div>	<div></div>	<div></div>	<div></div>	<div></div> (I)

CTNNB1 p.(D32Y) c.94G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tegatrabetan	<div></div>	<div></div>	<div></div>	<div></div>	<div></div> (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
LOH percentage	0.0%
Not Detected	Not Applicable

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from [www.fda.gov](http://www.fda.gov) and is current as of 2025-05-14. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-05-01. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-05-14. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search [www.clinicaltrials.gov](http://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. 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
2. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
3. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol.* 2013;31:529-61. PMID: 23298204
4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
5. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
6. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
7. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. *Cancers (Basel).* 2020 Jul 2;12(7). PMID: 32630675
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. Valenta et al. The many faces and functions of  $\beta$ -catenin. *EMBO J.* 2012 Jun 13;31(12):2714-36. PMID: 22617422
11. Korinek et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma. *Science.* 1997 Mar 21;275(5307):1784-7. PMID: 9065401
12. Aberle et al. beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J.* 1997 Jul 1;16(13):3797-804. PMID: 9233789
13. Winston et al. The SCFbeta-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates IkappaBalpha ubiquitination in vitro. *Genes Dev.* 1999 Feb 1;13(3):270-83. PMID: 9990852
14. Kitagawa et al. An F-box protein, FWD1, mediates ubiquitin-dependent proteolysis of beta-catenin. *EMBO J.* 1999 May 4;18(9):2401-10. PMID: 10228155
15. Gao et al. Exon 3 mutations of CTNNB1 drive tumorigenesis: a review. *Oncotarget.* 2018 Jan 12;9(4):5492-5508. PMID: 29435196
16. Liu et al. Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism. *Cell.* 2002 Mar 22;108(6):837-47. PMID: 11955436
17. Miyoshi et al. Activation of the beta-catenin gene in primary hepatocellular carcinomas by somatic alterations involving exon 3. *Cancer Res.* 1998 Jun 15;58(12):2524-7. PMID: 9635572
18. Morin et al. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. *Science.* 1997 Mar 21;275(5307):1787-90. PMID: 9065402
19. Schulze et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat. Genet.* 2015 May;47(5):505-511. PMID: 25822088
20. Ahn et al. Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification. *Hepatology.* 2014 Dec;60(6):1972-82. PMID: 24798001
21. Harding et al. Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies. *Clin. Cancer Res.* 2018 Oct 29. PMID: 30373752
22. Cancer et al. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013 May 2;497(7447):67-73. PMID: 23636398
23. Soumerai et al. Clinical Utility of Prospective Molecular Characterization in Advanced Endometrial Cancer. *Clin. Cancer Res.* 2018 Dec 1;24(23):5939-5947. PMID: 30068706
24. Blakely et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. *Nat. Genet.* 2017 Dec;49(12):1693-1704. PMID: 29106415
25. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 5.2024]
26. Moreno et al. High frequency of WNT-activated medulloblastomas with CTNNB1 wild type suggests a higher proportion of hereditary cases in a Latin-Iberian population. *Front Oncol.* 2023;13:1237170. PMID: 37746264
27. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021 Aug 2;23(8):1231-1251. PMID: 34185076
28. Amé et al. The PARP superfamily. *Bioessays.* 2004 Aug;26(8):882-93. PMID: 15273990
29. 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

## References (continued)

30. Prawira et al. Assessment of PARP4 as a candidate breast cancer susceptibility gene. *Breast Cancer Res Treat.* 2019 Aug;177(1):145-153. PMID: 31119570
31. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. *Clin Cancer Res.* 2019 Jul 1;25(13):3759-3771. PMID: 30760478
32. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. *Science.* 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
33. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/208558s028lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf)
34. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/209115s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf)
35. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/217439s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf)
36. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/214876s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf)
37. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
38. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol.* 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
39. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
40. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. *Front Microbiol.* 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
41. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998 Nov 15;58(22):5248-57. PMID: 9823339
42. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. *Cancer Res.* 2002 Jan 1;62(1):53-7. PMID: 11782358
43. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
44. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
45. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
46. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. *Medicine (Baltimore).* 2015 Dec;94(50):e2260. PMID: 26683947
47. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J. Clin. Oncol.* 2019 Feb 1;37(4):286-295. PMID: 30376427
48. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
49. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
50. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125514s174lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf)
51. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125554s129lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf)
52. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/761174s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf)
53. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
54. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125377s133lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf)
55. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003 Jul 17;349(3):247-57. PMID: 12867608
56. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann. Oncol.* 2015 Jan;26(1):126-32. PMID: 25361982
57. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
58. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
59. Volinia et al. Molecular cloning, cDNA sequence, and chromosomal localization of the human phosphatidylinositol 3-kinase p110 alpha (PIK3CA) gene. *Genomics.* 1994 Dec;24(3):472-7. PMID: 7713498
60. Whale et al. Functional characterization of a novel somatic oncogenic mutation of PIK3CB. *Signal Transduct Target Ther.* 2017;2:17063. PMID: 29279775
61. Osaki et al. PI3K-Akt pathway: its functions and alterations in human cancer. *Apoptosis.* 2004 Nov;9(6):667-76. PMID: 15505410



## References (continued)

62. Cantley. The phosphoinositide 3-kinase pathway. *Science*. 2002 May 31;296(5573):1655-7. PMID: 12040186
63. Fruman et al. The PI3K Pathway in Human Disease. *Cell*. 2017 Aug 10;170(4):605-635. PMID: 28802037
64. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat. Rev. Genet.* 2006 Aug;7(8):606-19. PMID: 16847462
65. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. *Nat. Rev. Mol. Cell Biol.* 2012 Feb 23;13(3):195-203. PMID: 22358332
66. Yuan et al. PI3K pathway alterations in cancer: variations on a theme. *Oncogene*. 2008 Sep 18;27(41):5497-510. PMID: 18794884
67. Liu et al. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discov.* 2009 Aug;8(8):627-44. PMID: 19644473
68. Hanahan et al. Hallmarks of cancer: the next generation. *Cell*. 2011 Mar 4;144(5):646-74. PMID: 21376230
69. Brito et al. PIK3CA Mutations in Diffuse Gliomas: An Update on Molecular Stratification, Prognosis, Recurrence, and Aggressiveness. *Clin Med Insights Oncol.* 2022;16:11795549211068804. PMID: 35023985
70. Huret et al. Atlas of genetics and cytogenetics in oncology and haematology in 2013. *Nucleic Acids Res.* 2013 Jan;41(Database issue):D920-4. PMID: 23161685
71. Miled et al. Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. *Science*. 2007 Jul 13;317(5835):239-42. PMID: 17626883
72. Burke et al. Synergy in activating class I PI3Ks. *Trends Biochem. Sci.* 2015 Feb;40(2):88-100. PMID: 25573003
73. Burke et al. Oncogenic mutations mimic and enhance dynamic events in the natural activation of phosphoinositide 3-kinase p110 $\alpha$  (PIK3CA). *Proc. Natl. Acad. Sci. U.S.A.* 2012 Sep 18;109(38):15259-64. PMID: 22949682
74. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/212526s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf)
75. Mayer et al. A Phase Ib Study of Alpelisib (BYL719), a PI3K $\alpha$ -Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. *Clin. Cancer Res.* 2017 Jan 1;23(1):26-34. PMID: 27126994
76. Mayer et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). *Clin. Cancer Res.* 2019 Feb 5. PMID: 30723140
77. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/218197s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf)
78. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/219249s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219249s000lbl.pdf)
79. Jung et al. Pilot study of sirolimus in patients with PIK3CA mutant/amplified refractory solid cancer. *Mol Clin Oncol.* 2017 Jul;7(1):27-31. PMID: 28685070
80. Janku et al. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. *Mol. Cancer Ther.* 2011 Mar;10(3):558-65. PMID: 21216929