

Patient Name: 김길남  
Gender: Male  
Sample ID: N26-17

Primary Tumor Site: Urinary bladder  
Collection Date: 2024.01.12

## Sample Cancer Type: Bladder Cancer

### Table of Contents

Variant Details	1
Biomarker Descriptions	2
Relevant Therapy Summary	5

### Report Highlights

1 Relevant Biomarkers  
0 Therapies Available  
2 Clinical Trials

## Relevant Bladder Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR2	None detected	NTRK3	None detected
FGFR3	None detected	RET	None detected
Genomic Alteration	Finding		
Tumor Mutational Burden	<b>2.85 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>CTNNB1 p.(S37F) c.110C&gt;T</b> catenin beta 1 Allele Frequency: 78.24% Locus: chr3:41266113 Transcript: NM_001904.4	None*	None*	2

\* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

\* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Line of therapy: I: First-line therapy, II: Other line of therapy

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists*. J Mol Diagn. 2017 Jan;19(1):4-23.

## Prevalent cancer biomarkers without relevant evidence based on included data sources

CDKN1A p.(L73Pfs\*16) c.217\_218insC, Microsatellite stable, TERT c.-124C>T, Tumor Mutational Burden

## Variant Details

### DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CTNNB1	p.(S37F)	c.110C>T	COSM5662	chr3:41266113	78.24%	NM_001904.4	missense

Disclaimer: The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. The data version is 2025.12(007). The content of this report has not been evaluated or approved by the FDA, EMA or other regulatory agencies.

## Variant Details (continued)

### DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CDKN1A	p.(L73Pfs*16)	c.217_218insC	.	chr6:36652093	68.64%	NM_078467.3	frameshift Insertion
TERT	p.(?)	c.-124C>T	VCV001299388	chr5:1295228	55.45%	NM_198253.3	unknown
GRID2	p.(F758S)	c.2273T>C	.	chr4:94547499	2.74%	NM_001510.4	missense
MAML3	p.(Q491Pfs*32)	c.1472_1506delAGCAG . CAGCAGCAGCAGCAG CAGCAGCAGCAGCAG nsCAGCAGCAGCAGC AGCAGCAGCAA	.	chr4:140811084	54.10%	NM_018717.5	frameshift Block Substitution
MAML3	p.(Q488_Q494delinsHD S)	c.1464_1506delGCAAC . AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGCAGCAGinsCGACA GCCAGCAGCAGCAGC AGCAGCAGCAA	.	chr4:140811084	44.26%	NM_018717.5	nonframeshift Block Substitution
APC	p.(E1374Q)	c.4120G>C	.	chr5:112175411	66.20%	NM_000038.6	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT CA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
ATM	p.(?)	c.7308-1G>T	.	chr11:108200940	76.64%	NM_000051.4	unknown
ERCC2	p.([R156=;F157S])	c.468_470delATTinsCT C	.	chr19:45868307	2.99%	NM_000400.4	synonymous, missense

### Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
TPP2	chr13:103249399	6.58	2.65
CUL4A	chr13:113863977	6.92	2.77

## Biomarker Descriptions

### CTNNB1 p.(S37F) c.110C>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>1</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>2</sup>. Steady-state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis<sup>3,4,5</sup>. CTNNB1 exon 3 mutations can lead to persistent activation of the WNT/ $\beta$ -catenin pathway and alter downstream nuclear transcription<sup>6</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>6,7,8,9</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>10,11,12,13,14,15,16</sup>. Alterations in CTNNB1 are also observed in pediatric cancers<sup>15,16</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>15,16</sup>.

## Biomarker Descriptions (continued)

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>17</sup>. Mutation of CTNNB1 is considered an ancillary diagnostic biomarker for desmoid fibromatosis and WNT-activated medulloblastoma<sup>18,19,20</sup>.

### CDKN1A p.(L73Pfs\*16) c.217\_218insC

*cyclin dependent kinase inhibitor 1A*

Background: The CDKN1A gene encodes the cyclin-dependent kinase inhibitor 1A protein, also known as p21 or WAF1<sup>48,49</sup>. CDKN1A belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1B (also known as KIP/p27) and CDKN2C (also known as KIP2/p57)<sup>49,50</sup>. Through inhibition of cyclin dependent kinases, including CDK1 and CDK2, CDKN1A impacts several biological processes, including cell cycle arrest, differentiation, gene transcription, apoptosis, and DNA repair<sup>51</sup>. CDKN1A is also capable of binding to proliferating cell nuclear antigen (PCNA) and inhibiting PCNA-dependent DNA polymerase activity<sup>51</sup>. Deregulation of CDKN1A, including loss of expression, is observed in several tumor types, supporting a tumor suppressor role for CDKN1A<sup>51</sup>.

Alterations and prevalence: Somatic mutations in CDKN1A are observed in 10% of bladder urothelial carcinoma, 3% of kidney chromophobe, and 2% of skin cutaneous melanoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma<sup>15,16</sup>. Biallelic deletion of CDKN1A is observed in 2% of kidney chromophobe and 1% of sarcoma<sup>15,16</sup>.

Potential relevance: Currently, no therapies are approved for CDKN1A 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<sup>26</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>27,28</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>29</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>30</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>30</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>31,32,33,34,35</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>28</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>27,28,32,36</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>27,28,37,38</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>37,38</sup>.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>39</sup> (2014) and nivolumab<sup>40</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>39</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 approved with a tumor agnostic indication<sup>39</sup>. Dostarlimab<sup>41</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>33,42</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>43</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>33,44,45</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>45</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>46,47</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>46,47</sup>.

### TERT c.-124C>T

*telomerase reverse transcriptase*

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)<sup>21</sup>. TERT is repressed in most differentiated cells, resulting in telomerase silencing<sup>21</sup>. In cancer, telomerase reactivation is known to contribute to cellular immortalization<sup>21,22</sup>. Increased TERT expression results in

## Biomarker Descriptions (continued)

telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization<sup>21</sup>. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness<sup>21</sup>.

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma<sup>15,16</sup>. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)<sup>22</sup>. Specifically, TERT promoter mutations at C228T and C250T are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription<sup>21</sup>. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma<sup>15,16</sup>. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen<sup>23</sup>. Alterations in TERT are rare in pediatric cancers<sup>15,16</sup>. Somatic mutations are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)<sup>15,16</sup>. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)<sup>15,16</sup>.

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendrogloma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma<sup>24,25</sup>. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy<sup>23</sup>.

## 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, MYD88L, 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, SNCAP, 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, 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, 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, LAT51, LAT52, 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, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, 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,

## Genes Assayed (continued)

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

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, 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, 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, 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, TGFB2, 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

### CTNNB1 p.(S37F) c.110C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
FOG-001, nivolumab	✗	✗	✗	✗	● (I/II)
tegatrabetan	✗	✗	✗	✗	● (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	26.17%
ATM	LOH, 11q22.3(108098341-108236285)x3
CHEK1	LOH, 11q24.2(125496639-125525271)x3
RAD51B	LOH, 14q24.1(68290164-69061406)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 (6.2.4 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](http://www.fda.gov) and is current as of 2025-11-25. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-11-03. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-11-25. ESMO information was sourced from [www.esmo.org](http://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](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. Valenta et al. The many faces and functions of  $\beta$ -catenin. *EMBO J.* 2012 Jun 13;31(12):2714-36. PMID: 22617422
2. 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
3. Aberle et al. beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J.* 1997 Jul 1;16(13):3797-804. PMID: 9233789
4. Winston et al. The SCF $\beta$ -TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in  $\beta$ -catenin and stimulates  $\beta$ -catenin ubiquitination in vitro. *Genes Dev.* 1999 Feb 1;13(3):270-83. PMID: 9990852
5. 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
6. Gao et al. Exon 3 mutations of CTNNB1 drive tumorigenesis: a review. *Oncotarget.* 2018 Jan 12;9(4):5492-5508. PMID: 29435196
7. Liu et al. Control of  $\beta$ -catenin phosphorylation/degradation by a dual-kinase mechanism. *Cell.* 2002 Mar 22;108(6):837-47. PMID: 11955436
8. 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
9. 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
10. 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
11. 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
12. 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
13. Cancer Genome Atlas Research et al. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013 May 2;497(7447):67-73. PMID: 23636398
14. 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
15. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
16. 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
17. 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
18. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
19. 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
20. 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
21. Yuan et al. Mechanisms underlying the activation of TERT transcription and telomerase activity in human cancer: old actors and new players. *Oncogene.* 2019 Aug;38(34):6172-6183. PMID: 31285550
22. Colebatch et al. TERT gene: its function and dysregulation in cancer. *J Clin Pathol.* 2019 Apr;72(4):281-284. PMID: 30696697
23. Mizukoshi et al. Telomerase-Targeted Cancer Immunotherapy. *Int J Mol Sci.* 2019 Apr 12;20(8). PMID: 31013796
24. NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2025]
25. Arita et al. TERT promoter mutation confers favorable prognosis regardless of 1p/19q status in adult diffuse gliomas with IDH1/2 mutations. *Acta Neuropathol Commun.* 2020 Nov 23;8(1):201. PMID: 33228806
26. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
27. 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
28. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
29. 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

## References (continued)

30. 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
31. 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
32. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
33. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
34. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
35. 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
36. 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
37. 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
38. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
39. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125514s178lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf)
40. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125554s131lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf)
41. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/761174s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf)
42. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
43. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125377s136lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf)
44. 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
45. 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
46. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
47. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
48. 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
49. Kreis et al. The Multifaceted p21 (Cip1/Waf1/CDKN1A) in Cell Differentiation, Migration and Cancer Therapy. *Cancers (Basel).* 2019 Aug 21;11(9). PMID: 31438587
50. Chu et al. The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. *Nat. Rev. Cancer.* 2008 Apr;8(4):253-67. PMID: 18354415
51. Abbas et al. p21 in cancer: intricate networks and multiple activities. *Nat Rev Cancer.* 2009 Jun;9(6):400-14. PMID: 19440234