

Patient Name: 김성호
Gender: Male
Sample ID: N26-65

Primary Tumor Site: brain
Collection Date: 2026.02.04

Sample Cancer Type: Glioblastoma IDH-wildtype (Grade 4)

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Relevant Glioblastoma IDH-wildtype (Grade 4) Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
EGFR	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	TERT	TERT c.-124C>T

Genomic Alteration	Finding
Tumor Mutational Burden	5.67 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	TERT c.-124C>T telomerase reverse transcriptase Allele Frequency: 21.72% Locus: chr5:1295228 Transcript: NM_198253.3 Diagnostic significance: Glioblastoma IDH-wildtype (Grade 4)	None*	None*	1
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	6
IIC	CDKN2B deletion cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	3

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

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

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

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>CHEK2</i> deletion checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	<i>RAD51D</i> deletion RAD51 paralog D Locus: chr17:33427950	None*	None*	1

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

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

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

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

FGFR4 p.(D127H) c.379G>C, *Microsatellite stable*, *PTPN11* p.(E69K) c.205G>A, *RAD51B* deletion, *RAD52* p.(S346*) c.1037C>A, *STAG2* p.(S202*) c.605C>G, *HLA-B* deletion, *ARID5B* deletion, *NQO1* 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
TERT	p.(?)	c.-124C>T	VCV001299388	chr5:1295228	21.72%	NM_198253.3	unknown
FGFR4	p.(D127H)	c.379G>C	.	chr5:176517769	47.55%	NM_213647.3	missense
PTPN11	p.(E69K)	c.205G>A	COSM13013	chr12:112888189	18.76%	NM_002834.5	missense
RAD52	p.(S346*)	c.1037C>A	.	chr12:1023218	49.45%	NM_134424.4	nonsense
STAG2	p.(S202*)	c.605C>G	.	chrX:123179156	43.06%	NM_001042749.2	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.60%	NM_000903.3	missense
MYCN	p.(G309V)	c.926G>T	.	chr2:16085750	50.45%	NM_005378.6	missense
TAP2	p.(D183G)	c.548A>G	.	chr6:32805374	59.34%	NM_018833.2	missense
CYP2C9	p.(C179S)	c.535T>A	.	chr10:96707589	35.52%	NM_000771.4	missense
CDK12	p.(R344Q)	c.1031G>A	.	chr17:37619355	51.23%	NM_016507.4	missense
POLD1	p.(Q1022R)	c.3065A>G	.	chr19:50919978	51.20%	NM_001256849.1	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0	0.49
CDKN2B	chr9:22005728	0.19	0.56
CHEK2	chr22:29083868	1	0.83
RAD51D	chr17:33427950	1	1.06
RAD51B	chr14:68290164	1	0.79

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0	0.5
ARID5B	chr10:63661463	0.65	0.68

Biomarker Descriptions

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)⁶⁸. TERT is repressed in most differentiated cells, resulting in telomerase silencing⁶⁸. In cancer, telomerase reactivation is known to contribute to cellular immortalization^{68,69}. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization⁶⁸. 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 stemness⁶⁸.

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^{4,5}. 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)⁶⁹. 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 transcription⁶⁸. 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^{4,5}. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen⁷⁰. Alterations in TERT are rare in pediatric cancers^{4,5}. 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)^{4,5}. 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)^{4,5}.

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma^{71,72}. 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 therapy⁷⁰.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)²⁸. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{29,30,31}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions³². Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation^{1,32,33}. CDKN2A aberrations commonly co-occur with CDKN2B²⁸. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation³⁴. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{35,36}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations³⁷. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma^{4,5}. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32%

Biomarker Descriptions (continued)

of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{4,5}. Alterations in CDKN2A are also observed in pediatric cancers⁵. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors⁵. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)⁵.

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors^{38,39,40}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma⁴¹. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib^{42,43,44}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme⁴⁵. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer^{46,47,48,49}.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression^{1,28}. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)²⁸. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{29,30,31}. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A²⁸. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma^{1,50,51}.

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B-cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{4,5}. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma^{4,5}. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers^{4,5}. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)^{4,5}.

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma⁴¹.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, a cell cycle checkpoint regulator¹. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis⁹⁵. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)^{96,97,98}. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer^{99,100,101}. Reduced expression of CHEK2 is associated with several cancers including breast cancer, colorectal cancer, and prostate cancer, supporting its role as a tumor suppressor¹⁰⁰.

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations¹⁰². Somatic mutations in CHEK2 are observed in 7% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, and 2% of diffuse large B-cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, lung adenocarcinoma, colorectal adenocarcinoma, and kidney chromophobe^{4,5}. Deletion of CHEK2 is observed in 3% of adrenocortical carcinoma and thymoma, and 2% of bladder urothelial carcinoma^{4,5}. Alterations in CHEK2 are also observed in pediatric cancers⁵. Somatic mutations in CHEK2 are observed in less than 1% of bone cancer (2 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and peripheral nervous system cancers (1 in 1158 cancers)⁵. Deletion of CHEK2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)⁵.

Biomarker Descriptions (continued)

Potential relevance: The PARP inhibitor, olaparib⁶⁴ (2020) is approved for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including CHEK2. Additionally, talazoparib¹⁰³(2023) in combination with enzalutamide is approved for mCRPC with mutations in HRR genes, including CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁵, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD51D deletion

RAD51 paralog D

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁵⁸. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁵⁹. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁶⁰. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{61,62}. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer⁶³.

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer⁴.

Potential relevance: The PARP inhibitor, olaparib⁶⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors⁶¹. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁵, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FGFR4 p.(D127H) c.379G>C

fibroblast growth factor receptor 4

Background: The FGFR4 gene encodes fibroblast growth receptor 4, a member of the fibroblast growth-factor receptor (FGFR) family that also includes FGFR1, 2, and 3¹. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain¹⁰⁴. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival^{105,106,107}. FGFR4 selectively binds the ligand FGF19, wherein FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma^{108,109}.

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions; the majority of these aberrations result in gain of function¹¹⁰. Recurrent somatic mutations in FGFR4 are observed in 6% of skin cutaneous melanoma, 5% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma, lung adenocarcinoma, and colorectal adenocarcinoma^{4,5}. FGFR4 amplification is observed in 7% of kidney renal clear cell carcinoma, 4% of adrenocortical carcinoma, and 2% of sarcoma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, uterine carcinosarcoma, and lung adenocarcinoma^{4,5}. Alterations in FGFR4 are also observed in the pediatric population⁵. Somatic mutations in FGFR4 are observed in 13% of soft tissue sarcoma (5 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases), Hodgkin lymphoma (1 in 61 cases), and bone cancer (4 in 327 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), leukemia (2 in 311 cases), embryonal tumor (2 in 332 cases), and glioma (1 in 297 cases). FGFR4 amplification is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and B-lymphoblastic leukemia/lymphoma (6 in 731 cases)⁵.

Potential relevance: Currently, no targeted therapies are approved for FGFR4 aberrations. However, FDA-approved multi-kinase inhibitors known to inhibit FGFR family members, including regorafenib (2013), ponatinib (2012), lenvatinib (2015), nintedanib (2014), and pazopanib (2009), have demonstrated anti-tumor activity in select cancer types harboring FGFR alterations^{111,112,113,114,115,116,117}.

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 genome⁷³. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{74,75}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁷⁶. 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 D17S250⁷⁷. 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)⁷⁷. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{78,79,80,81,82}. MSI-H is a hallmark of Lynch

Biomarker Descriptions (continued)

syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes⁷⁵. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{74,75,79,83}.

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^{74,75,84,85}. 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^{84,85}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁸⁶ (2014) and nivolumab⁸⁷ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁸⁶ 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 indication⁸⁶. Dostarlimab⁸⁸ (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^{80,89}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁹⁰ (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^{80,91,92}. 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 patients⁹². 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^{93,94}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{93,94}.

PTPN11 p.(E69K) c.205G>A

protein tyrosine phosphatase, non-receptor type 11

Background: The PTPN11 gene encodes a tyrosine phosphatase non-receptor type 11 protein, and is also known as Src homology region 2 domain-containing phosphatase-2 (SHP-2)^{1,6}. PTPN11 is a member of the protein tyrosine phosphatase (PTP) family that is ubiquitously expressed and regulates cellular growth, differentiation, mitotic cycle, and oncogenic transformation⁷. PTPN11 contains two tandem N-terminal Src homology-2 domains (N-SH2 and C-SH2), a PTP catalytic domain, and uncharacterized C-terminal domain⁸. PTPN11 regulates various signaling processes including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, and JAK/STAT pathways^{9,10}. Germline mutations in PTPN11 are associated with LEOPARD syndrome and Noonan syndrome with a predisposition to juvenile myelomonocytic leukemia (JMML) or myeloproliferative neoplasms (MPN)^{11,12}. Somatic mutations in PTPN11 are associated with JMML^{13,14} and solid tumors such as lung, colon, and thyroid^{8,15}.

Alterations and prevalence: Somatic alterations in PTPN11 include mutations and amplification^{11,16}. Somatic mutations in PTPN11 occur in 5% uterine corpus endometrial carcinoma and acute myeloid leukemia, 3% of skin cutaneous melanoma, glioblastoma multiforme, and colorectal adenocarcinoma, and 2% of stomach adenocarcinoma, uterine carcinosarcoma, lung adenocarcinoma, and brain lower grade glioma^{4,5}. Mutations including E76K and D61Y result in PTPN11 activation and are associated with 30% of JMML¹⁰. PTPN11 fusion is observed in 2% of uterine carcinosarcoma^{4,5}. Amplification of PTPN11 is observed in 2% of bladder urothelial carcinoma, sarcoma, uterine carcinosarcoma, and esophageal adenocarcinoma^{4,5}. Alterations in PTPN11 are also observed in pediatric cancers⁵. Somatic mutations in PTPN11 are observed in 4% of leukemia (15 in 354 cases), 3% of B-lymphoblastic leukemia/lymphoma (7 in 252 cases) and soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases), 1% of glioma (3 in 297 cases), and less than 1% of peripheral nervous system tumors (7 in 1158 cases) and bone cancer (1 in 327 cases)⁵.

Potential relevance: Currently, no therapies are approved for PTPN11 aberrations. Somatic mutations in PTPN11 confer drug resistance to venetoclax and azacitidine in AML^{17,18}.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁵⁸. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁵⁹. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁶⁰. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{61,62}. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild

Biomarker Descriptions (continued)

hypersensitivity to DNA-damaging agents⁶⁶. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk⁶⁷.

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer^{4,5}. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk⁶⁷.

Potential relevance: The PARP inhibitor, olaparib⁶⁴ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶⁵, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD52 p.(S346*) c.1037C>A

RAD52 homolog, DNA repair protein

Background: The RAD52 gene encodes the RAD52 homolog, DNA repair protein¹. RAD52 binds to single- and double-stranded DNA and enables strand exchange for double-strand break (DSB) repair by binding to RAD51¹⁹. RAD52 also promotes DSB repair through homologous recombination repair (HRR) by recruiting BRCA1 to sites of DSBs, which leads to the removal of TP53BP1 and prevents DSB repair by non-homologous end joining (NHEJ)²⁰.

Alterations and prevalence: Somatic mutations in RAD52 are observed in 2% of uterine corpus endometrial carcinoma, uterine carcinosarcoma, and skin cutaneous melanoma^{4,5}.

Potential relevance: Currently, no therapies are approved for RAD52 aberrations.

STAG2 p.(S202*) c.605C>G

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division^{21,22}. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs^{23,24}. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer^{23,25}.

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, and splice site variants¹². Somatic mutations in STAG2 are observed in 14% of bladder cancer, 10% of uterine cancer, 5% of glioblastoma multiforme, 4% of lung adenocarcinoma and skin cutaneous melanoma, 3% of acute myeloid leukemia, stomach adenocarcinoma, kidney renal papillary cell carcinoma, and lung squamous cell carcinoma, and 2% of cholangiocarcinoma, diffuse large B-cell lymphoma, colorectal adenocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, uterine carcinosarcoma, breast invasive carcinoma, and esophageal adenocarcinoma⁵. Biallelic deletion of STAG2 is observed in 2% of uterine carcinosarcoma and 1% of sarcoma and acute myeloid leukemia⁵. Alterations in STAG2 are also observed in pediatric cancers⁵. Somatic mutations in STAG2 are observed in 10% of bone cancer (34 in 327 cases), 5% of soft tissue sarcoma (2 in 38 cases), 2% of embryonal tumors (5 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 252 cases) and peripheral nervous system cancers (1 in 1158 cases)⁵. Structural variants in STAG2 are observed in 2% of leukemia (1 in 64 cases) and less than 1% of bone cancer (1 in 150 cases)⁵. Biallelic deletion of STAG2 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of leukemia (1 in 250 cases)⁵.

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and acute myeloid leukemia^{12,26}. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors²⁷.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B¹. 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 cells⁵². MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁵³. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{54,55,56}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B⁵⁷.

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

Biomarker Descriptions (continued)

adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma^{4,5}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{4,5}.

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

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein¹. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2^{2,3}. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes³. ARID5B is known to be essential for the development of hematopoietic cells³. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)³.

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma^{4,5}. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma^{4,5}.

Potential relevance: Currently, no therapies are approved for ARID5B 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, CTNNA1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDN, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABC1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, 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, ERF1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDN, 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, SLC1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB1,

Genes Assayed (continued)

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

TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, 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, CBF3, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRF1, 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

TERT c.-124C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab, chemotherapy, radiation therapy	×	×	×	×	● (III)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	● (II)
palbociclib, abemaciclib	×	×	×	×	● (II)
ribociclib, everolimus	×	×	×	×	● (II)
AMG 193	×	×	×	×	● (I/II)
ABSK-131	×	×	×	×	● (I)
CID-078	×	×	×	×	● (I)

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

Relevant Therapy Summary (continued)

In this cancer type
 In other cancer type
 In this cancer type and other cancer types
 No evidence

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	×	×	×	×	● (II)
ribociclib, everolimus	×	×	×	×	● (II)
CID-078	×	×	×	×	● (I)

CHEK2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (II)

RAD51D deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	● (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	9.24%
CDK12	SNV, R344Q, AF:0.51
CHEK2	CNV, CN:1.0
CHEK2	LOH, 22q12.1(29083868-29130729)x1
RAD51B	CNV, CN:1.0
RAD51B	LOH, 14q24.1(68290164-69061406)x1
RAD51D	CNV, CN:1.0
RAD51D	LOH, 17q12(33427950-33430583)x1

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

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

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. Patsialou et al. DNA-binding properties of ARID family proteins. *Nucleic Acids Res.* 2005;33(1):66-80. PMID: 15640446
3. Wang et al. The Role of ARID5B in Acute Lymphoblastic Leukemia and Beyond. *Front Genet.* 2020;11:598. PMID: 32595701
4. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
5. 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
6. Tartaglia et al. Somatic PTPN11 mutations in childhood acute myeloid leukaemia. *Br. J. Haematol.* 2005 May;129(3):333-9. PMID: 15842656
7. Chan et al. PTPN11 is the first identified proto-oncogene that encodes a tyrosine phosphatase. *Blood.* 2007 Feb 1;109(3):862-7. PMID: 17053061
8. Chan et al. The tyrosine phosphatase Shp2 (PTPN11) in cancer. *Cancer Metastasis Rev.* 2008 Jun;27(2):179-92. PMID: 18286234
9. Steelman et al. Roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and sensitivity to therapy-implications for cancer and aging. *Aging (Albany NY).* 2011 Mar;3(3):192-222. PMID: 21422497
10. Liu et al. Inhibition of the Gab2/PI3K/mTOR signaling ameliorates myeloid malignancy caused by Ptpn11 (Shp2) gain-of-function mutations. *Leukemia.* 2017 Jun;31(6):1415-1422. PMID: 27840422
11. Tartaglia et al. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. *Nat. Genet.* 2003 Jun;34(2):148-50. PMID: 12717436
12. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
13. Tartaglia et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat. Genet.* 2001 Dec;29(4):465-8. PMID: 11704759
14. Tartaglia et al. Diversity and functional consequences of germline and somatic PTPN11 mutations in human disease. *Am. J. Hum. Genet.* 2006 Feb;78(2):279-90. PMID: 16358218
15. Jongmans et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. *Eur. J. Hum. Genet.* 2011 Aug;19(8):870-4. PMID: 21407260
16. Liu et al. Gain-of-function mutations of Ptpn11 (Shp2) cause aberrant mitosis and increase susceptibility to DNA damage-induced malignancies. *Proc. Natl. Acad. Sci. U.S.A.* 2016 Jan 26;113(4):984-9. PMID: 26755576
17. Chyla et al. Genetic Biomarkers Of Sensitivity and Resistance to Venetoclax Monotherapy in Patients With Relapsed Acute Myeloid Leukemia. *Am. J. Hematol.* 2018 May 17. PMID: 29770480
18. Zhang et al. Biomarkers Predicting Venetoclax Sensitivity and Strategies for Venetoclax Combination Treatment. *Blood* 2018 132:175; doi: <https://doi.org/10.1182/blood-2018-175>. 10.1182/blood-2018-99-119806
19. Jalan et al. Emerging Roles of RAD52 in Genome Maintenance. *Cancers (Basel).* 2019 Jul 23;11(7). PMID: 31340507
20. Yasuhara et al. Human Rad52 Promotes XPG-Mediated R-loop Processing to Initiate Transcription-Associated Homologous Recombination Repair. *Cell.* 2018 Oct 4;175(2):558-570.e11. PMID: 30245011
21. Mehta et al. Cohesin: functions beyond sister chromatid cohesion. *FEBS Lett.* 2013 Aug 2;587(15):2299-312. PMID: 23831059
22. Aquila et al. The role of STAG2 in bladder cancer. *Pharmacol. Res.* 2018 May;131:143-149. PMID: 29501732
23. Mullegama et al. De novo loss-of-function variants in STAG2 are associated with developmental delay, microcephaly, and congenital anomalies. *Am. J. Med. Genet. A.* 2017 May;173(5):1319-1327. PMID: 28296084
24. van der Lelij et al. Synthetic lethality between the cohesin subunits STAG1 and STAG2 in diverse cancer contexts. *Elife.* 2017 Jul 10;6. PMID: 28691904
25. Solomon et al. Mutational inactivation of STAG2 causes aneuploidy in human cancer. *Science.* 2011 Aug 19;333(6045):1039-43. PMID: 21852505
26. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood.* 2022 Sep 22;140(12):1345-1377. PMID: 35797463
27. Solomon et al. Frequent truncating mutations of STAG2 in bladder cancer. *Nat. Genet.* 2013 Dec;45(12):1428-30. PMID: 24121789
28. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. *Nat Commun.* 2021 Apr 6;12(1):2047. PMID: 33824349
29. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. *Am. J. Respir. Cell Mol. Biol.* 2018 Aug;59(2):200-214. PMID: 29420051
30. Rousset. The INK4 family of cell cycle inhibitors in cancer. *Oncogene.* 1999 Sep 20;18(38):5311-7. PMID: 10498883

References (continued)

31. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). *Biochem. Biophys. Res. Commun.* 1999 Aug 27;262(2):534-8. PMID: 10462509
32. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet.* 2013;14:257-79. PMID: 23875803
33. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell.* 2006 Oct 20;127(2):265-75. PMID: 17055429
34. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
35. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
36. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
37. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. *Clin Cancer Res.* 2021 Jul 15;27(14):4025-4035. PMID: 34074656
38. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2026]
39. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2026]
40. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
41. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol.* 2020 Jul;30(4):844-856. PMID: 32307792
42. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med.* 2019 Jul 29;17(1):245. PMID: 31358010
43. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. *Anticancer Res.* 2013 Aug;33(8):2997-3004. PMID: 23898052
44. von Witzleben et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway. *Cancer Res.* 2015 Sep 15;75(18):3823-31. PMID: 26183925
45. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. *Neuro-oncology.* 2012 Jul;14(7):870-81. PMID: 22711607
46. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. *Oncotarget.* 2018 Sep 7;9(70):33247-33248. PMID: 30279955
47. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J. Clin. Oncol.* 2014 Dec 10;32(35):3930-8. PMID: 25267748
48. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. *J. Natl. Cancer Inst.* 2018 Dec 1;110(12):1393-1399. PMID: 29878161
49. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. *Cancer Clin Oncol.* 2013;2(1):51-61. PMID: 23935769
50. Jafri et al. Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma. *Cancer Discov.* 2015 Jul;5(7):723-9. PMID: 25873077
51. Tu et al. CDKN2B deletion is essential for pancreatic cancer development instead of unmeaningful co-deletion due to juxtaposition to CDKN2A. *Oncogene.* 2018 Jan 4;37(1):128-138. PMID: 28892048
52. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
53. 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
54. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
55. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
56. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
57. 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
58. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. *Genes (Basel).* 2018 Dec 13;9(12). PMID: 30551670
59. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. *Semin. Cell Dev. Biol.* 2011 Oct;22(8):898-905. PMID: 21821141

References (continued)

60. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. *Mol. Cell. Biol.* 2013 Jan;33(2):387-95. PMID: 23149936
61. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. *Endocr. Relat. Cancer.* 2016 Jun;23(6):R267-85. PMID: 27226207
62. Lord et al. BRCAness revisited. *Nat. Rev. Cancer.* 2016 Feb;16(2):110-20. PMID: 26775620
63. Godin et al. Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication. *Biochem. Cell Biol.* 2016 Oct;94(5):407-418. PMID: 27224545
64. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
65. <https://www.senhwabio.com/en/news/20220125>
66. Date et al. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. *Cancer Res.* 2006 Jun 15;66(12):6018-24. PMID: 16778173
67. Pelttari et al. RAD51B in Familial Breast Cancer. *PLoS ONE.* 2016;11(5):e0153788. PMID: 27149063
68. 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
69. Colebatch et al. TERT gene: its function and dysregulation in cancer. *J Clin Pathol.* 2019 Apr;72(4):281-284. PMID: 30696697
70. Mizukoshi et al. Telomerase-Targeted Cancer Immunotherapy. *Int J Mol Sci.* 2019 Apr 12;20(8). PMID: 31013796
71. NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2025]
72. 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
73. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
74. 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
75. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
76. 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
77. 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
78. 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
79. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
80. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
81. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
82. 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
83. 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
84. 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
85. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
86. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
87. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
88. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
89. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]
90. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
91. 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

References (continued)

92. 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
93. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
94. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
95. Matsuoka et al. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. *Science.* 1998 Dec 4;282(5395):1893-7. PMID: 9836640
96. Cai et al. Structure and activation mechanism of the CHK2 DNA damage checkpoint kinase. *Mol. Cell.* 2009 Sep 24;35(6):818-29. PMID: 19782031
97. Zhang et al. Chk2 phosphorylation of BRCA1 regulates DNA double-strand break repair. *Mol. Cell. Biol.* 2004 Jan;24(2):708-18. PMID: 14701743
98. Huang et al. Chk1 and Chk2 are differentially involved in homologous recombination repair and cell cycle arrest in response to DNA double-strand breaks induced by camptothecins. *Mol. Cancer Ther.* 2008 Jun;7(6):1440-9. PMID: 18566216
99. Apostolou et al. Current perspectives on CHEK2 mutations in breast cancer. *Breast Cancer (Dove Med Press).* 2017;9:331-335. PMID: 28553140
100. Nevanlinna et al. The CHEK2 gene and inherited breast cancer susceptibility. *Oncogene.* 2006 Sep 25;25(43):5912-9. PMID: 16998506
101. Näslund-Koch et al. Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. *J. Clin. Oncol.* 2016 Apr 10;34(11):1208-16. PMID: 26884562
102. Cybulski et al. CHEK2 is a multiorgan cancer susceptibility gene. *Am J Hum Genet.* 2004 Dec;75(6):1131-5. PMID: 15492928
103. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
104. Mohammadi et al. Structural basis for fibroblast growth factor receptor activation. *Cytokine Growth Factor Rev.* 2005 Apr;16(2):107-37. PMID: 15863029
105. Babina et al. Advances and challenges in targeting FGFR signalling in cancer. *Nat. Rev. Cancer.* 2017 May;17(5):318-332. PMID: 28303906
106. Ahmad et al. Mechanisms of FGFR-mediated carcinogenesis. *Biochim. Biophys. Acta.* 2012 Apr;1823(4):850-60. PMID: 22273505
107. Sarabipour et al. Mechanism of FGF receptor dimerization and activation. *Nat Commun.* 2016 Jan 4;7:10262. doi: 10.1038/ncomms10262. PMID: 26725515
108. Repana et al. Targeting FGF19/FGFR4 Pathway: A Novel Therapeutic Strategy for Hepatocellular Carcinoma. *Diseases.* 2015 Oct 28;3(4):294-305. PMID: 28943626
109. Lu et al. Fibroblast Growth Factor Receptor 4 (FGFR4) Selective Inhibitors as Hepatocellular Carcinoma Therapy: Advances and Prospects. *J. Med. Chem.* 2018 Nov 16. PMID: 30403487
110. Helsten et al. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. *Clin. Cancer Res.* 2016 Jan 1;22(1):259-67. PMID: 26373574
111. Cha et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers in vitro. *Mol Oncol.* 2018 Jun;12(7):993-1003. PMID: 29573334
112. Chae et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. *Oncotarget.* 2017 Feb 28;8(9):16052-16074. PMID: 28030802
113. Porta et al. FGFR a promising druggable target in cancer: Molecular biology and new drugs. *Crit. Rev. Oncol. Hematol.* 2017 May;113:256-267. PMID: 28427515
114. Gozgit et al. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. *Mol. Cancer Ther.* 2012 Mar;11(3):690-9. PMID: 22238366
115. Yamamoto et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell.* 2014 Sep 6;6:18. doi: 10.1186/2045-824X-6-18. eCollection 2014. PMID: 25197551
116. Kim et al. Pazopanib, a novel multitargeted kinase inhibitor, shows potent in vitro antitumor activity in gastric cancer cell lines with FGFR2 amplification. *Mol. Cancer Ther.* 2014 Nov;13(11):2527-36. PMID: 25249557
117. Hibi et al. FGFR gene alterations in lung squamous cell carcinoma are potential targets for the multikinase inhibitor nintedanib. *Cancer Sci.* 2016 Nov;107(11):1667-1676. PMID: 27581340