Samkwang Medical Lab

Patient Name:	노도정	**Primary Tumor Site:**	Lung
Gender:	M	**Collection Date:**	2025.07.17
Sample ID:	N25-126		

Sample Cancer Type: Lung Cancer

Table of Contents

Report Highlights

2 Relevant Biomarkers
3 Therapies Available
2 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	*15.22 Mut/Mb measured*

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib [II+] olaparib [II+] rucaparib [II+]	2
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1

* Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, 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

CDKN2A p.(D108H) c.322G>C, CIC p.(S1104T) c.3310T>A, MSH6 p.(K1358Dfs*2) c.4068_4071dup, Microsatellite stable, NF1 p.(Q543*) c.1627C>T, TP53 p.(R342*) c.1024C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CDKN2A	p.(D108H)	c.322G>C	COSM13520	chr9:21971036	29.71%	NM_001195132.2	missense
CIC	p.(S1104T)	c.3310T>A	.	chr19:42796852	52.25%	NM_015125.5	missense
MSH6	p.(K1358Dfs*2)	c.4068_4071dup	.	chr2:48033981	48.76%	NM_000179.3	frameshift Insertion
NF1	p.(Q543*)	c.1627C>T	.	chr17:29546122	18.22%	NM_001042492.3	nonsense
TP53	p.(R342*)	c.1024C>T	COSM11073	chr17:7574003	31.75%	NM_000546.6	nonsense
C8A	p.(D77Y)	c.229G>T	.	chr1:57340679	5.55%	NM_000562.3	missense
BRINP3	p.(G615W)	c.1843G>T	.	chr1:190067606	3.35%	NM_199051.3	missense
OR2L2	p.(S196R)	c.588C>A	.	chr1:248202157	9.43%	NM_001004686.2	missense
REG1B	p.(L102I)	c.304C>A	.	chr2:79313510	3.61%	NM_006507.4	missense
INPP4B	p.(G86V)	c.257G>T	.	chr4:143324206	13.96%	NM_001101669.3	missense
CDH10	p.(V332L)	c.994G>T	.	chr5:24511444	14.71%	NM_006727.5	missense
CDH10	p.(N301K)	c.903T>A	.	chr5:24511535	19.73%	NM_006727.5	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGCGGCCGCAGCGGC	.	chr5:79950707	60.82%	NM_002439.5	nonframeshift Deletion
MET	p.(E1396*)	c.4186G>T	.	chr7:116436137	9.41%	NM_001127500.3	nonsense
POT1	p.(D598Y)	c.1792G>T	.	chr7:124465306	23.25%	NM_015450.3	missense
POT1	p.(D77Y)	c.229G>T	.	chr7:124510991	15.13%	NM_015450.3	missense
CSMD3	p.(L406P)	c.1217T>C	.	chr8:113988191	20.58%	NM_198123.2	missense
PRPF19	p.(T345R)	c.1034C>G	.	chr11:60666354	13.81%	NM_014502.5	missense
YAP1	p.(P38S)	c.112C>T	.	chr11:101981691	48.85%	NM_001130145.3	missense
PARP4	p.(?)	c.3285_3285+5delinsAGT	.	chr13:25021149	100.00%	NM_006437.4	unknown
ABCC12	p.(C1110F)	c.3329G>T	.	chr16:48122602	2.95%	NM_033226.2	missense
ZFHX3	p.(Q1763E)	c.5287C>G	.	chr16:72831294	52.81%	NM_006885.4	missense
NF1	p.(?)	c.7322-1G>T	.	chr17:29677200	15.11%	NM_001042492.3	unknown
AXIN2	p.(R538L)	c.1613G>T	.	chr17:63533541	3.41%	NM_004655.4	missense
NOL4	p.(A130S)	c.388G>T	.	chr18:31709861	2.60%	NM_003787.5	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.87
CHEK2	chr22:29083868	1	0.92

Biomarker Descriptions

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[70,71]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[70,71]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[72,73,74]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[72,75].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[76,77,78,79,80,81,82,83]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[15,16].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[84]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[85,86]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[87] (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[87] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[88] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[89] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[89] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib[90] (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. Niraparib in combination with abiraterone acetate[91] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[92]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[93]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[94], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[95], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[96]. 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)[97,98,99]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[100,101,102].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[15,16]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[15,16].

Potential relevance: The PARP inhibitor, olaparib[87] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[89] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA

Biomarker Descriptions (continued)

granted fast track designation to the small molecule inhibitor, pidnarulex[94], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CDKN2A p.(D108H) c.322G>C

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. 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)[103]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[104,105,106]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[107]. 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[1,107,108]. CDKN2A aberrations commonly co-occur with CDKN2B[103]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[109]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[110,111].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[112]. 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[15,16]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% 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[15,16]. Alterations in CDKN2A are also observed in pediatric cancers[16]. 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 tumors[16]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[16].

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[24,113,114]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[115]. 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[116,117,118]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[119]. 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[120,121,122,123].

CIC p.(S1104T) c.3310T>A

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,22]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,22]. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5[22]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[22].

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[15,16]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[15,16]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[22,23].

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma[24,25].

Biomarker Descriptions (continued)

MSH6 p.(K1358Dfs*2) c.4068_4071dup

mutS homolog 6

Background: The MSH6 gene encodes the mutS homolog 6 protein[1]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[2]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[2]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication[2]. Mutations in MSH2 result in the degradation of MSH6[3]. MSH6, along with MLH1, MSH2, and PMS2, form the core components of the MMR pathway[2]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[2]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[4]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[5,6,7]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[5,8]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[6,8,9,10]. Specifically, MSH6 mutations are associated with an increased risk of ovarian and pancreatic cancer[11,12,13,14].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[15,16]. Alterations in MSH6 are observed in pediatric cancers[15,16]. Somatic mutations are observed in 9% of hepatobiliary cancer, 2% of T-lymphoblastic leukemia/lymphoma, 1% of B-lymphoblastic leukemia/lymphoma, and less than 1% of glioma (2 in 297 cases) and bone cancer (2 in 327 cases)[15,16].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[17]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[18,19]. MSH6 mutations are consistent with high grade in pediatric diffuse gliomas[20,21].

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[56]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[6,8]. 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[7]. 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[57]. 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)[57]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[9,58,59,60,61]. 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[8]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[6,8,9,10].

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[6,8,62,63]. 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[62,63].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[17] (2014) and nivolumab[18] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[17] 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[17]. Dostarlimab[64] (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[59,65]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[19] (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[59,66,67]. 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[67]. 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[68,69]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[68,69].

Biomarker Descriptions (continued)

NF1 p.(Q543*) c.1627C>T

neurofibromin 1

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[26]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[26,27]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[26]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[26,28,29].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[26]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[26,30]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[26,29].

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)[24].

TP53 p.(R342*) c.1024C>T

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[31]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[32]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[33,34].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[15,16,35,36,37,38]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[15,16]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[39,40,41,42]. Alterations in TP53 are also observed in pediatric cancers[15,16]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[15,16]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[15,16].

Potential relevance: The small molecule p53 reactivator, PC14586[43] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[44], (2019) and breakthrough designation[45] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[46,47]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[48]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[29,49,50,51,52,53]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[54]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[55].

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

BRCA2 deletion

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

CHEK2 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	*28.93%*
BRCA2	*CNV, CN:1.0*
BRCA2	*LOH, 13q13.1(32890491-32972932)x1*
CHEK2	*CNV, CN:1.0*
CHEK2	*LOH, 22q12.1(29083868-29130729)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 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 (6.1.1 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 and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from 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 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. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157

3. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482

4. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149

5. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756

6. 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

7. 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

8. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854

9. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460

10. 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

11. Bonadona et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun 8;305(22):2304-10. PMID: 21642682

12. Engel et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012 Dec 10;30(35):4409-15. PMID: 23091106

13. Grant et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015 Mar;148(3):556-64. PMID: 25479140

14. Hu et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018 Jun 19;319(23):2401-2409. PMID: 29922827

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. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf

18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf

19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf

20. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. Genes (Basel). 2022 Mar 31;13(4). PMID: 35456430

21. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875

22. Wong et al. Making heads or tails - the emergence of capicua (CIC) as an important multifunctional tumour suppressor. J Pathol. 2020 Apr;250(5):532-540. PMID: 32073140

23. Huang et al. Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations. Am J Surg Pathol. 2016 May;40(5):645-55. PMID: 26735859

24. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 5.2024]

25. NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2025]

26. Philpott et al. The NF1 somatic mutational landscape in sporadic human cancers. 2017 Jun 21;11(1):13. doi: 10.1186/s40246-017-0109-3. PMID: 28637487

27. Scheffzek et al. The Ras-RasGAP complex: structural basis for GTPase activation and its loss in oncogenic Ras mutants. Science. 1997 Jul 18;277(5324):333-8. PMID: 9219684

28. Fioretos et al. Isochromosome 17q in blast crisis of chronic myeloid leukemia and in other hematologic malignancies is the result of clustered breakpoints in 17p11 and is not associated with coding TP53 mutations. Blood. 1999 Jul 1;94(1):225-32. PMID: 10381517

29. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]

References (continued)

30. Brems et al. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol. 2009 May;10(5):508-15. PMID: 19410195

31. Nag et al. The MDM2-p53 pathway revisited. J Biomed Res. 2013 Jul;27(4):254-71. PMID: 23885265

32. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012

33. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1):a001008. PMID: 20182602

34. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529

35. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745

36. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445

37. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780

38. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061

39. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum. Mutat. 2002 Jun;19(6):607-14. PMID: 12007217

40. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. Genes Cancer. 2011 Apr;2(4):466-74. PMID: 21779514

41. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007 Apr 2;26(15):2157-65. PMID: 17401424

42. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. Hum. Mutat. 2014 Jun;35(6):766-78. PMID: 24729566

43. https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html

44. https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation

45. http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167

46. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534

47. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165

48. 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

49. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]

50. 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

51. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 1.2025]

52. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2025]

53. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 3.2024]

54. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]

55. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829

56. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011

57. 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

58. 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

References (continued)

59. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]

60. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785

61. 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

62. 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

63. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653

64. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf

65. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]

66. 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

67. 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

68. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522

69. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031

70. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. Breast Cancer Res. 2002;4(1):9-13. PMID: 11879553

71. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002 Dec 16;21(58):8981-93. PMID: 12483514

72. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416. PMID: 28632866

73. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J. Natl. Cancer Inst. 2007 Dec 5;99(23):1811-4. PMID: 18042939

74. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823

75. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis . JNCI Cancer Spectr. 2020 Aug;4(4):pkaa029. PMID: 32676552

76. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425

77. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clin. Proc. 2010 Dec;85(12):1111-20. PMID: 21123638

78. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. U.S.A. 2011 Nov 1;108(44):18032-7. PMID: 22006311

79. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J. Clin. Oncol. 2012 Jul 20;30(21):2654-63. PMID: 22711857

80. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol. Biomarkers Prev. 2004 Dec;13(12):2078-83. PMID: 15598764

81. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. PMID: 14576434

82. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br. J. Cancer. 2000 Nov;83(10):1301-8. PMID: 11044354

83. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen. 2022 Jul;63(6):308-316. PMID: 36054589

84. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br. J. Cancer. 2018 Nov;119(11):1401-1409. PMID: 30353044

85. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913-7. PMID: 15829966

86. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. PMID: 15829967

References (continued)

87. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf

88. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf

89. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf

90. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf

91. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf

92. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J. Pathol. 2013 Feb;229(3):422-9. PMID: 23165508

93. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437

94. https://www.senhwabio.com//en/news/20220125

95. https://ir.tangotx.com//news-releases/news-release-details/tango-therapeutics-reports-third-quarter-2023-financial-results

96. 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

97. 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

98. Zhang et al. Chk2 phosphorylation of BRCA1 regulates DNA double-strand break repair. Mol. Cell. Biol. 2004 Jan;24(2):708-18. PMID: 14701743

99. 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

100. Apostolou et al. Current perspectives on CHEK2 mutations in breast cancer. Breast Cancer (Dove Med Press). 2017;9:331-335. PMID: 28553140

101. Nevanlinna et al. The CHEK2 gene and inherited breast cancer susceptibility. Oncogene. 2006 Sep 25;25(43):5912-9. PMID: 16998506

102. 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

103. 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

104. 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

105. Roussel. The INK4 family of cell cycle inhibitors in cancer. Oncogene. 1999 Sep 20;18(38):5311-7. PMID: 10498883

106. 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

107. Hill et al. The genetics of melanoma: recent advances. Annu Rev Genomics Hum Genet. 2013;14:257-79. PMID: 23875803

108. Kim et al. The regulation of INK4/ARF in cancer and aging. Cell. 2006 Oct 20;127(2):265-75. PMID: 17055429

109. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. Mayo Clin. Proc. 2008 Jul;83(7):825-46. PMID: 18613999

110. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. J. Invest. Dermatol. 2007 May;127(5):1234-43. PMID: 17218939

111. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. Ann. Surg. 2002 Dec;236(6):730-7. PMID: 12454511

112. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. Clin Cancer Res. 2021 Jul 15;27(14):4025-4035. PMID: 34074656

113. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2025]

114. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2025]

115. 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

116. 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

117. 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

References (continued)

118. von et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmocological Inhibitors of the CDK4/6 Cell-Cycle Pathway. Cancer Res. 2015 Sep 15;75(18):3823-31. PMID: 26183925

119. 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

120. 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

121. 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

122. 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

123. 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