Samkwang Medical Lab

Patient Name:	유영삼	**Primary Tumor Site:**	Lung
Gender:	M	**Collection Date:**	20250623
Sample ID:	N25-77		

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

6 Relevant Biomarkers
17 Therapies Available
212 Clinical Trials

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	MET	None detected
BRAF	None detected	NRG1	None detected
EGFR	**EGFR p.(L858R) c.2573T>G**	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	ROS1	None detected
KRAS	None detected		

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	*EGFR p.(L858R) c.2573T>G* epidermal growth factor receptor Allele Frequency: 60.43% Locus: chr7:55259515 Transcript: NM_005228.5	**afatinib** [1, 2 / I, II+] **amivantamab + lazertinib** [1, 2 / I, II+] **bevacizumab† + erlotinib** [2 / I, II+] **dacomitinib** [1, 2 / I, II+] **erlotinib** [2 / I, II+] **erlotinib + ramucirumab** [1, 2 / I, II+] **gefitinib** [1, 2 / I, II+] **osimertinib** [1, 2 / I, II+] **osimertinib + chemotherapy** [1, 2 / I] **amivantamab + chemotherapy** [1, 2 / II+] **BAT1706 + erlotinib** [2] gefitinib + chemotherapy [I]	None*	200

* Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
† Includes biosimilars/generics
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
		atezolizumab + bevacizumab + chemotherapy [II+]		
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	8
IIC	*TP53 p.(R249S) c.747G>T* tumor protein p53 Allele Frequency: 45.95% Locus: chr17:7577534 Transcript: NM_000546.6	None*	None*	7
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	*ARID1A p.(A339Gfs*56) c.1016_1029delCTGCGGCGGCGGCA* AT-rich interaction domain 1A Allele Frequency: 9.25% Locus: chr1:27023909 Transcript: NM_006015.6	None*	None*	1
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1

* **Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
* **Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
† **Includes biosimilars/generics**
Line of therapy: I: First-line therapy, II+: Other line of therapy
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⚠ **Alerts informed by public data sources:** ⊘ Contraindicated, 🛡 Resistance, 🚀 Breakthrough, 🅰 Fast Track

EGFR p.(L858R) c.2573T>G	🚀 **patritumab deruxtecan** [1]

Public data sources included in alerts: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

*MAP2K4 deletion, Microsatellite stable, RIT1 amplification, NOTCH4 p.(L9Pfs*51) c.26_27delTG, NOTCH4 p.(L6Pfs*53) c.17_21delTGCTG, 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
EGFR	p.(L858R)	c.2573T>G	COSM6224	chr7:55259515	60.43%	NM_005228.5	missense
TP53	p.(R249S)	c.747G>T	COSM10817	chr17:7577534	45.95%	NM_000546.6	missense
ARID1A	p.(A339Gfs*56)	c.1016_1029delCTGCG .GCGGCGGCA		chr1:27023909	9.25%	NM_006015.6	frameshift Deletion

Disclaimer: The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. The data version is 2025.05(007).

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NOTCH4	p.(L9Pfs*51)	c.26_27delTG	.	chr6:32191678	98.06%	NM_004557.4	frameshift Deletion
NOTCH4	p.(L6Pfs*53)	c.17_21delTGCTG	.	chr6:32191684	1.41%	NM_004557.4	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.30%	NM_000903.3	missense
IGFN1	p.(A105T)	c.313G>A	.	chr1:201166391	7.85%	NM_001164586.2	missense
ADAMTS12	p.(Q813H)	c.2439G>C	.	chr5:33614431	43.77%	NM_030955.4	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGCGGCCGCAGCGGC	.	chr5:79950707	60.36%	NM_002439.5	nonframeshift Deletion
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	99.93%	NM_005514.8	missense, missense
ABCB1	p.(V908I)	c.2722G>A	.	chr7:87150156	32.42%	NM_000927.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	0.41	0.54
CDKN2A	chr9:21968178	0.1	0.45
CDKN2B	chr9:22005728	0.24	0.49
MAP2K4	chr17:11924164	0.52	0.57
RIT1	chr1:155870154	7.72	2.66

Biomarker Descriptions

EGFR p.(L858R) c.2573T>G

epidermal growth factor receptor

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR), a member of the ERBB/human epidermal growth factor receptor (HER) tyrosine kinase family[1]. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[70]. EGFR ligand-induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways, including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways[71]. Activation of these pathways promotes cell proliferation, differentiation, and survival[72,73].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[7,8,74,75]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[76]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer[76]. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[77,78,79,80]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[81]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain includes R108K, A289V and G598V and are primarily observed in glioblastoma[76,82]. Amplification of EGFR is observed in several cancer types including 44% of glioblastoma multiforme, 12% of esophageal adenocarcinoma, 10% of head and neck squamous cell carcinoma, 8% of brain lower grade glioma, 6% of lung squamous cell carcinoma, 5% of bladder urothelial carcinoma cancer, lung adenocarcinoma, and stomach adenocarcinoma, 3% of cholangiocarcinoma, and 2% of cervical squamous cell carcinoma, sarcoma, and breast invasive carcinoma[7,8,20,75,82]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of

Biomarker Descriptions (continued)

glioblastoma[83,84,85]. Alterations in EGFR are rare in pediatric cancers[7,8]. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)[7,8]. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)[7,8].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[86] (2004) and gefitinib[87] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations[88]. Second-generation TKIs afatinib[89] (2013) and dacomitinib[90] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies[91,92,93,94]. However, BDTX-189[95] was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutations. In 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)[96] and sunvozertinib[97], for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[98]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[76]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M[98]. Osimertinib[99] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases[98]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[100]. T790M and C797S can occur in either cis or trans allelic orientation[100]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[100]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[100,101]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[100]. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535[102] (2024), a CNS-penetrating small molecule inhibitor, that received fast track designation from the FDA for the treatment of patients with EGFR C797S-positive NSCLC who have disease progression on or after a third-generation EGFR TKI. EGFR-targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations[103]. The bispecific antibody, amivantamab[104] (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib[105] (2024), was approved in combination with amivantamab as a first-line treatment for adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations. In 2024, a CNS penetrating small molecule, ERAS-801[106] received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42[107], an anti-EFGR-antibody-drug conjugate (ADC) consisting of an anti-EGFR monoclonal antibody conjugated with a novel high potency DNA topoisomerase I (topo I) inhibitor, also received fast track designation (2024) for the treatment of patients with advanced or metastatic EGFR-mutated non-small cell lung cancer whose disease has progressed on a third-generation EGFR tyrosine kinase inhibitor. CPO301[108] (2023) received a fast track designation from the FDA for the treatment of EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors, including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid[109] (2020), in combination with osimertinib, received fast track designation from the FDA for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. Amplification and mutations of EGFR commonly occur in H3-wild type IDH-wild type diffuse pediatric high-grade glioma[110,111,112].

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[113,114]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[114].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[114,115]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma,

Biomarker Descriptions (continued)

stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[7,8]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[7,8].

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

TP53 p.(R249S) c.747G>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[15]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[16]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[17,18].

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%)[7,8,19,20,21,22]. 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[7,8]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[23,24,25,26]. Alterations in TP53 are also observed in pediatric cancers[7,8]. 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)[7,8]. 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)[7,8].

Potential relevance: The small molecule p53 reactivator, PC14586[27] (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[28], (2019) and breakthrough designation[29] (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[30,31]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[32]. 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)[33,34,35,36,37,38]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[39]. 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[40].

CDKN2A deletion

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)[122]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[123,124,125]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[126]. 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[1,126,127]. CDKN2A aberrations commonly co-occur with CDKN2B[122]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[128]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[129,130].

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[131]. 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[7,8]. 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

Biomarker Descriptions (continued)

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[7,8]. Alterations in CDKN2A are also observed in pediatric cancers[8]. 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[8]. 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)[8].

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[132,133,134]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[112]. 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[135,136,137]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[138]. 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[139,140,141,142].

ARID1A p.(A339Gfs*56) c.1016_1029delCTGCGGCGGCGGCA

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,116]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[116,117]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[117]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[117,118]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[116]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[116].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[118]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[116]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[7,8,117]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[119].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[120], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[121], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,122]. 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)[122]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[123,124,125]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[122]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,143,144].

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[7,8]. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma[7,8]. 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[7,8]. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)[7,8].

Biomarker Descriptions (continued)

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 astrocytoma[112].

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[9]. Activation of MAPK proteins occurs through a kinase signaling cascade[9,10,11]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[9,10,11]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[9,10,11]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[12].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[7,8]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[7,8]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[13,14].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[48]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[49,50]. 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[51]. 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[52]. 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)[52]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[53,54,55,56,57]. 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[50]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[49,50,54,58].

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[49,50,59,60]. 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[59,60].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[61] (2014) and nivolumab[62] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[61] 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[61]. Dostarlimab[63] (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[55,64]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[65] (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[55,66,67]. 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)

RIT1 amplification

Ras like without CAAX 1

Background: The RIT1 gene encodes the ras-like without CAAX1 protein[1]. RIT1 is a member of the Ras family, possessing intrinsic GTP hydrolysis activity[2]. Specifically, RIT1 is ubiquitously expressed and plays a role in neuron survival following oxidative stress and dendritic cell retraction[2,3,4]. RIT1 mutations have been shown to activate PI3K and MEK signaling pathways and likely promotes tumorigenesis[5]. Hereditary mutations in RIT1 lead to constitutive activation of RAS and MAPK pathways resulting in Noonan syndrome, a type of RASopathy[5,6].

Alterations and prevalence: Somatic mutations in RIT1 are observed in 3% of cholangiocarcinoma, 2% of uterine corpus endometrial carcinoma and lung adenocarcinoma, and 1% of cervical squamous cell carcinoma, skin cutaneous melanoma, and acute myeloid leukemia (AML)[7,8]. Amplifications in RIT1 are observed in 14% of uterine carcinosarcoma, 11% of liver hepatocellular and cholangiocarcinoma, 8% of lung adenocarcinoma, breast invasive carcinoma, uterine corpus endometrial carcinoma, and 6% of ovarian serous cystadenocarcinoma[7,8].

Potential relevance: Currently, no therapies are approved for RIT1 aberrations.

NOTCH4 p.(L9Pfs*51) c.26_27delTG, NOTCH4 p.(L6Pfs*53) c.17_21delTGCTG

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[41]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[42,43]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[44,45,46,47].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[7].

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

Alerts Informed By Public Data Sources

Current FDA Information

🚫 Contraindicated   ⊖ Not recommended   🛡 Resistance   🚀 Breakthrough   🇦 Fast Track

FDA information is current as of 2025-04-16. For the most up-to-date information, search www.fda.gov.

EGFR p.(L858R) c.2573T>G

🚀 **patritumab deruxtecan**

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation or EGFRi sensitizing mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to a potential first-in-class HER3 directed antibody-drug conjugate, patritumab deruxtecan, for metastatic or locally advanced, EGFR-mutant non-small cell lung cancer.

Reference:

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-status-to-patritumab-deruxtecan-for-egfr-metastatic-nsclc

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,

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Disclaimer: The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. The data version is 2025.05(007).

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, 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

EGFR p.(L858R) c.2573T>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	●	●	●	●	● (III)
afatinib	●	●	●	●	● (II)
dacomitinib	●	●	●	●	● (II)
gefitinib	●	●	●	●	● (II)
erlotinib + ramucirumab	●	●	●	●	✖
amivantamab + carboplatin + pemetrexed	●	●	●	✖	✖
amivantamab + lazertinib	●	●	●	✖	✖
osimertinib + chemotherapy + pemetrexed	●	✖	●	✖	✖
bevacizumab + erlotinib	✖	●	●	●	✖
erlotinib	✖	●	●	●	✖

* 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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib + carboplatin + pemetrexed	✖	●	✖	✖	✖
osimertinib + cisplatin + pemetrexed	✖	●	✖	✖	✖
BAT1706 + erlotinib	✖	✖	●	✖	✖
bevacizumab (Allergan) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Biocon) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Celltrion) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Mabxience) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Pfizer) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Samsung Bioepis) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Stada) + erlotinib	✖	✖	●	✖	✖
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
gefitinib + carboplatin + pemetrexed	✖	✖	✖	●	✖
adebrelimab, bevacizumab, chemotherapy	✖	✖	✖	✖	● (IV)
afatinib, bevacizumab, chemotherapy	✖	✖	✖	✖	● (IV)
befotertinib	✖	✖	✖	✖	● (IV)
bevacizumab, almonertinib, chemotherapy	✖	✖	✖	✖	● (IV)
catequentinib, toripalimab	✖	✖	✖	✖	● (IV)
EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (IV)
gefitinib, chemotherapy	✖	✖	✖	✖	● (IV)
gefitinib, endostatin	✖	✖	✖	✖	● (IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	✖	✖	✖	✖	● (IV)
almonertinib, apatinib	✖	✖	✖	✖	● (III)
almonertinib, catequentinib	✖	✖	✖	✖	● (III)
almonertinib, chemotherapy	✖	✖	✖	✖	● (III)
almonertinib, radiation therapy	✖	✖	✖	✖	● (III)
almonertinib, radiation therapy, chemotherapy	✖	✖	✖	✖	● (III)
befotertinib, icotinib hydrochloride	✖	✖	✖	✖	● (III)
bevacizumab, osimertinib	✖	✖	✖	✖	● (III)

* 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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BL-B01D1	✖	✖	✖	✖	● (III)
BL-B01D1, osimertinib	✖	✖	✖	✖	● (III)
CK-101, gefitinib	✖	✖	✖	✖	● (III)
datopotamab deruxtecan, osimertinib	✖	✖	✖	✖	● (III)
FHND9041, afatinib	✖	✖	✖	✖	● (III)
furmonertinib	✖	✖	✖	✖	● (III)
furmonertinib, osimertinib, chemotherapy	✖	✖	✖	✖	● (III)
gefitinib, afatinib, erlotinib, metformin hydrochloride	✖	✖	✖	✖	● (III)
icotinib hydrochloride, catequentinib	✖	✖	✖	✖	● (III)
icotinib hydrochloride, chemotherapy	✖	✖	✖	✖	● (III)
icotinib hydrochloride, radiation therapy	✖	✖	✖	✖	● (III)
JMT-101, osimertinib	✖	✖	✖	✖	● (III)
osimertinib, bevacizumab	✖	✖	✖	✖	● (III)
osimertinib, chemotherapy	✖	✖	✖	✖	● (III)
osimertinib, datopotamab deruxtecan	✖	✖	✖	✖	● (III)
sacituzumab tirumotecan	✖	✖	✖	✖	● (III)
sacituzumab tirumotecan, osimertinib	✖	✖	✖	✖	● (III)
savolitinib, osimertinib	✖	✖	✖	✖	● (III)
SH-1028	✖	✖	✖	✖	● (III)
targeted therapy	✖	✖	✖	✖	● (III)
TY-9591, osimertinib	✖	✖	✖	✖	● (III)
ABSK-043, furmonertinib	✖	✖	✖	✖	● (II)
almonertinib	✖	✖	✖	✖	● (II)
almonertinib, adebrelimab, chemotherapy	✖	✖	✖	✖	● (II)
almonertinib, bevacizumab	✖	✖	✖	✖	● (II)
almonertinib, chemoradiation therapy	✖	✖	✖	✖	● (II)
almonertinib, dacomitinib	✖	✖	✖	✖	● (II)
amivantamab, chemotherapy	✖	✖	✖	✖	● (II)
amivantamab, lazertinib, chemotherapy	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

⬤ In this cancer type   ◯ In other cancer type   ◑ In this cancer type and other cancer types   ✖ No evidence

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab, bevacizumab, tiragolumab	✖	✖	✖	✖	⬤ (II)
befotertinib, bevacizumab, chemotherapy	✖	✖	✖	✖	⬤ (II)
bevacizumab, afatinib	✖	✖	✖	✖	⬤ (II)
bevacizumab, furmonertinib	✖	✖	✖	✖	⬤ (II)
cadonilimab, chemotherapy, catequentinib	✖	✖	✖	✖	⬤ (II)
camrelizumab, apatinib	✖	✖	✖	✖	⬤ (II)
capmatinib, osimertinib, ramucirumab	✖	✖	✖	✖	⬤ (II)
catequentinib, almonertinib	✖	✖	✖	✖	⬤ (II)
chemotherapy, atezolizumab, bevacizumab	✖	✖	✖	✖	⬤ (II)
dacomitinib, osimertinib	✖	✖	✖	✖	⬤ (II)
EGFR tyrosine kinase inhibitor, osimertinib, chemotherapy	✖	✖	✖	✖	⬤ (II)
EGFR tyrosine kinase inhibitor, radiation therapy	✖	✖	✖	✖	⬤ (II)
erlotinib, chemotherapy	✖	✖	✖	✖	⬤ (II)
erlotinib, OBI-833	✖	✖	✖	✖	⬤ (II)
furmonertinib, bevacizumab	✖	✖	✖	✖	⬤ (II)
furmonertinib, bevacizumab, chemotherapy	✖	✖	✖	✖	⬤ (II)
furmonertinib, catequentinib	✖	✖	✖	✖	⬤ (II)
furmonertinib, chemotherapy	✖	✖	✖	✖	⬤ (II)
furmonertinib, chemotherapy, bevacizumab	✖	✖	✖	✖	⬤ (II)
furmonertinib, icotinib hydrochloride	✖	✖	✖	✖	⬤ (II)
gefitinib, bevacizumab, chemotherapy	✖	✖	✖	✖	⬤ (II)
gefitinib, icotinib hydrochloride	✖	✖	✖	✖	⬤ (II)
gefitinib, thalidomide	✖	✖	✖	✖	⬤ (II)
icotinib hydrochloride	✖	✖	✖	✖	⬤ (II)
icotinib hydrochloride, autologous RAK cell	✖	✖	✖	✖	⬤ (II)
icotinib hydrochloride, osimertinib	✖	✖	✖	✖	⬤ (II)
ivonescimab, chemotherapy	✖	✖	✖	✖	⬤ (II)
lazertinib	✖	✖	✖	✖	⬤ (II)
lazertinib, bevacizumab	✖	✖	✖	✖	⬤ (II)

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

Relevant Therapy Summary (continued)

⬤ In this cancer type   ◯ In other cancer type   ◑ In this cancer type and other cancer types   ✖ No evidence

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
lazertinib, chemotherapy	✖	✖	✖	✖	⬤ (II)
lenvatinib, pembrolizumab	✖	✖	✖	✖	⬤ (II)
osimertinib, bevacizumab, chemotherapy	✖	✖	✖	✖	⬤ (II)
osimertinib, chemoradiation therapy	✖	✖	✖	✖	⬤ (II)
osimertinib, radiation therapy	✖	✖	✖	✖	⬤ (II)
PLB-1004, bozitinib, osimertinib	✖	✖	✖	✖	⬤ (II)
ramucirumab, erlotinib	✖	✖	✖	✖	⬤ (II)
sacituzumab govitecan	✖	✖	✖	✖	⬤ (II)
sacituzumab tirumotecan, chemotherapy, osimertinib	✖	✖	✖	✖	⬤ (II)
sunvozertinib	✖	✖	✖	✖	⬤ (II)
sunvozertinib, catequentinib	✖	✖	✖	✖	⬤ (II)
sunvozertinib, golidocitinib	✖	✖	✖	✖	⬤ (II)
tislelizumab, chemotherapy, bevacizumab	✖	✖	✖	✖	⬤ (II)
toripalimab	✖	✖	✖	✖	⬤ (II)
toripalimab, bevacizumab, Clostridium butyricum, chemotherapy	✖	✖	✖	✖	⬤ (II)
toripalimab, chemotherapy	✖	✖	✖	✖	⬤ (II)
zorifertinib, pirotinib	✖	✖	✖	✖	⬤ (II)
AFM-24_I, atezolizumab	✖	✖	✖	✖	⬤ (I/II)
almonertinib, icotinib hydrochloride	✖	✖	✖	✖	⬤ (I/II)
BDTX-1535	✖	✖	✖	✖	⬤ (I/II)
BEBT-908, BEBT-109	✖	✖	✖	✖	⬤ (I/II)
benmelstobart, catequentinib	✖	✖	✖	✖	⬤ (I/II)
BH-30643	✖	✖	✖	✖	⬤ (I/II)
bozitinib, osimertinib	✖	✖	✖	✖	⬤ (I/II)
bozitinib, PLB-1004	✖	✖	✖	✖	⬤ (I/II)
BPI-361175	✖	✖	✖	✖	⬤ (I/II)
cetrelimab, amivantamab	✖	✖	✖	✖	⬤ (I/II)
dacomitinib, catequentinib	✖	✖	✖	✖	⬤ (I/II)
DAJH-1050766	✖	✖	✖	✖	⬤ (I/II)

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

Relevant Therapy Summary (continued)

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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
DB-1310, osimertinib	✖	✖	✖	✖	● (I/II)
dositinib	✖	✖	✖	✖	● (I/II)
FWD-1509	✖	✖	✖	✖	● (I/II)
H-002	✖	✖	✖	✖	● (I/II)
ifebemtinib, furmonertinib	✖	✖	✖	✖	● (I/II)
MRTX0902	✖	✖	✖	✖	● (I/II)
necitumumab, osimertinib	✖	✖	✖	✖	● (I/II)
quaratusugene ozeplasmid, osimertinib	✖	✖	✖	✖	● (I/II)
RC-108, furmonertinib, toripalimab	✖	✖	✖	✖	● (I/II)
sotiburafusp alfa, HB-0030	✖	✖	✖	✖	● (I/II)
sunvozertinib, chemotherapy	✖	✖	✖	✖	● (I/II)
TAS-3351	✖	✖	✖	✖	● (I/II)
TQ-B3525, osimertinib	✖	✖	✖	✖	● (I/II)
TRX-221	✖	✖	✖	✖	● (I/II)
WSD-0922	✖	✖	✖	✖	● (I/II)
afatinib, chemotherapy	✖	✖	✖	✖	● (I)
AZD-9592	✖	✖	✖	✖	● (I)
BG-60366	✖	✖	✖	✖	● (I)
BPI-1178, osimertinib	✖	✖	✖	✖	● (I)
catequentinib, gefitinib, metformin hydrochloride	✖	✖	✖	✖	● (I)
cemiplimab, sarilumab	✖	✖	✖	✖	● (I)
DZD-6008	✖	✖	✖	✖	● (I)
EGFR tyrosine kinase inhibitor, catequentinib	✖	✖	✖	✖	● (I)
genolimzumab, fruquintinib	✖	✖	✖	✖	● (I)
IBI-318, lenvatinib	✖	✖	✖	✖	● (I)
KQB-198, osimertinib	✖	✖	✖	✖	● (I)
LAVA-1223	✖	✖	✖	✖	● (I)
MRX-2843, osimertinib	✖	✖	✖	✖	● (I)
osimertinib, carotuximab	✖	✖	✖	✖	● (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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib, Minnelide	✖	✖	✖	✖	⬤ (I)
osimertinib, tegatrabetan	✖	✖	✖	✖	⬤ (I)
patritumab deruxtecan	✖	✖	✖	✖	⬤ (I)
repotrectinib, osimertinib	✖	✖	✖	✖	⬤ (I)
VIC-1911, osimertinib	✖	✖	✖	✖	⬤ (I)
WJ13404	✖	✖	✖	✖	⬤ (I)
WTS-004	✖	✖	✖	✖	⬤ (I)
YH-013	✖	✖	✖	✖	⬤ (I)
YL-202	✖	✖	✖	✖	⬤ (I)

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	⬤ (I/II)
MRTX-1719	✖	✖	✖	✖	⬤ (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	⬤ (I/II)
TNG-462	✖	✖	✖	✖	⬤ (I/II)
GTA-182	✖	✖	✖	✖	⬤ (I)
ISM-3412	✖	✖	✖	✖	⬤ (I)
S-095035	✖	✖	✖	✖	⬤ (I)
SYH-2039	✖	✖	✖	✖	⬤ (I)

TP53 p.(R249S) c.747G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
almonertinib, catequentinib	✖	✖	✖	✖	⬤ (III)
osimertinib, chemotherapy	✖	✖	✖	✖	⬤ (III)
osimertinib, bevacizumab, chemotherapy	✖	✖	✖	✖	⬤ (II)
sunvozertinib, catequentinib	✖	✖	✖	✖	⬤ (II)
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	⬤ (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

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)

ARID1A p.(A339Gfs*56) c.1016_1029delCTGCGGCGGCGGCA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✖	✖	✖	✖	● (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	*23.68%*
BRCA1	*LOH, 17q21.31(41197602-41276123)x4*
BRCA2	*LOH, 13q13.1(32890491-32972932)x2*
ATM	*LOH, 11q22.3(108098341-108236285)x2*
BRIP1	*LOH, 17q23.2(59760627-59938976)x4*
CDK12	*LOH, 17q12(37618286-37687611)x4*
CHEK1	*LOH, 11q24.2(125496639-125525271)x2*
FANCL	*LOH, 2p16.1(58386886-58468467)x3*
RAD51C	*LOH, 17q22(56769933-56811619)x4*

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 2025.05(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 2025-04-16. NCCN information was sourced from www.nccn.org and is current as of 2025-04-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-04-16. ESMO information was sourced from www.esmo.org and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. 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. Feng et al. RIT1 suppresses esophageal squamous cell carcinoma growth and metastasis and predicts good prognosis. Cell Death Dis. 2018 Oct 22;9(11):1085. PMID: 30348939

3. Andres et al. Rit signaling contributes to interferon-gamma-induced dendritic retraction via p38 mitogen-activated protein kinase activation. J Neurochem. 2008 Dec;107(5):1436-47. PMID: 18957053

4. Cai et al. Rit GTPase regulates a p38 MAPK-dependent neuronal survival pathway. Neurosci Lett. 2012 Dec 7;531(2):125-30. PMID: 23123784

5. Berger et al. Oncogenic RIT1 mutations in lung adenocarcinoma. Oncogene. 2014 Aug 28;33(35):4418-23. PMID: 24469055

6. Aoki et al. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. Am J Hum Genet. 2013 Jul 11;93(1):173-80. PMID: 23791108

7. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849

8. 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

9. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. Clin. Cancer Res. 2013 May 1;19(9):2301-9. PMID: 23406774

10. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. Int J Mol Sci. 2020 Feb 7;21(3). PMID: 32046099

11. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. Br J Pharmacol. 2014 Jan;171(1):24-37. PMID: 24117156

12. Ahn et al. Map2k4 functions as a tumor suppressor in lung adenocarcinoma and inhibits tumor cell invasion by decreasing peroxisome proliferator-activated receptor γ2 expression. Mol. Cell. Biol. 2011 Nov;31(21):4270-85. PMID: 21896780

13. Robinson et al. Mitogen-activated protein kinase kinase 4/c-Jun NH2-terminal kinase kinase 1 protein expression is subject to translational regulation in prostate cancer cell lines. Mol. Cancer Res. 2008 Mar;6(3):501-8. PMID: 18337456

14. Xue et al. MAP3K1 and MAP2K4 mutations are associated with sensitivity to MEK inhibitors in multiple cancer models. Cell Res. 2018 Jul;28(7):719-729. PMID: 29795445

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

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

17. 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

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

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

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

21. 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

22. 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

23. 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

24. 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

25. 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

26. 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

27. 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

References (continued)

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

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

30. 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

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

32. 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

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

34. 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

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

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

37. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 2.2025]

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

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

40. 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

41. Sakamoto et al. Distinct roles of EGF repeats for the Notch signaling system. Exp. Cell Res. 2005 Jan 15;302(2):281-91. PMID: 15561108

42. Bray. Notch signalling in context. Nat. Rev. Mol. Cell Biol. 2016 Nov;17(11):722-735. PMID: 27507209

43. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. Cell. 2009 Apr 17;137(2):216-33. PMID: 19379690

44. Lobry et al. Oncogenic and tumor suppressor functions of Notch in cancer: it's NOTCH what you think. J. Exp. Med. 2011 Sep 26;208(10):1931-5. PMID: 21948802

45. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. Nat Rev Urol. 2018 Jun;15(6):345-357. PMID: 29643502

46. Wang et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc. Natl. Acad. Sci. U.S.A. 2011 Oct 25;108(43):17761-6. PMID: 22006338

47. Xiu et al. The role of oncogenic Notch2 signaling in cancer: a novel therapeutic target. Am J Cancer Res. 2019;9(5):837-854. PMID: 31218097

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

49. 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

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

51. 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

52. 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

53. 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

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

55. NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2025]

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

57. 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

58. 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

References (continued)

59. 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

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

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

62. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125554s127lbl.pdf

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

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

65. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s132lbl.pdf

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. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6. PMID: 2992089

71. Liu et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. Mol Cancer. 2018 Feb 19;17(1):53. PMID: 29455669

72. Zhixiang. ErbB Receptors and Cancer. Methods Mol. Biol. 2017;1652:3-35. PMID: 28791631

73. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711

74. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. FEBS Lett. 2010 Jun 18;584(12):2699-706. PMID: 20388509

75. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552

76. da et al. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192

77. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol. Cancer Ther. 2013 Feb;12(2):220-9. PMID: 23371856

78. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. Clin Cancer Res. 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867

79. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med. 2013 Dec 18;5(216):216ra177. PMID: 24353160

80. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. J Thorac Oncol. 2015 May;10(5):793-9. PMID: 25668120

81. Karachaliou et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013 May;14(3):205-14. PMID: 23122493

82. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142

83. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. FEBS J. 2010 Jan;277(2):301-8. PMID: 19922469

84. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293

85. Gan et al. The EGFRvIII variant in glioblastoma multiforme. J Clin Neurosci. 2009 Jun;16(6):748-54. PMID: 19324552

86. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf

87. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf

88. Riely et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. Clin Cancer Res. 2006 Feb 1;12(3 Pt 1):839-44. PMID: 16467097

89. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf

90. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf

References (continued)

91. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2025]

92. Naidoo et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer. 2015 Sep 15;121(18):3212-3220. PMID: 26096453

93. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5. PMID: 30854234

94. Yi et al. A comparison of epidermal growth factor receptor mutation testing methods in different tissue types in non-small cell lung cancer. Int J Mol Med. 2014 Aug;34(2):464-74. PMID: 24891042

95. https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda

96. https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys

97. https://www.prnewswire.com/news-releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceuticals-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion-301469692.html

98. Madic et al. EGFR C797S, EGFR T790M and EGFR sensitizing mutations in non-small cell lung cancer revealed by six-color crystal digital PCR. Oncotarget. 2018 Dec 21;9(100):37393-37406. PMID: 30647840

99. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208065s033lbl.pdf

100. Niederst et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. Clin. Cancer Res. 2015 Sep 1;21(17):3924-33. PMID: 25964297

101. Wang et al. Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance. J Thorac Oncol. 2017 Nov;12(11):1723-1727. PMID: 28662863

102. https://investors.blackdiamondtherapeutics.com//news-releases/news-release-details/black-diamond-therapeutics-announces-corporate-update-and

103. Ciardiello et al. The role of anti-EGFR therapies in EGFR-TKI-resistant advanced non-small cell lung cancer. Cancer Treat Rev. 2024 Jan;122:102664. PMID: 38064878

104. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s007lbl.pdf

105. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000lbledt.pdf

106. https://investors.erasca.com//news-releases/news-release-details/erasca-granted-fda-fast-track-designation-cns-penetrant-egfr

107. https://iis.aastocks.com/20231227/11015917-0.PDF

108. http://iis.aastocks.com/20230612/10770455-0.PDF

109. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/

110. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 2.2025]

111. 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

112. 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

113. Harasawa et al. Chemotherapy targeting methylthioadenosine phosphorylase (MTAP) deficiency in adult T cell leukemia (ATL). Leukemia. 2002 Sep;16(9):1799-807. PMID: 12200696

114. Bertino et al. Targeting tumors that lack methylthioadenosine phosphorylase (MTAP) activity: current strategies. Cancer Biol Ther. 2011 Apr 1;11(7):627-32. PMID: 21301207

115. Katya et al. Cancer Dependencies: PRMT5 and MAT2A in MTAP/p16-Deleted Cancers. 10.1146/annurev-cancerbio-030419-033444

116. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. Cancer Discov. 2013 Jan;3(1):35-43. PMID: 23208470

117. Wilson et al. SWI/SNF nucleosome remodellers and cancer. Nat. Rev. Cancer. 2011 Jun 9;11(7):481-92. PMID: 21654818

118. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. Nat Commun. 8;14648. PMID: 28262751

119. Mehrvarz et al. ARID1A Mutation May Define an Immunologically Active Subgroup in Patients with Microsatellite Stable Colorectal Cancer. Clin Cancer Res. 2021 Mar 15;27(6):1663-1670. PMID: 33414133

120. https://nuvectis.com/press-release-view/?i=114174

References (continued)

121. https://www.morphosys.com/en/news/morphosys-receives-us-fda-fast-track-designation-tulmimetostat-endometrial-cancer

122. 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

123. 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

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

125. 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

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

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

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

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

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

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

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

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

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

135. 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

136. 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

137. 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

138. 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

139. 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

140. 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

141. 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

142. 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

143. 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

144. 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