![Samkwang Medical Lab logo](SML Samkwang Medical Lab)

삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Report Date: 27 Jun 2025   1 of 19

Patient Name: 서상원	**Primary Tumor Site:** Bronchus
Gender: M	**Collection Date:** 2025.06.04
Sample ID: N25-62	

Sample Cancer Type: Lung Cancer

Table of Contents

Report Highlights

3 Relevant Biomarkers
17 Therapies Available
200 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	*EGFR exon 19 deletion*	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	*2.85 Mut/Mb measured*

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EGFR exon 19 deletion* epidermal growth factor receptor Allele Frequency: 36.42% Locus: chr7:55242465 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] atezolizumab + bevacizumab + chemotherapy [II+]	None*	194

* **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
IIC	*CDK4 amplification* cyclin dependent kinase 4 Locus: chr12:58142242	None*	None*	6
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3

* **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.

⚠ **Alerts informed by public data sources:** ⊘ Contraindicated, 🛡 Resistance, 🚀 Breakthrough, 🅰 Fast Track

EGFR exon 19 deletion	🚀 **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

MAP2K7 deletion, MDM2 amplification, RAD52 p.(S346*) c.1037C>A, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, NOTCH1 deletion, STAT6 amplification, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
EGFR	p.(E746_A750del)	c.2236_2250delGAATT AAGAGAAGCA	COSM6225	chr7:55242465	36.42%	NM_005228.5	nonframeshift Deletion
RAD52	p.(S346*)	c.1037C>A	.	chr12:1023218	49.17%	NM_134424.4	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	54.50%	NM_000463.3	missense
APC	p.(L795V)	c.2383C>G	.	chr5:112173674	58.11%	NM_000038.6	missense
CSMD3	p.(L112V)	c.334C>G	.	chr8:114326867	4.81%	NM_198123.2	missense
CHEK2	p.(A247V)	c.740C>T	.	chr22:29107949	26.20%	NM_007194.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDK4	chr12:58142242	14.63	4.79
CDKN2A	chr9:21968178	0.42	0.52
MAP2K7	chr19:7968792	0.83	0.65
MDM2	chr12:69202958	20.15	6.44
HLA-A	chr6:29910229	0.33	0.5
NOTCH1	chr9:139390441	0.55	0.57
STAT6	chr12:57490294	5	1.9

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)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	2	0.79
PRDM9	chr5:23509577	0.7	0.61
TAP2	chr6:32796585	6.78	2.43
TAP1	chr6:32814849	6.28	2.28
POLE	chr12:133201214	5.18	1.96
SETBP1	chr18:42281265	0.77	0.63

Biomarker Descriptions

EGFR exon 19 deletion

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[18]. 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[19]. Activation of these pathways promotes cell proliferation, differentiation, and survival[20,21].

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[8,9,22,23]. 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[24]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer[24]. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[25,26,27,28]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[29]. 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[24,30]. 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[8,9,23,30,31]. 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 glioblastoma[32,33,34]. Alterations in EGFR are rare in pediatric cancers[8,9]. 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)[8,9]. 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)[8,9].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[35] (2004) and gefitinib[36] (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[37]. Second-generation TKIs afatinib[38] (2013) and dacomitinib[39] (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[40,41,42,43]. However, BDTX-189[44] 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)[45] and sunvozertinib[46], 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[47]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[24]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M[47]. Osimertinib[48] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer

Biomarker Descriptions (continued)

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[47]. 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[49]. T790M and C797S can occur in either cis or trans allelic orientation[49]. 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[49]. 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[49,50]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[49]. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535[51] (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[52]. The bispecific antibody, amivantamab[53] (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib[54] (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[55] received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42[56], 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[57] (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[58] (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[59,60,61].

CDK4 amplification

cyclin dependent kinase 4

Background: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[97,98]. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[99]. Germline mutations in CDK4 are associated with familial melanoma[100,101,102].

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A[103,104,105]. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)[8,9,23,30].

Potential relevance: Currently, no therapies are approved for CDK4 aberrations. Amplification of region 12q14-15, which includes CDK4, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/welldifferentiated liposarcoma (ALT/WDLS)[17]. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015), abemaciclib (2017), and ribociclib (2017), are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

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)[77]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[78,79,80]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[81]. 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[1,81,82]. CDKN2A aberrations commonly co-occur with CDKN2B[77]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[83]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[84,85].

Biomarker Descriptions (continued)

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[86]. 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[8,9]. 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[8,9]. Alterations in CDKN2A are also observed in pediatric cancers[9]. 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[9]. 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)[9].

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[17,87,88]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[61]. 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[89,90,91]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[92]. 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[93,94,95,96].

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7[1]. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10[62,63,64]. Activation of MAPK proteins occurs through a kinase signaling cascade[62,63,65]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[62,63,65]. 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[62,63,65].

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma[8,9]. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma[8,9].

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING domain[12]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[12]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[13]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[13]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[13].

Alterations and prevalence: MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma[8,9]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[14]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[15,16].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[17].

Biomarker Descriptions (continued)

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

RAD52 homolog, DNA repair protein

Background: The RAD52 gene encodes the RAD52 homolog, DNA repair protein[1]. RAD52 binds to single- and double-stranded DNA and enables strand exchange for double-strand break (DSB) repair by binding to RAD51[10]. RAD52 also promotes DSB repair through homologous recombination repair (HRR) by recruiting BRCA1 to sites of DSBs, which leads to the removal of TP53BP1 and prevents DSB repair by non-homologous end joining (NHEJ)[11].

Alterations and prevalence: Somatic mutations in RAD52 are observed in 2% of uterine corpus endometrial carcinoma, uterine carcinosarcoma, and skin cutaneous melanoma[8,9].

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

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,106]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[106,107]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[108]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[108,109,110,111]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[112].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[2]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[3]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[4,5,6]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[7].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[8,9]. Biallelic loss of HLA-A is observed in 4% of DLBCL[8,9].

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

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. 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[66]. 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[67,68]. In cancer, depending on the tumor type,

---

Biomarker Descriptions (continued)

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[69,70,71,72].

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers[8,9,31]. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia[73,74].

Potential relevance: Currently, no therapies are approved for NOTCH1 aberrations.

STAT6 amplification

signal transducer and activator of transcription 6

Background: The STAT6 gene encodes the signal transducer and activator of transcription 6. STAT6, a transcription factor, is a member of a highly conserved signal transducer and activator of transcription (STAT) family which also includes STAT1-4, STAT5A, and STAT5B[75]. Inactive STAT transcription factors in the cytoplasm are activated by tyrosine phosphorylation, resulting in STAT dimerization and nuclear translocation[75]. Following translocation to the nucleus, STAT dimers interact with specific enhancers and promote transcriptional initiation of target genes[75]. Specifically, STAT6 activation is facilitated by IL-3 or IL-13 mediated cytokine receptor stimulation resulting in Th2 mediated immune responses, eosinophil recruitment during allergic inflammation, and immunoglobulin class switching to IgE[76]. Abnormal STAT6 activation contributes to oncogenesis by increasing the expression of proteins involved in proliferation, migration, and invasion, supporting an oncogenic role for STAT6[76].

Alterations and prevalence: Amplifications in STAT6 are observed in 3% of sarcoma and 2% of lung adenocarcinoma and cholangiocarcinoma[8,9]. Somatic mutations in STAT6 are observed in 9% of diffuse large B-cell lymphoma (DLBCL), 5% of uterine cancer, and 4% of melanoma[8,9].

Potential relevance: Currently, no therapies are approved for STAT6 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 exon 19 deletion

🚀 **patritumab deruxtecan**

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion 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,

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 exon 19 deletion

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 exon 19 deletion (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, chemotherapy	✖	✖	✖	✖	● (III)
almonertinib, radiation therapy	✖	✖	✖	✖	● (III)
almonertinib, radiation therapy, chemotherapy	✖	✖	✖	✖	● (III)
befotertinib, icotinib hydrochloride	✖	✖	✖	✖	● (III)
bevacizumab, osimertinib	✖	✖	✖	✖	● (III)
BL-B01D1	✖	✖	✖	✖	● (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 exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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)
atezolizumab, bevacizumab, tiragolumab	✖	✖	✖	✖	⬤ (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 exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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, 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)
lazertinib, chemotherapy	✖	✖	✖	✖	● (II)
lenvatinib, pembrolizumab	✖	✖	✖	✖	● (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 exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib, chemoradiation therapy	✖	✖	✖	✖	● (II)
osimertinib, dalpiciclib	✖	✖	✖	✖	● (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)
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)
DB-1310, osimertinib	✖	✖	✖	✖	● (I/II)
dositinib	✖	✖	✖	✖	● (I/II)
FWD-1509	✖	✖	✖	✖	● (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 exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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)
alisertib, osimertinib	✖	✖	✖	✖	⬤ (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)
osimertinib, Minnelide	✖	✖	✖	✖	⬤ (I)
osimertinib, tegatrabetan	✖	✖	✖	✖	⬤ (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 exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
patritumab deruxtecan	✖	✖	✖	✖	⬤ (I)
PB-101 (Precision Biotech Taiwan Corp), EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	⬤ (I)
repotrectinib, osimertinib	✖	✖	✖	✖	⬤ (I)
VIC-1911, osimertinib	✖	✖	✖	✖	⬤ (I)
WJ13404	✖	✖	✖	✖	⬤ (I)
WTS-004	✖	✖	✖	✖	⬤ (I)
YH-013	✖	✖	✖	✖	⬤ (I)
YL-202	✖	✖	✖	✖	⬤ (I)

CDK4 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	⬤ (II)
osimertinib, dalpiciclib	✖	✖	✖	✖	⬤ (II)
palbociclib	✖	✖	✖	✖	⬤ (II)
palbociclib, abemaciclib	✖	✖	✖	✖	⬤ (II)
PF-07220060, midazolam	✖	✖	✖	✖	⬤ (I/II)

CDKN2A deletion

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

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

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. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087

3. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. Annu Rev Immunol. 2013;31:529-61. PMID: 23298204

4. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333

5. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024

6. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710

7. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. Cancers (Basel). 2020 Jul 2;12(7). PMID: 32630675

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

9. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877

10. Jalan et al. Emerging Roles of RAD52 in Genome Maintenance. Cancers (Basel). 2019 Jul 23;11(7). PMID: 31340507

11. Yasuhara et al. Human Rad52 Promotes XPG-Mediated R-loop Processing to Initiate Transcription-Associated Homologous Recombination Repair. Cell. 2018 Oct 4;175(2):558-570.e11. PMID: 30245011

12. Toledo et al. MDM2 and MDM4: p53 regulators as targets in anticancer therapy. Int. J. Biochem. Cell Biol. 2007;39(7-8):1476-82. PMID: 17499002

13. Zhao et al. The regulation of MDM2 oncogene and its impact on human cancers. Acta Biochim. Biophys. Sin. (Shanghai). 2014 Mar;46(3):180-9. PMID: 24389645

14. Helei et al. The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. Cancer Cell International volume 19, Article number: 216 (2019). PMID: 31440117

15. Dembla et al. Prevalence of MDM2 amplification and coalterations in 523 advanced cancer patients in the MD Anderson phase 1 clinic. Oncotarget. 2018 Sep 4;9(69):33232-33243. PMID: 30237864

16. Momand et al. The MDM2 gene amplification database. Nucleic Acids Res. 1998 Aug 1;26(15):3453-9. PMID: 9671804

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

18. 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

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

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

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

22. 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

23. 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

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

25. 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

26. 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

27. 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

28. 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

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

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

References (continued)

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

32. 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

33. 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

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

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

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

37. 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

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

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

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

41. 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

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

43. 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

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

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

46. 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

47. 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

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

49. 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

50. 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

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

52. 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

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

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

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

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

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

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

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

60. 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

61. 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

References (continued)

62. 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

63. 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

64. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiol Mol Biol Rev. 2011 Mar;75(1):50-83. PMID: 21372320

65. 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

66. 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

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

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

69. 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

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

71. 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

72. 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

73. Weng et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science. 2004 Oct 8;306(5694):269-71. PMID: 15472075

74. Breit et al. Activating NOTCH1 mutations predict favorable early treatment response and long-term outcome in childhood precursor T-cell lymphoblastic leukemia. Blood. 2006 Aug 15;108(4):1151-7. PMID: 16614245

75. Kamran et al. Role of STAT3 in cancer metastasis and translational advances. Biomed Res Int. 2013;2013:421821. PMID: 24199193

76. Delgado-Ramirez et al. Signal transducer and activator of transcription 6 as a target in colon cancer therapy. Oncol Lett. 2020 Jul;20(1):455-464. PMID: 32565970

77. 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

78. 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

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

80. 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

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

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

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

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

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

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

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

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

89. 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

90. 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)

91. 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

92. 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

93. 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

94. 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

95. 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

96. 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

97. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148

98. Sherr et al. Targeting CDK4 and CDK6: From Discovery to Therapy. Cancer Discov. 2016 Apr;6(4):353-67. PMID: 26658964

99. Weinberg. The retinoblastoma protein and cell cycle control. Cell. 1995 May 5;81(3):323-30. PMID: 7736585

100. Rane et al. Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. Mol. Cell. Biol. 2002 Jan;22(2):644-56. PMID: 11756559

101. Zuo et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat. Genet. 1996 Jan;12(1):97-9. PMID: 8528263

102. Molven et al. A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. Genes Chromosomes Cancer. 2005 Sep;44(1):10-8. PMID: 15880589

103. Ceha et al. Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein. Biochem. Biophys. Res. Commun. 1998 Aug 19;249(2):550-5. PMID: 9712735

104. Tsao et al. Novel mutations in the p16/CDKN2A binding region of the cyclin-dependent kinase-4 gene. Cancer Res. 1998 Jan 1;58(1):109-13. PMID: 9426066

105. Sotillo et al. Invasive melanoma in Cdk4-targeted mice. Proc. Natl. Acad. Sci. U.S.A. 2001 Nov 6;98(23):13312-7. PMID: 11606789

106. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. Front Cell Neurosci. 2014;8:349. PMID: 25389387

107. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. Oncogene. 2006 Mar 13;25(11):1659-72. PMID: 16550166

108. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. Br J Cancer. 2020 Apr;122(9):1277-1287. PMID: 32047295

109. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. Mol Carcinog. 2014 Apr;53(4):314-24. PMID: 23143693

110. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. Oncotarget. 2017 Jan 10;8(2):3640-3648. PMID: 27690298

111. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. PLoS One. 2015;10(5):e0127524. PMID: 26010150

112. Karas et al. JCO Oncol Pract. 2021 Dec 3:OP2100624. PMID: 34860573