

Patient Name: 이창철
Gender: M
Sample ID: N25-144

Primary Tumor Site: Lung
Collection Date: 2025.07.21

Sample Cancer Type: Lung Cancer

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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	3.79 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: 23.94% 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*	195

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², 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	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	MTAP deletion methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	9
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: FDA¹, NCCN, EMA², 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: FDA¹, NCCN, EMA², ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
APC p.(K1165Nfs*17) c.3495delA, MAP2K7 deletion, MDM2 amplification, Microsatellite stable, PPP2R2A deletion, SMAD4 p.(I383R) c.1148T>G, NOTCH1 deletion, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
EGFR	p.(E746_A750del)	c.2236_2250delGAATT AAGAGAAGCA	COSM6225	chr7:55242465	23.94%	NM_005228.5	nonframeshift Deletion
APC	p.(K1165Nfs*17)	c.3495delA	.	chr5:112174782	33.26%	NM_000038.6	frameshift Deletion
SMAD4	p.(I383R)	c.1148T>G	.	chr18:48593397	31.89%	NM_005359.6	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.07%	NM_000903.3	missense
HLA-B	p.(E176T)	c.526_527delGAinsAC	.	chr6:31324036	6.49%	NM_005514.8	missense
CDKN2A	p.(R128W)	c.382C>T	.	chr9:21970976	5.56%	NM_001195132.2	missense

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.84
MTAP	chr9:21802646	0.16	0.59

Variant Details (continued)

Copy Number Variations (continued)			
Gene	Locus	Copy Number	CNV Ratio
CDK4	chr12:58142242	8.25	2.37
CDKN2A	chr9:21968178	0	0.46
MAP2K7	chr19:7968792	0.07	0.58
MDM2	chr12:69202958	14.52	3.75
PPP2R2A	chr8:26149298	0.32	0.63
NOTCH1	chr9:139390441	0.23	0.61
SETBP1	chr18:42281265	0.3	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 family⁵⁰. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4⁵¹. 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 pathways⁵². Activation of these pathways promotes cell proliferation, differentiation, and survival^{53,54}.

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^{6,7,55,56}. 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 21⁵⁷. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer⁵⁷. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{58,59,60,61}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations⁶². 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^{57,63}. 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^{6,7,56,63,64}. 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^{65,66,67}. Alterations in EGFR are rare in pediatric cancers^{6,7}. 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)^{6,7}. 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)^{6,7}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib⁶⁸ (2004) and gefitinib⁶⁹ (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 mutations⁷⁰. Second-generation TKIs afatinib⁷¹ (2013) and dacomitinib⁷² (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^{73,74,75,76}. However, BDTX-189⁷⁷ 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)⁷⁸ and sunvozertinib⁷⁹, 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 resistance⁸⁰. The primary resistance mutation that emerges following treatment with first-

Biomarker Descriptions (continued)

generation TKI is T790M, accounting for 50-60% of resistant cases⁵⁷. Third generation TKIs were developed to maintain sensitivity in the presence of T790M⁸⁰. Osimertinib⁸¹ (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 cases⁸⁰. 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 versa⁸². T790M and C797S can occur in either cis or trans allelic orientation⁸². 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 TKIs⁸². 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^{82,83}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs⁸². Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535⁸⁴ (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 mutations⁸⁵. The bispecific antibody, amivantamab⁸⁶ (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib⁸⁷ (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-801⁸⁸ received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42⁸⁹, an anti-EGFR-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. CPO301⁹⁰ (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 ozeplasmid⁹¹ (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^{92,93,94}.

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{99,100}. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{99,100}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{101,102,103}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{101,104}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{105,106,107,108,109,110,111,112}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme^{6,7}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)¹¹³. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{114,115}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib¹¹⁶ (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib¹¹⁶ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib¹¹⁷ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib¹¹⁸ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib¹¹⁸ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib¹¹⁹ (2017) is another PARPi approved for the treatment of

Biomarker Descriptions (continued)

epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate¹²⁰ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported¹²¹. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality¹²². In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex²⁰, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348¹²³, a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase⁵⁰. 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^{131,132}. 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 deprivation¹³².

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^{132,133}. 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, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma^{6,7}. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma^{6,7}.

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

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^{163,164}. 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 progression¹⁶⁵. Germline mutations in CDK4 are associated with familial melanoma^{166,167,168}.

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^{169,170,171}. 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%)^{6,7,56,63}.

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/well-differentiated liposarcoma (ALT/WDLS)²⁷. 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 progression⁵⁰. 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)¹⁴³. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{144,145,146}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions¹⁴⁷. 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

Biomarker Descriptions (continued)

its degradation^{50,147,148}. CDKN2A aberrations commonly co-occur with CDKN2B¹⁴³. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation¹⁴⁹. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{150,151}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations¹⁵². 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^{6,7}. 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^{6,7}. Alterations in CDKN2A are also observed in pediatric cancers⁶. 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 tumors⁶. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)⁶.

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^{27,153,154}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma⁹⁴. 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^{155,156,157}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme¹⁵⁸. 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^{159,160,161,162}.

APC p.(K1165Nfs*17) c.3495delA

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β -catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation¹²⁴. APC is an antagonist of WNT signaling as it targets β -catenin for proteasomal degradation^{125,126}. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine^{124,127}. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer¹²⁸.

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma^{6,7,8}. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation^{129,130}.

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

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7⁵⁰. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10^{95,96,97}. Activation of MAPK proteins occurs through a kinase signaling cascade^{95,96,98}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{95,96,98}. 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^{95,96,98}.

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^{6,7}. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma^{6,7}.

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

Biomarker Descriptions (continued)

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 domain²². 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 domains²². 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 levels²³. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53²³. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2²³.

Alterations and prevalence: MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma^{6,7}. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers²⁴. The most common co-occurring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation^{25,26}.

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 liposarcoma²⁷.

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 genome²⁸. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{29,30}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2³¹. 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 D17S250³². 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)³². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{33,34,35,36,37}. 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 genes³⁰. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{29,30,34,38}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endometrial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{29,30,39,40}. 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^{39,40}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁴¹ (2014) and nivolumab⁴² (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁴¹ 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 indication⁴¹. Dostarlimab⁴³ (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^{35,44}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁴⁵ (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^{35,46,47}. 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 patients⁴⁷. 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^{48,49}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{48,49}.

PPP2R2A deletion

protein phosphatase 2 regulatory subunit B alpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)^{15,16}. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-

Biomarker Descriptions (continued)

apoptotic activity through negative regulation of the PI3K/AKT pathway¹⁷. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway¹⁵.

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer^{15,16,18,19}. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma⁷.

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex²⁰, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib¹⁵. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit²¹.

SMAD4 p.(I383R) c.1148T>G

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7^{1,2}. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF- β and BMP signaling pathways that are implicated in cancer initiation and progression^{2,3,4}. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC^{1,2}.

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)¹. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF- β signaling^{4,5,6}. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers^{6,7,8}.

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers^{2,4,9,10,11}. Importantly, SMAD4 is a predictive biomarker for fluorouracil based chemotherapy^{12,13}. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)¹³. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors¹⁴.

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 signaling¹³⁴. 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^{135,136}. 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^{137,138,139,140}.

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^{6,7,64}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{141,142}.

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-05-14. 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-nsccl>

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, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBF1, 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, ERFFI1, 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, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBF2,

Genes Assayed (continued)

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

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

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSP02, RSP03, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBF3, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERFF1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

Relevant Therapy Summary

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

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	✕	✕	✕	●	✕
adebreliumab, 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)
SCTB-14, chemotherapy	✕	✕	✕	✕	● (II/III)
ABSK-043, furmonertinib	✕	✕	✕	✕	● (II)
almonertinib	✕	✕	✕	✕	● (II)
almonertinib, adbrelimab, 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 exon 19 deletion (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 exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
lazertinib, chemotherapy	✕	✕	✕	✕	● (II)
lenvatinib, pembrolizumab	✕	✕	✕	✕	● (II)
osimertinib, chemoradiation therapy	✕	✕	✕	✕	● (II)
osimertinib, daltapiciclib	✕	✕	✕	✕	● (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)
TY-9591, chemotherapy	✕	✕	✕	✕	● (II)
zorifertinib, pirotinib	✕	✕	✕	✕	● (II)
AFM-24_I, atezolizumab	✕	✕	✕	✕	● (I/II)
almonertinib, icotinib hydrochloride	✕	✕	✕	✕	● (I/II)
benmelstobart, catequentinib	✕	✕	✕	✕	● (I/II)
BH-30643	✕	✕	✕	✕	● (I/II)
bozitinib, osimertinib	✕	✕	✕	✕	● (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)

* 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*
FWD-1509	✕	✕	✕	✕	● (I/II)
H-002	✕	✕	✕	✕	● (I/II)
ifebemt看inib, 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)
almonertinib, midazolam	✕	✕	✕	✕	● (I)
ASKC-202	✕	✕	✕	✕	● (I)
AZD-9592	✕	✕	✕	✕	● (I)
BG-60366	✕	✕	✕	✕	● (I)
BPI-1178, osimertinib	✕	✕	✕	✕	● (I)
catequentinib, gefitinib, metformin hydrochloride	✕	✕	✕	✕	● (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
 ① In this cancer type and other cancer types
 ✕ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib, Minnelide	✕	✕	✕	✕	● (I)
osimertinib, tegatrabetan	✕	✕	✕	✕	● (I)
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)

BRCA2 deletion

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✕	✕	✕	✕	● (I/II)
TNG-456, abemaciclib	✕	✕	✕	✕	● (I/II)
TNG-462	✕	✕	✕	✕	● (I/II)
GTA-182	✕	✕	✕	✕	● (I)
ISM-3412	✕	✕	✕	✕	● (I)
MRTX-1719	✕	✕	✕	✕	● (I)
PH020-803	✕	✕	✕	✕	● (I)
S-095035	✕	✕	✕	✕	● (I)
SYH-2039	✕	✕	✕	✕	● (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

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.

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	32.2%
BRCA2	CNV, CN:1.0
BRCA2	LOH, 13q13.1(32890491-32972932)x1

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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