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Report Date: 27 Jun 2025 1 of 24

Patient Name: 장은애 Gender: F Sample ID: N25-59 Primary Tumor Site: Lung
Collection Date: 2025.06.10

Sample Cancer Type: Lung Cancer

Table of Contents	Page
Variant Details	2
Biomarker Descriptions	3
Alert Details	10
Relevant Therapy Summary	11

Report Highlights 5 Relevant Biomarkers 17 Therapies Available 203 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 Alt	teration	Finding			
Tumor Mu	utational Burden	5.7 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: 30.01% Locus: chr7:55242464 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*	198

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

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

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

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

[†] Includes biosimilars/generics

2 of 24

Report Date: 27 Jun 2025

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	TP53 p.(H115Qfs*34) c.344_345insA tumor protein p53 Allele Frequency: 44.16% Locus: chr17:7579342 Transcript: NM_000546.6	None*	None*	6
IIC	MYC amplification MYC proto-oncogene, bHLH transcription factor Locus: chr8:128748847	None*	None*	4
IIC	PTEN p.(E114*) c.340G>T phosphatase and tensin homolog Allele Frequency: 37.86% Locus: chr10:89692856 Transcript: NM_000314.8	None*	None*	2
IIC	RB1 deletion RB transcriptional corepressor 1 Locus: chr13:48877953	None*	None*	1

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

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

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

🛕 Alerts informed by public data sources: 🤣 Contraindicated, 🛡 Resistance, 🧳 Breakthrough, 🔼 Fast Track

EGFR exon 19 deletion

Public data sources included in alerts: FDA1, NCCN, EMA2, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

MLH1 p.(V384D) c.1151T>A, MSH6 p.(K1358Dfs*2) c.4068_4071dup, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, RAC1 amplification, FAM135B amplification, NQO1 p.(P187S) c.559C>T, ZFHX3 p.(Q3197Sfs*45) c.9588_9589insAG, Tumor Mutational Burden

Variant Details

DNA Sequence Variants Allele Gene **Amino Acid Change** Coding Variant ID Locus Frequency Transcript **Variant Effect** c.2235_2249delGGAAT COSM6223 30.01% **FGFR** p.(E746_A750del) chr7:55242464 NM 005228.5 nonframeshift TAAGAGAAGC Deletion TP53 p.(H115Qfs*34) c.344_345insA chr17:7579342 44.16% NM_000546.6 frameshift Insertion **PTEN** c.340G>T chr10:89692856 37.86% NM_000314.8 p.(E114*) nonsense MLH1 p.(V384D) c.1151T>A chr3:37067240 70.07% NM_000249.4 missense MSH6 p.(K1358Dfs*2) c.4068_4071dup chr2:48033981 41.57% NM_000179.3 frameshift Insertion UGT1A1 p.(G71R) c.211G>A COSM4415616 chr2:234669144 50.10% NM_000463.3 missense

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

[†] Includes biosimilars/generics

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NQ01	p.(P187S)	c.559C>T		chr16:69745145	30.52%	NM_000903.3	missense
ZFHX3	p.(Q3197Sfs*45)	c.9588_9589insAG		chr16:72822586	7.88%	NM_006885.4	frameshift Insertion
NSUN7	p.(V619M)	c.1855G>A		chr4:40810654	51.96%	NM_024677.6	missense
HLA-B	p.([G231=;F232L])	c.693_694delTTinsCC		chr6:31323295	2.63%	NM_005514.8	synonymous, missense
HLA-B	p.(?)	c.72_73+1delinsTGT		chr6:31324862	3.81%	NM_005514.8	unknown
STAG2	p.(R146Q)	c.437G>A		chrX:123176470	28.49%	NM_001042749.2	missense

Copy Numbe	er Variations			
Gene	Locus	Copy Number	CNV Ratio	
MYC	chr8:128748847	5.63	2.01	
RB1	chr13:48877953	0.55	0.59	
HLA-A	chr6:29910229	0.5	0.58	
RAC1	chr7:6426823	9.96	3.23	
FAM135B	chr8:139144776	5.45	1.97	
BRCA2	chr13:32890491	3	1.35	
PMS2	chr7:6012922	7.11	2.43	
RECQL4	chr8:145736758	9.98	3.24	

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 family¹. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4¹08. 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 pathways¹09. Activation of these pathways promotes cell proliferation, differentiation, and survival¹¹10,¹111.

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 15,16,112,113. 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 21¹¹⁴. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer 114. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{115,116,117,118}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations 119. 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 114,120. 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 15,16,71,113,120. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRVIII), results in overexpression of a ligand-independent constitutively active

Biomarker Descriptions (continued)

protein and is observed in approximately 30% of glioblastoma^{121,122,123}. Alterations in EGFR are rare in pediatric cancers^{15,16}. 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)^{15,16}. 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)^{15,16}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib124 (2004) and gefitinib125 (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 mutations¹²⁶. Second-generation TKIs afatinib¹²⁷ (2013) and dacomitinib¹²⁸ (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^{129,130,131,132}. However, BDTX-189¹³³ 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)¹³⁴ and sunvozertinib¹³⁵, 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 resistance¹³⁶. The primary resistance mutation that emerges following treatment with firstgeneration TKI is T790M, accounting for 50-60% of resistant cases¹¹⁴. Third generation TKIs were developed to maintain sensitivity in the presence of T790M¹³⁶. Osimertinib¹³⁷ (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 firstgeneration TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases¹³⁶. 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 versa¹³⁸. T790M and C797S can occur in either cis or trans allelic orientation¹³⁸. 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 TKIs138. 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 138,139. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs¹³⁸. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535140 (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 mutations¹⁴¹. The bispecific antibody, amivantamab¹⁴² (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib¹⁴³ (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-801144 received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42145, 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. CPO301146 (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 guaratusugene ozeplasmid¹⁴⁷ (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^{20,148,149}.

TP53 p.(H115Qfs*34) c.344_345insA

tumor protein p53

<u>Background</u>: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair¹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis⁶⁶. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential⁶⁷. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{68,69}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{15,16,70,71,72,73}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282^{15,16}. Invariably, recurrent missense

Biomarker Descriptions (continued)

mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{74,75,76,77}. Alterations in TP53 are also observed in pediatric cancers^{15,16}. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases) ^{15,16}. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases) ^{15,16}.

Potential relevance: The small molecule p53 reactivator, PC14586⁷⁸ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt⁷⁹, (2019) and breakthrough designation⁸⁰ (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{81,82}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma⁸³. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{46,84,85,86,87,88}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁴¹. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system⁸⁹.

MYC amplification

MYC proto-oncogene, bHLH transcription factor

Background: The MYC gene encodes the MYC proto-oncogene, bHLH transcription factor (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation^{31,32,33,34}. MYC is part of the MYC oncogene family, which includes the related transcription factors, MYCN and MYCL, and regulates transcription in 10-15% of promoter regions³⁵. MYC functions as a heterodimer in complex with the transcription factor MAX^{32,36}.

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including those at codon T58, are infrequent and hypothesized to increase the stability of the MYC protein^{37,38}. Amplification of the MYC gene is observed in 15-30% of ovarian serous cystadenocarcinoma, esophageal adenocarcinoma, uterine carcinosarcoma, and breast invasive carcinoma, 10-15% of pancreatic adenocarcinoma, stomach adenocarcinoma, and liver hepatocellular carcinoma, 5-10% of head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, prostate adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, and 2-5% of skin cutaneous melanoma, brain lower grade glioma, sarcoma, cervical squamous cell carcinoma, uveal melanoma, diffuse B-cell lymphoma, glioblastoma, and kidney chromophobe^{15,16}. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, resulting in increased MYC expression^{39,40}. Overall, MYC translocations are observed in 2% of diffuse large B-cell lymphoma^{15,16}. Somatic mutations in MYC are observed in 7% of diffuse large B-cell lymphoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and stomach adenocarcinoma^{15,16}. Alterations in MYC are also observed in pediatric cancers¹⁶. Somatic mutations in MYC have been observed in 59% of non-Hodgkin lymphoma, 2% of leukemia, and less than 1% of bone cancer (2 in 327 cases) and B-lymphoblastic leukemia/lymphoma (1 in 252 cases)16. Amplification of MYC is observed in 6% of embryonal tumor, 5% of bone cancer, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and MYC translocations are observed in 5% of T-lymphoblastic leukemia/lymphoma¹⁶.

Potential relevance: B-cell lymphoma with MYC translocations that co-occur with BCL2 or BCL6 are referred to as double hit lymphoma, while co-occurrence with BCL2 and BCL6 rearrangements is referred to as triple-hit lymphoma^{41,42}. MYC translocations are a diagnostic marker of Burkitt Lymphoma^{43,44}. MYC translocations are also indicative of high risk for multiple myeloma and are associated with poor risk in acute lymphoblastic leukemia^{45,46}. Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression^{31,47,48,49}.

PTEN p.(E114*) c.340G>T

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities⁵⁰. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT^{51,52}. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency⁵³. Germline mutations in PTEN are linked to

Biomarker Descriptions (continued)

hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation⁵⁴. PTEN germline mutations are also associated with inherited cancer risk in several cancer types⁵⁵.

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer^{15,16}. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN^{52,56,57,58,59}. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer^{15,16}.

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors^{60,61}. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁶², for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib⁶³ in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation^{150,151}. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase¹⁵². Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation^{150,151,153}. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma¹⁵⁴.

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)¹⁶. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)¹⁶. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)^{155,156,157}.

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

MLH1 p.(V384D) c.1151T>A

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein¹. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex². The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2².³. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia²8.²9. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway². The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication². Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes⁴. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue⁵.6,7. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes⁵.8. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer⁶.8,9,10. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer¹1,12,13,1⁴.

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma^{15,16}. Alterations in MLH1 are observed in pediatric cancers^{15,16}. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)^{15,16}.

Potential relevance: The PARP inhibitor, talazoparib³⁰ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies¹⁷. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-

Biomarker Descriptions (continued)

lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment^{18,19}. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas^{20,21}.

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

mutS homolog 6

Background: The MSH6 gene encodes the mutS homolog 6 protein¹. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex². The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides². DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication². Mutations in MSH2 result in the degradation of MSH6³. MSH6, along with MLH1, MSH2, and PMS2, form the core components of the MMR pathway². The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication². Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes⁴. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue⁵.6.7. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes⁵.8. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{6,8,9,10}. Specifically, MSH6 mutations are associated with an increased risk of ovarian and pancreatic cancer^{11,12,13,14}.

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

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies¹⁷. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment^{18,19}. MSH6 mutations are consistent with high grade in pediatric diffuse gliomas^{20,21}.

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^{1,158}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{158,159}. 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 resistance¹⁶⁰. 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^{160,161,162,163}. 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-38¹⁶⁴.

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^{15,16}.

<u>Potential relevance:</u> 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, A1. 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 cells²². MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M²³. 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^{24,25,26}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A²⁷.

Biomarker Descriptions (continued)

<u>Alterations and prevalence:</u> 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^{15,16}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{15,16}.

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

RAC1 amplification

ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)

Background: The RAC1 gene encodes Rac family small GTPase 1¹. RAC1 is one of 23 members of the RHO subfamily of GTPases within the RAS superfamily¹¹00,¹01,¹02. The RAS superfamily includes the RHO, RAS, RAB, ARF, RHEB, and Ga subfamilies¹00,¹01,¹02,¹03. RHO subfamily members are known for the regulation of several pathways involved in cell morphology, motility, and proliferation¹04,¹05,¹06. RAC1 can exist in an inactive GDP-bound form as well as in an active GTP-bound form¹02. Guanine nucleotide exchange factors (GEFs) activate RAC1 by facilitating the release of GDP to allow for binding of GTP, while GTPase-activating proteins (GAPs) facilitate the reverse, that is converting GTP-bound RAC1 to an inactive state¹02.

Alterations and prevalence: Somatic mutations in RAC1 are observed in 6% of skin cutaneous melanoma and 2% of uterine carcinosarcoma^{15,16}. The P29S mutation is recurrent in melanoma and is potentially associated with resistance to BRAF inhibitors^{15,16,107}. RAC1 is amplified in 6% of esophageal squamous cell carcinoma, 4% of uterine carcinosarcoma, bladder urothelial carcinoma, and sarcoma, as well as 2% of skin cutaneous melanoma and esophageal adenocarcinoma^{15,16}.

Potential relevance: Currently, no therapies are approved for RAC1 aberrations.

FAM135B amplification

family with sequence similarity 135 member B

Background: The FAM135B gene encodes the family with sequence similarity 135 member B protein¹. While the function of FAM135B is not well characterized, FAM135B has been proposed to contribute to the activation of the PIK3CA/AKT/MTOR pathway and has been suggested to contribute to tumor progression, proliferation, and migration in esophageal squamous cell carcinoma (ESCC)^{64,65}.

Alterations and prevalence: Somatic mutations of FAM135B are observed in 28% of skin cutaneous melanoma, 24% of lung squamous cell carcinoma, 15% lung adenocarcinoma, 14% of uterine corpus endometrial carcinoma, 10% of head and neck squamous cell carcinoma, 8% of stomach adenocarcinoma, 7% of colorectal adenocarcinoma and uterine carcinosarcoma, 5% of esophageal adenocarcinoma, and bladder urothelial carcinoma, 4% of cervical squamous cell carcinoma, 3% of adrenocortical carcinoma and pancreatic adenocarcinoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, glioblastoma multiforme, liver hepatocellular carcinoma, and sarcoma^{15,16}. Amplification of FAM135B is observed in 27% of ovarian serous cystadenocarcinoma, 12% of esophageal adenocarcinoma, 10% of breast invasive carcinoma and liver hepatocellular carcinoma, 9% of pancreatic adenocarcinoma, 7% of head and neck squamous cell carcinoma and uterine carcinosarcoma, 6% of prostate adenocarcinoma, 5% of lung adenocarcinoma, and stomach adenocarcinoma, 4% of skin cutaneous melanoma and lung squamous cell carcinoma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, brain lower grade glioma, bladder urothelial carcinoma, and uveal melanoma, and 2% of cervical squamous cell carcinoma and sarcoma^{15,16}.

Potential relevance: Currently, no therapies are approved for FAM135B aberrations.

ZFHX3 p.(Q3197Sfs*45) c.9588_9589insAG

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains 1,90,91 . Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation 91,92 . ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth 93,94,95,96,97 . In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3 93,96,98,99 .

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia^{15,16}. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3%

Report Date: 27 Jun 2025 9 of 24

Biomarker Descriptions (continued)

of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma^{15,16}.

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

Report Date: 27 Jun 2025 10 of 24

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.

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

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, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XP01, 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, 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, FGR3, 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, ERRF11, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCE, FANCG, FANCI, FANCI, FANCH, FA

Relevant Therapy Summary

In this cancer type	O In other cancer type	In this cancer type and other cancer types	No evidence
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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	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib + carboplatin + pemetrexed	×		×	×	×
osimertinib + cisplatin + pemetrexed	×	•	×	×	×
BAT1706 + erlotinib	×	×		×	×
bevacizumab (Allergan) + erlotinib	×	×		×	×
bevacizumab (Biocon) + erlotinib	×	×	•	×	×
bevacizumab (Celltrion) + erlotinib	×	×	•	×	×
bevacizumab (Mabxience) + erlotinib	×	×	•	×	×
bevacizumab (Pfizer) + erlotinib	×	×	•	×	×
bevacizumab (Samsung Bioepis) + erlotinib	×	×	•	×	×
bevacizumab (Stada) + erlotinib	×	×	•	×	×
atezolizumab + bevacizumab + carboplatin + paclitaxel	×	×	×	•	×
gefitinib + carboplatin + pemetrexed	×	×	×	•	×
adebrelimab, bevacizumab, chemotherapy	×	×	×	×	(IV)
afatinib, bevacizumab, chemotherapy	×	×	×	×	(IV)
befotertinib	×	×	×	×	(IV)
bevacizumab, almonertinib, chemotherapy	×	×	×	×	(IV)
catequentinib, toripalimab	×	×	×	×	(IV)
EGFR tyrosine kinase inhibitor	×	×	×	×	(IV)
gefitinib, chemotherapy	×	×	×	×	(IV)
gefitinib, endostatin	×	×	×	×	(IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	×	×	×	×	● (IV)
almonertinib, apatinib	×	×	×	×	(III)
almonertinib, catequentinib	×	×	×	×	(III)
almonertinib, chemotherapy	×	×	×	×	(III)
almonertinib, radiation therapy	×	×	×	×	(III)
almonertinib, radiation therapy, chemotherapy	×	×	×	×	(III)
befotertinib, icotinib hydrochloride	×	×	×	×	(III)
bevacizumab, osimertinib	×	×	×	×	(III)

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

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

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

Relevant Therapy	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, 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)

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
lenvatinib, pembrolizumab	×	×	×	×	(II)
osimertinib, bevacizumab, chemotherapy	×	×	×	×	(II)
osimertinib, chemoradiation therapy	×	×	×	×	(II)
osimertinib, radiation therapy	×	×	×	×	(II)
PLB-1004, bozitinib, osimertinib	×	×	×	×	(II)
ramucirumab, erlotinib	×	×	×	×	(II)
sacituzumab govitecan	×	×	×	×	(II)
sacituzumab tirumotecan, chemotherapy, osimertinib	×	×	×	×	(II)
sunvozertinib	×	×	×	×	(II)
sunvozertinib, catequentinib	×	×	×	×	(II)
sunvozertinib, golidocitinib	×	×	×	×	(II)
tislelizumab, chemotherapy, bevacizumab	×	×	×	×	(II)
toripalimab	×	×	×	×	(II)
toripalimab, bevacizumab, Clostridium butyricum, chemotherapy	×	×	×	×	(II)
toripalimab, chemotherapy	×	×	×	×	(II)
zorifertinib, pirotinib	×	×	×	×	(II)
AFM-24_I, atezolizumab	×	×	×	×	(I/II)
almonertinib, icotinib hydrochloride	×	×	×	×	(I/II)
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	×	×	×	×	(1/11)
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	FDA	NCCN	EMA	ESMO	Clinical Trials*
FWD-1509	×	×	×	×	(/)
H-002	×	×	×	×	(/)
ifebemtinib, furmonertinib	×	×	×	×	(/)
MRTX0902	×	×	×	×	(1/11)
necitumumab, osimertinib	×	×	×	×	(1/11)
quaratusugene ozeplasmid, osimertinib	×	×	×	×	(1/11)
RC-108, furmonertinib, toripalimab	×	×	×	×	(1/11)
sotiburafusp alfa, HB-0030	×	×	×	×	(I/II)
sunvozertinib, chemotherapy	×	×	×	×	(I/II)
TAS-3351	×	×	×	×	(I/II)
TQ-B3525, osimertinib	×	×	×	×	(I/II)
TRX-221	×	×	×	×	(I/II)
WSD-0922	×	×	×	×	(I/II)
afatinib, chemotherapy	×	×	×	×	(I)
AZD-9592	×	×	×	×	(I)
BG-60366	×	×	×	×	(I)
BPI-1178, osimertinib	×	×	×	×	(I)
catequentinib, gefitinib, metformin hydrochloride	×	×	×	×	(I)
cemiplimab, sarilumab	×	×	×	×	(I)
DZD-6008	×	×	×	×	(I)
EGFR tyrosine kinase inhibitor, catequentinib	×	×	×	×	(I)
genolimzumab, fruquintinib	×	×	×	×	(I)
IBI-318, lenvatinib	×	×	×	×	(I)
KQB-198, osimertinib	×	×	×	×	(I)
LAVA-1223	×	×	×	×	(I)
MRX-2843, osimertinib	×	×	×	×	(I)
osimertinib, carotuximab	×	×	×	×	(I)
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.

In this cancer type

O In other cancer type

In this cancer type and other cancer types

X No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
patritumab deruxtecan	×	×	×	×	(1)
PB-101 (Precision Biotech Taiwan Corp), EGFR tyrosine kinase inhibitor	×	×	×	×	(1)
repotrectinib, osimertinib	×	×	×	×	(I)
VIC-1911, osimertinib	×	×	×	×	(I)
WJ13404	×	×	×	×	(1)
WTS-004	×	×	×	×	(1)
YH-013	×	×	×	×	(I)
YL-202	×	×	×	×	(I)

TP53 p.(H115Qfs*34) c.344_345insA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
almonertinib, catequentinib	×	×	×	×	(III)
osimertinib, chemotherapy	×	×	×	×	(III)
osimertinib, bevacizumab, chemotherapy	×	×	×	×	(II)
sunvozertinib, catequentinib	×	×	×	×	(II)

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CCS-1477	×	×	×	×	(/)
entinostat, nivolumab	×	×	×	×	(/)
nedisertib, tuvusertib	×	×	×	×	(l)
talazoparib, palbociclib	×	×	×	×	(I)

PTEN p.(E114*) c.340G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib, chemotherapy	×	×	×	×	(III)
TQ-B3525, osimertinib	×	×	×	×	(/)

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

Report Date: 27 Jun 2025 18 of 24

Relevant Therapy Summary (continued)

RB1 deletion					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	×	×	×	×	(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.

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24 of 24

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