

Patient Name:

구정순

Gender:

F

Sample ID:

N25-120

Primary Tumor Site:

lung

Collection Date:

2025.07.09

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	MET	None detected
BRAF	None detected	NRG1	None detected
EGFR	EGFR exon 19 deletion	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	ROS1	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	7.6 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: 32.02% 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	None*	199

* 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
		atezolizumab + bevacizumab + chemotherapy ^{II+}		
IIC	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib ^{II+} olaparib ^{II+} rucaparib ^{II+}	2
IIC	TP53 p.(F109Sfs*14) c.326delT tumor protein p53 Allele Frequency: 34.94% Locus: chr17:7579360 Transcript: NM_000546.6	None*	None*	6

* 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
Microsatellite stable, TET2 p.(R1216*) c.3646C>T, ACVR2A p.(S18*) c.53C>G, MAP3K1 p.(A150Pfs*35) c.447delC, NOTCH4 p.(G349Afs*49) c.1044delC, NOTCH1 deletion, 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	32.02%	NM_005228.5	nonframeshift Deletion
TP53	p.(F109Sfs*14)	c.326delT	.	chr17:7579360	34.94%	NM_000546.6	frameshift Deletion
TET2	p.(R1216*)	c.3646C>T	COSM42029	chr4:106164778	7.40%	NM_001127208.3	nonsense
ACVR2A	p.(S18*)	c.53C>G	.	chr2:148602774	10.59%	NM_001616.5	nonsense
MAP3K1	p.(A150Pfs*35)	c.447delC	.	chr5:56111844	100.00%	NM_005921.2	frameshift Deletion
NOTCH4	p.(G349Afs*49)	c.1044delC	.	chr6:32188296	28.88%	NM_004557.4	frameshift Deletion
MUTYH	p.(?)	c.1187-3C>T	.	chr1:45797231	2.30%	NM_001128425.2	unknown
BRINP3	p.(S202F)	c.605C>T	.	chr1:190234008	8.26%	NM_199051.3	missense
TET2	p.(G614E)	c.1841G>A	.	chr4:106156940	10.45%	NM_001127208.3	missense
C8orf89	p.(I57S)	c.170T>G	.	chr8:74169319	57.36%	NM_001243237.1	missense
PLCG1	p.(Y353C)	c.1058A>G	.	chr20:39792608	5.70%	NM_002660.3	missense

Variant Details (continued)

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.81
NOTCH1	chr9:139390441	0.25	0.65
U2AF1L5	chr21:44513260	6.03	1.81

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 family²². In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4⁸¹. 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 pathways⁸². Activation of these pathways promotes cell proliferation, differentiation, and survival^{83,84}.

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^{14,15,85,86}. 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 21⁸⁷. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer⁸⁷. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{88,89,90,91}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations⁹². 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^{87,93}. 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^{14,15,28,86,93}. 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^{94,95,96}. Alterations in EGFR are rare in pediatric cancers^{14,15}. 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)^{14,15}. 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)^{14,15}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib⁹⁷ (2004) and gefitinib⁹⁸ (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 mutations⁹⁹. Second-generation TKIs afatinib¹⁰⁰ (2013) and dacomitinib¹⁰¹ (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^{102,103,104,105}. However, BDTX-189¹⁰⁶ 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)¹⁰⁷ and sunvozertinib¹⁰⁸, 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 resistance¹⁰⁹. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases⁸⁷. Third generation TKIs were developed to maintain sensitivity in the presence of T790M¹⁰⁹. Osimertinib¹¹⁰ (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 cases¹⁰⁹. 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 versa¹¹¹. T790M and C797S can occur in either cis or trans allelic orientation¹¹¹. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to

Biomarker Descriptions (continued)

first-generation TKIs¹¹¹. 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^{111,112}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs¹¹¹. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535¹¹³ (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 mutations¹¹⁴. The bispecific antibody, amivantamab¹¹⁵ (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib¹¹⁶ (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-801¹¹⁷ received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42¹¹⁸, 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. CPO301¹¹⁹ (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 ozeplasmid¹²⁰ (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^{121,122,123}.

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. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{1,2}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer³ and in men for breast and prostate cancer^{4,5}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer⁶. 테스트 입니다.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer^{7,8,9,10,11,12,13}. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers^{14,15}.

Potential clinical 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)¹⁶. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{17,18}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib¹⁹ (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 who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Rucaparib²⁰ (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with two or more chemotherapies. Talazoparib²¹ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Due to efficacy in both gBRCAm and non-gBRCAm patients, Niraparib (2017) is another PARPi approved for maintenance of epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of BRCA status¹⁹. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported²⁰. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality²¹.

TP53 p.(F109Sfs*14) c.326delT

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair²². In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis²³. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential²⁴. Germline mutations in TP53 are

Biomarker Descriptions (continued)

the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{25,26}.

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%)^{14,15,27,28,29,30}. 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^{14,15}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{31,32,33,34}. Alterations in TP53 are also observed in pediatric cancers^{14,15}. 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)^{14,15}. 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)^{14,15}.

Potential relevance: The small molecule p53 reactivator, PC14586³⁵ (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, eprenetapopt³⁶, (2019) and breakthrough designation³⁷ (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^{38,39}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma⁴⁰. 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)^{41,42,43,44,45,46}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁴⁷. 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 system⁴⁸.

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 genome⁵⁹. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{60,61}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁶². 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 D17S250⁶³. 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)⁶³. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{64,65,66,67,68}. 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 genes⁶¹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{60,61,65,69}.

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^{60,61,70,71}. 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^{70,71}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁷² (2014) and nivolumab⁷³ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁷² 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 indication⁷². Dostarlimab⁷⁴ (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^{66,75}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁷⁶ (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^{66,77,78}. 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 patients⁷⁸. 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^{79,80}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{79,80}.

Biomarker Descriptions (continued)

TET2 p.(R1216*) c.3646C>T

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3^{22,124}. The TET enzymes are involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine^{125,126}. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded β -helix domain (DSBH)^{125,126}. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites^{125,126}. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies^{124,127,128}.

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)⁴³. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies^{127,129}. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe^{14,15}. Alterations in TET2 are also observed in the pediatric population¹⁵. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in 1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)¹⁵. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)¹⁵.

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations⁴⁴. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia¹³⁰. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)¹³¹.

ACVR2A p.(S18*) c.53C>G

activin A receptor type 2A

Background: The ACVR2A gene encodes the activin A type 2A receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGF β) receptor family^{22,49}. ACVR2A is a type II receptor that forms heterotetrametric complex with at least two type I receptors (ACVR1 and ACVR1B) and two type II receptors (including BMPR2 and ACVR2B)^{49,50}. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrametric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream signaling^{49,50}. Downregulation of ACVR2A has been associated with increased cell migration, tumor progression, and metastases in colon cancer⁵¹.

Alterations and prevalence: Somatic mutations of ACVR2A are observed in 11% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 7% of colorectal adenocarcinoma, 3% of liver hepatocellular carcinoma, skin cutaneous melanoma, and cholangiocarcinoma, 2% of cervical squamous cell carcinoma, and 1% of kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, and glioblastoma multiforme, and esophageal adenocarcinoma^{14,15}. Biallelic deletion of ACVR2A is observed in 4% of prostate adenocarcinoma, 2% of liver hepatocellular carcinoma, and 1% of stomach adenocarcinoma, thymoma, testicular germ cell tumors, esophageal adenocarcinoma, and colorectal adenocarcinoma^{14,15}.

Potential relevance: Currently, no therapies are approved for ACVR2A aberrations.

MAP3K1 p.(A150Pfs*35) c.447delC

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1²². Activation of MAPK proteins occurs through a kinase signaling cascade^{132,133,134}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{132,133,134}. 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^{132,133,134}. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain¹³⁵. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to

Biomarker Descriptions (continued)

promote apoptosis¹³⁵. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitinating c-JUN and MAPK1/MAPK3¹³⁵.

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma^{14,15}. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes¹³⁵. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma^{14,15}.

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

NOTCH4 p.(G349Afs*49) c.1044delC

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling⁵². 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^{53,54}. 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^{55,56,57,58}.

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers¹⁴.

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

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling⁵². 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^{53,54}. 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^{55,56,57,58}.

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^{14,15,28}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{136,137}.

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, ERF1, 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, catequentinib	✕	✕	✕	✕	● (III)
almonertinib, chemotherapy	✕	✕	✕	✕	● (III)
almonertinib, radiation therapy	✕	✕	✕	✕	● (III)
almonertinib, radiation therapy, chemotherapy	✕	✕	✕	✕	● (III)
befotertinib, icotinib hydrochloride	✕	✕	✕	✕	● (III)
bevacizumab, osimertinib	✕	✕	✕	✕	● (III)

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

Relevant Therapy Summary (continued)

● In this cancer type
 ○ In other cancer type
 ● In this cancer type and other cancer types
 ✕ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BL-B01D1	✕	✕	✕	✕	● (III)
BL-B01D1, osimertinib	✕	✕	✕	✕	● (III)
CK-101, gefitinib	✕	✕	✕	✕	● (III)
datopotamab deruxtecan, osimertinib	✕	✕	✕	✕	● (III)
FHND9041, afatinib	✕	✕	✕	✕	● (III)
furmonertinib	✕	✕	✕	✕	● (III)
furmonertinib, osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
gefitinib, afatinib, erlotinib, metformin hydrochloride	✕	✕	✕	✕	● (III)
icotinib hydrochloride, catequentinib	✕	✕	✕	✕	● (III)
icotinib hydrochloride, chemotherapy	✕	✕	✕	✕	● (III)
icotinib hydrochloride, radiation therapy	✕	✕	✕	✕	● (III)
JMT-101, osimertinib	✕	✕	✕	✕	● (III)
osimertinib, bevacizumab	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, datopotamab deruxtecan	✕	✕	✕	✕	● (III)
sacituzumab tirumotecan	✕	✕	✕	✕	● (III)
sacituzumab tirumotecan, osimertinib	✕	✕	✕	✕	● (III)
savolitinib, osimertinib	✕	✕	✕	✕	● (III)
SH-1028	✕	✕	✕	✕	● (III)
targeted therapy	✕	✕	✕	✕	● (III)
TY-9591, osimertinib	✕	✕	✕	✕	● (III)
SCTB-14, chemotherapy	✕	✕	✕	✕	● (II/III)
ABSK-043, furmonertinib	✕	✕	✕	✕	● (II)
almonertinib	✕	✕	✕	✕	● (II)
almonertinib, adebrelimab, chemotherapy	✕	✕	✕	✕	● (II)
almonertinib, bevacizumab	✕	✕	✕	✕	● (II)
almonertinib, chemoradiation therapy	✕	✕	✕	✕	● (II)
almonertinib, dacomitinib	✕	✕	✕	✕	● (II)
amivantamab, 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*
amivantamab, lazertinib, chemotherapy	✕	✕	✕	✕	● (II)
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)

* 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, bevacizumab	✕	✕	✕	✕	● (II)
lazertinib, chemotherapy	✕	✕	✕	✕	● (II)
lenvatinib, pembrolizumab	✕	✕	✕	✕	● (II)
osimertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
osimertinib, chemoradiation therapy	✕	✕	✕	✕	● (II)
osimertinib, radiation therapy	✕	✕	✕	✕	● (II)
PLB-1004, bozitinib, osimertinib	✕	✕	✕	✕	● (II)
ramucirumab, erlotinib	✕	✕	✕	✕	● (II)
sacituzumab govitecan	✕	✕	✕	✕	● (II)
sacituzumab tirumotecan, chemotherapy, osimertinib	✕	✕	✕	✕	● (II)
sunvozertinib	✕	✕	✕	✕	● (II)
sunvozertinib, catequentinib	✕	✕	✕	✕	● (II)
sunvozertinib, golidocitinib	✕	✕	✕	✕	● (II)
tislelizumab, chemotherapy, bevacizumab	✕	✕	✕	✕	● (II)
toripalimab	✕	✕	✕	✕	● (II)
toripalimab, bevacizumab, Clostridium butyricum, chemotherapy	✕	✕	✕	✕	● (II)
toripalimab, chemotherapy	✕	✕	✕	✕	● (II)
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)

* 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*
dositinib	×	×	×	×	● (I/II)
FWD-1509	×	×	×	×	● (I/II)
H-002	×	×	×	×	● (I/II)
ifebemtiniib, furmonertiniib	×	×	×	×	● (I/II)
MRTX0902	×	×	×	×	● (I/II)
necitumumab, osimertiniib	×	×	×	×	● (I/II)
quaratusugene ozeplasmid, osimertiniib	×	×	×	×	● (I/II)
RC-108, furmonertiniib, toripalimab	×	×	×	×	● (I/II)
sotiburafusp alfa, HB-0030	×	×	×	×	● (I/II)
sunvozertiniib, chemotherapy	×	×	×	×	● (I/II)
TAS-3351	×	×	×	×	● (I/II)
TQ-B3525, osimertiniib	×	×	×	×	● (I/II)
TRX-221	×	×	×	×	● (I/II)
WSD-0922	×	×	×	×	● (I/II)
afatinib, chemotherapy	×	×	×	×	● (I)
almonertiniib, midazolam	×	×	×	×	● (I)
ASKC-202	×	×	×	×	● (I)
AZD-9592	×	×	×	×	● (I)
BG-60366	×	×	×	×	● (I)
BPI-1178, osimertiniib	×	×	×	×	● (I)
catequentiniib, gefitinib, metformin hydrochloride	×	×	×	×	● (I)
DZD-6008	×	×	×	×	● (I)
EGFR tyrosine kinase inhibitor, catequentiniib	×	×	×	×	● (I)
genolimzumab, fruquintiniib	×	×	×	×	● (I)
IBI-318, lenvatinib	×	×	×	×	● (I)
KQB-198, osimertiniib	×	×	×	×	● (I)
LAVA-1223	×	×	×	×	● (I)
MRX-2843, osimertiniib	×	×	×	×	● (I)
osimertiniib, carotuximab	×	×	×	×	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type
 ○ In other cancer type
 ● In this cancer type and other cancer types
 ✕ No evidence

EGFR 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)

TP53 p.(F109Sfs*14) c.326delT

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	23.18%
BRCA1	LOH, 17q21.31(41197602-41276123)x3
BRCA2	CNV, CN:1.0
BRCA2	LOH, 13q13.1(32890491-32972932)x1
BRIP1	LOH, 17q23.2(59760627-59938976)x3
CDK12	LOH, 17q12(37618286-37687611)x3
RAD51C	LOH, 17q22(56769933-56811619)x3
RAD51D	LOH, 17q12(33427950-33446720)x3

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 OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint 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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