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Patient Name: 김정애 Gender: F Sample ID: N25-193 Primary Tumor Site: lung Collection Date: 2025.08.25

# Sample Cancer Type: Lung Cancer

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# **Relevant Lung Cancer Findings**

Gene	Finding		Gene	Finding
ALK	None detected		NTRK1	None detected
BRAF	None detected		NTRK2	None detected
EGFR	EGFR exon 19	deletion	NTRK3	None detected
ERBB2	None detected		RET	None detected
KRAS	None detected		ROS1	None detected
MET	None detected			
Genomic Alt	teration	Finding		
Tumor Mu	utational Burden	4.74 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: 25.06% Locus: chr7:55242465 Transcript: NM_005228.5	afatinib 1,2/1,II+ amivantamab + lazertinib 1,2/1,II+ bevacizumab† + erlotinib 2/1,II+ dacomitinib 1,2/1,III+ erlotinib 2/1,III+ erlotinib + ramucirumab 1,2/1,III+ gefitinib 1,2/1,III+ osimertinib 1,2/1,III+ osimertinib + chemotherapy 1,2/1 amivantamab + chemotherapy 1,2/II+ BAT1706 + erlotinib 2 gefitinib + chemotherapy I atezolizumab + bevacizumab + chemotherapy II+	None*	194

<sup>\*</sup> 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.

<sup>\*</sup> Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

<sup>†</sup> Includes biosimilars/generics

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# **Relevant Biomarkers (continued)**

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	PIK3CB amplification  phosphatidylinositol-4,5-bisphosphate 3- kinase catalytic subunit beta Locus: chr3:138374221	None*	None*	1

<sup>\*</sup> 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

Microsatellite stable, RAD52 p.(S346\*) c.1037C>A, SMAD4 p.(P356L) c.1067C>T, PDCD6::TERT fusion, HLA-B deletion, Tumor Mutational Burden

# **Variant Details**

DNA S	eauer	ice V	/ari	ants

					Allele		
Gene	Amino Acid Change	Coding	Variant ID	Locus	Frequency	Transcript	Variant Effect
EGFR	p.(E746_A750del)	c.2236_2250delGAATT AAGAGAAGCA	COSM6225	chr7:55242465	25.06%	NM_005228.5	nonframeshift Deletion
RAD52	p.(S346*)	c.1037C>A		chr12:1023218	34.33%	NM_134424.4	nonsense
SMAD4	p.(P356L)	c.1067C>T	COSM14049	chr18:48591904	30.95%	NM_005359.6	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGC GGCCGCAGCGGC		chr5:79950707	55.96%	NM_002439.5	nonframeshift Deletion
CPVL	p.(D437N)	c.1309G>A		chr7:29070204	24.30%	NM_019029.3	missense
RAB11FIP1	p.([A651V;L652=])	c.1952_1954delCCCins TCT		chr8:37730366	51.26%	NM_001002814.3	missense, synonymous
YES1	p.(E116G)	c.347A>G		chr18:751729	42.99%	NM_005433.4	missense

# **Gene Fusions**

Genes	Variant ID	Locus
PDCD6::TERT	PDCD6-TERT.P2T3	chr5:272887 - chr5:1282739

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Copy	nuum	nor 1	/ariai	rione
CODY	INUITI	DCI 1		כווטוו

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0.08	0.62

<sup>\*</sup> Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

<sup>†</sup> Includes biosimilars/generics

# **Variant Details (continued)**

# Copy Number Variations (continued) Gene Locus Copy Number CNV Ratio PIK3CB chr3:138374221 13.55 3.31 HLA-B chr6:31322252 0 0.59

# **Biomarker Descriptions**

#### EGFR exon 19 deletion

epidermal growth factor receptor

<u>Background</u>: The EGFR gene encodes the epidermal growth factor receptor (EGFR), a member of the ERBB/human epidermal growth factor receptor (HER) tyrosine kinase family<sup>1</sup>. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4<sup>51</sup>. EGFR ligand-induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways, including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways<sup>52</sup>. Activation of these pathways promotes cell proliferation, differentiation, and survival<sup>53,54</sup>.

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<sup>8,9,55,56</sup>. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 2157. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer<sup>57</sup>. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 2058,59,60,61. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations<sup>62</sup>. 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<sup>57,63</sup>. 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<sup>8,9,56,63,64</sup>. 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<sup>65,66,67</sup>. Alterations in EGFR are rare in pediatric cancers<sup>8,9</sup>. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)8,9. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)8,9.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib<sup>68</sup> (2004) and gefitinib<sup>69</sup> (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations<sup>70</sup>. Second-generation TKIs afatinib<sup>71</sup> (2013) and dacomitinib<sup>72</sup> (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763\_Y764insFQEA, confer resistance to the same therapies 73,74,75,76. However, BDTX-18977 was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutations. In 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)78 and sunvozertinib79, for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance80. The primary resistance mutation that emerges following treatment with firstgeneration TKI is T790M, accounting for 50-60% of resistant cases<sup>57</sup>. Third generation TKIs were developed to maintain sensitivity in the presence of T790M80. Osimertinib81 (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like firstgeneration TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases<sup>80</sup>. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa<sup>82</sup>. T790M and C797S can occur in either cis or trans allelic orientation<sup>82</sup>. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs82. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone<sup>82,83</sup>.

# **Biomarker Descriptions (continued)**

However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs<sup>82</sup>. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-153584 (2024), a CNS-penetrating small molecule inhibitor, that received fast track designation from the FDA for the treatment of patients with EGFR C797S-positive NSCLC who have disease progression on or after a third-generation EGFR TKI. EGFR-targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations85. The bispecific antibody, amivantamab86 (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib<sup>87</sup> (2024), was approved in combination with amivantamab as a first-line treatment for adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations. In 2024, a CNS penetrating small molecule, ERAS-80188 received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-4289, an anti-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. CPO30190 (2023) received a fast track designation from the FDA for the treatment of EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors, including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid<sup>91</sup> (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 glioma92,93,94.

#### **CDKN2A** deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)<sup>95</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>96,97,98</sup>. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions<sup>99</sup>. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation¹,99,100. CDKN2A aberrations commonly co-occur with CDKN2B<sup>95</sup>. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation¹0¹. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer¹02,10³.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations<sup>104</sup>. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma<sup>8,9</sup>. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe<sup>8,9</sup>. Alterations in CDKN2A are also observed in pediatric cancers<sup>9</sup>. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors<sup>9</sup>. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)<sup>9</sup>.

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors<sup>105,106,107</sup>. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma<sup>94</sup>. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib<sup>108,109,110</sup>. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme<sup>111</sup>. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer<sup>112,113,114,115</sup>.

# **Biomarker Descriptions (continued)**

#### **PIK3CB** amplification

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta

Background: The PIK3CB gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta of the class I phosphatidylinositol 3-kinase (PI3K) enzyme<sup>116</sup>. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases<sup>116,117</sup>. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively<sup>116</sup>. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction<sup>118,119</sup>. The reversible phosphorylation of inositol lipids regulate diverse aspects of cell growth and metabolism<sup>118,119,120,121</sup>. Aberrations in PIK3CB that lead to activation of the PI3K/AKT/MTOR pathway have been observed to promote tumor formation, suggesting an oncogenic role for PIK3CB<sup>116,122,123</sup>.

Alterations and prevalence: Somatic mutations in PIK3CB are predominantly missense with amino acid substitutions at D1067 being the most recurrent and observed to lead to hyperactivation of the PI3K pathway<sup>8,9,124</sup>. PIK3CB mutations are observed in about 9% of uterine cancer and 2-3% of melanoma, glioblastoma, cholangiocarcinoma, colorectal, bladder, stomach, esophageal, and squamous lung cancers<sup>8,9</sup>. Amplification of PIK3CB is also observed in 9% of squamous lung cancer, 7% of cervical cancer, and 5-6% of head and neck, ovarian, and esophageal cancers<sup>8,9</sup>.

Potential relevance: Currently, no therapies are approved for PIK3CB aberrations.

#### Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome<sup>29</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>30,31</sup>. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2<sup>32</sup>. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250<sup>33</sup>. 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)<sup>33</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>34,35,36,37,38</sup>. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes<sup>31</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>30,31,35,39</sup>.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma<sup>30,31,40,41</sup>. 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<sup>40,41</sup>.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>42</sup> (2014) and nivolumab<sup>43</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>42</sup> is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication<sup>42</sup>. Dostarlimab<sup>44</sup> (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<sup>36,45</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>46</sup> (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<sup>36,47,48</sup>. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients<sup>48</sup>. 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<sup>49,50</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>49,50</sup>.

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

RAD52 homolog, DNA repair protein

<u>Background:</u> The RAD52 gene encodes the RAD52 homolog, DNA repair protein<sup>1</sup>. RAD52 binds to single- and double-stranded DNA and enables strand exchange for double-strand break (DSB) repair by binding to RAD51<sup>15</sup>. RAD52 also promotes DSB repair through

# **Biomarker Descriptions (continued)**

homologous recombination repair (HRR) by recruiting BRCA1 to sites of DSBs, which leads to the removal of TP53BP1 and prevents DSB repair by non-homologous end joining (NHEJ)<sup>16</sup>.

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

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

#### SMAD4 p.(P356L) c.1067C>T

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7 $^{17,18}$ . SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression  $^{18,19,20}$ . Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC $^{17,18}$ 

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)<sup>17</sup>. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF- $\beta$  signaling<sup>9,20,21</sup>. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers<sup>8,9,22</sup>.

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers<sup>18,20,23,24,25</sup>. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy<sup>26,27</sup>. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)<sup>27</sup>. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors<sup>28</sup>.

#### PDCD6::TERT fusion

programmed cell death 6, telomerase reverse transcriptase

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)<sup>10</sup>. TERT is repressed in most differentiated cells, resulting in telomerase silencing<sup>10</sup>. In cancer, telomerase reactivation is known to contribute to cellular immortalization<sup>10,11</sup>. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization<sup>10</sup>. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness<sup>10</sup>.

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma<sup>8,9</sup>. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)<sup>11</sup>. Specifically, TERT promoter mutations at C228T and C250T are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription<sup>10</sup>. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma<sup>8,9</sup>. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen<sup>12</sup>. Alterations in TERT are rare in pediatric cancers<sup>8,9</sup>. Somatic mutations are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)<sup>8,9</sup>. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)<sup>8,9</sup>.

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma<sup>13,14</sup>. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy<sup>12</sup>.

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# **Biomarker Descriptions (continued)**

#### **HLA-B** deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B1. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells<sup>2</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>3</sup>. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the  $\alpha$  polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self<sup>4,5,6</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B<sup>7</sup>.

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma<sup>8,9</sup>. Biallelic loss of HLA-B is observed in 5% of DLBCL<sup>8,9</sup>.

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

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# 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.

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**

FGFR exon 19 deletion

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					<b>(III)</b>
afatinib	•	•	•	•	<b>(II)</b>
dacomitinib					<b>(II)</b>
gefitinib					<b>(II)</b>
erlotinib + ramucirumab					×
amivantamab + carboplatin + pemetrexed				×	×
amivantamab + lazertinib				×	×
osimertinib + chemotherapy + pemetrexed		×		×	×
bevacizumab + erlotinib	×				×
erlotinib	×	•	•		×

<sup>\*</sup> 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

O In other cancer type

In this cancer type and other cancer types

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials <sup>3</sup>
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	×	×	×	×	<b>●</b> (IV)
almonertinib, apatinib	×	×	×	×	<b>(III)</b>
almonertinib, chemotherapy	×	×	×	×	<b>(III)</b>
almonertinib, radiation therapy	×	×	×	×	<b>(III)</b>
almonertinib, radiation therapy, chemotherapy	×	×	×	×	<b>(III)</b>
befotertinib, icotinib hydrochloride	×	×	×	×	<b>(III)</b>
bevacizumab, osimertinib	×	×	×	×	<b>(III)</b>
BL-B01D1	×	×	×	×	<b>(III)</b>

<sup>\*</sup> 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

O In other cancer type

In this cancer type and other cancer types

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

<sup>\*</sup> 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

O In other cancer type

In this cancer type and other cancer types

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

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

# **Relevant Therapy Summary (continued)**

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
lazertinib, chemotherapy	×	×	×	×	<b>(II)</b>
lenvatinib, pembrolizumab	×	×	×	×	<b>(II)</b>
osimertinib, chemoradiation therapy	×	×	×	×	<b>(II)</b>
osimertinib, radiation therapy	×	×	×	×	<b>(II)</b>
PLB-1004, bozitinib, osimertinib	×	×	×	×	<b>(II)</b>
ramucirumab, erlotinib	×	×	×	×	<b>(II)</b>
sacituzumab govitecan	×	×	×	×	<b>(II)</b>
sacituzumab tirumotecan, chemotherapy, osimertinib	×	×	×	×	<b>(II)</b>
sunvozertinib	×	×	×	×	<b>(II)</b>
sunvozertinib, catequentinib	×	×	×	×	<b>(II)</b>
sunvozertinib, golidocitinib	×	×	×	×	<b>(II)</b>
tislelizumab, chemotherapy, bevacizumab	×	×	×	×	<b>(II)</b>
toripalimab	×	×	×	×	<b>(II)</b>
toripalimab, bevacizumab, Clostridium butyricum, chemotherapy	×	×	×	×	<b>(II)</b>
toripalimab, chemotherapy	×	×	×	×	<b>(II)</b>
TY-9591, chemotherapy	×	×	×	×	<b>(II)</b>
zorifertinib, pirotinib	×	×	×	×	<b>(II)</b>
AFM-24_I, atezolizumab	×	×	×	×	<b>(</b>  /  )
almonertinib, icotinib hydrochloride	×	×	×	×	<b>(</b> I/II)
benmelstobart, catequentinib	×	×	×	×	<b>(</b> I/II)
BH-30643	×	×	×	×	<b>(</b>  /  )
bozitinib, osimertinib	×	×	×	×	<b>(</b>  /  )
BPI-361175	×	×	×	×	<b>(</b>  /  )
cetrelimab, amivantamab	×	×	×	×	<b>(</b>  /  )
dacomitinib, catequentinib	×	×	×	×	<b>(</b> 1/11)
DAJH-1050766	×	×	×	×	<b>(</b> I/II)
DB-1310, osimertinib	×	×	×	×	<b>(</b> I/II)
dositinib	×	×	×	×	<b>(</b>  /  )
FWD-1509	×	×	×	×	(I/II)

<sup>\*</sup> 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

O In other cancer type

In this cancer type and other cancer types

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
H-002	×	×	×	×	<b>(</b>  /  )
ifebemtinib, furmonertinib	×	×	×	×	<b>(</b> I/II)
MRTX0902	×	×	×	×	<b>(</b> I/II)
necitumumab, osimertinib	×	×	×	×	<b>(</b> I/II)
quaratusugene ozeplasmid, osimertinib	×	×	×	×	<b>(</b> I/II)
RC-108, furmonertinib, toripalimab	×	×	×	×	<b>(</b>  /  )
sotiburafusp alfa, HB-0030	×	×	×	×	<b>(</b>  /  )
sunvozertinib, chemotherapy	×	×	×	×	<b>(</b> I/II)
TAS-3351	×	×	×	×	<b>(</b> 1/11)
TQ-B3525, osimertinib	×	×	×	×	<b>(</b> 1/11)
TRX-221	×	×	×	×	<b>(</b> 1/11)
WSD-0922	×	×	×	×	<b>(</b> 1/11)
afatinib, chemotherapy	×	×	×	×	<b>(</b> I)
alisertib, osimertinib	×	×	×	×	(I)
almonertinib, midazolam	×	×	×	×	<b>(</b> I)
ASKC-202	×	×	×	×	<b>(</b> 1)
AZD-9592	×	×	×	×	<b>(</b> 1)
BG-60366	×	×	×	×	<b>(</b> 1)
BPI-1178, osimertinib	×	×	×	×	<b>(</b> 1)
catequentinib, gefitinib, metformin hydrochloride	×	×	×	×	<b>(</b> I)
DZD-6008	×	×	×	×	<b>(</b> l)
EGFR tyrosine kinase inhibitor, catequentinib	×	×	×	×	<b>(</b> 1)
genolimzumab, fruquintinib	×	×	×	×	<b>(</b> I)
IBI-318, lenvatinib	×	×	×	×	<b>(</b> I)
KQB-198, osimertinib	×	×	×	×	<b>(</b> I)
LAVA-1223	×	×	×	×	<b>(</b> l)
MRX-2843, osimertinib	×	×	×	×	(I)
osimertinib, carotuximab	×	×	×	×	(I)
osimertinib, Minnelide	×	×	×	×	(I)

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

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# **Relevant Therapy Summary (continued)**

■ In this cancer type
In other cancer type
In this cancer type and other cancer types
X No evidence

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

#### **CDKN2A** deletion FDA NCCN **ESMO Clinical Trials\* Relevant Therapy EMA** palbociclib (II) × × × × palbociclib, abemaciclib × × × × (II) AMG 193 × × × × (I/II)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TQ-B3525, osimertinib	×	×	×	×	<b>(</b> 1/11)

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

# **HRR Details**

PIK3CB amplification

Gene/Genomic Alteration	Finding
LOH percentage	26.14%
BRCA2	LOH, 13q13.1(32890491-32972932)x2
BARD1	LOH, 2q35(215593375-215674382)x2
FANCL	LOH, 2p16.1(58386886-58468467)x2

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

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## References

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