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**Report Date**: 23 Sep 2025 1 of 24

Patient Name: 전순애 Gender: F Sample ID: N25-209 Primary Tumor Site: lung
Collection Date: 2025.08.28

# Sample Cancer Type: Lung Cancer

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

Report Highlights 4 Relevant Biomarkers 17 Therapies Available 204 Clinical Trials

# **Relevant Lung Cancer Findings**

Gene	Finding		Gene	Finding
ALK	None detected		NTRK1	None detected
BRAF	None detected		NTRK2	None detected
EGFR	EGFR exon 19	deletion	NTRK3	None detected
ERBB2	None detected		RET	None detected
KRAS	None detected		ROS1	None detected
MET	None detected			
Genomic Alt	eration	Finding		
Tumor Mu	ıtational Burden	2.84 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: 37.68% Locus: chr7:55242469 Transcript: NM_005228.5	afatinib 1,2/I,II+ amivantamab + lazertinib 1,2/I,II+ bevacizumab† + erlotinib 2/I,II+ dacomitinib 1,2/I,III+ erlotinib 2/I,III+ erlotinib + ramucirumab 1,2/I,III+ gefitinib 1,2/I,III+ osimertinib 1,2/I,III+ osimertinib + chemotherapy 1,2/I amivantamab + chemotherapy 1,2/II+ BAT1706 + erlotinib 2 gefitinib + chemotherapy I atezolizumab + bevacizumab + chemotherapy II+	None*	201

<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

2 of 24

Report Date: 23 Sep 2025

# **Relevant Biomarkers (continued)**

Tier IIC	Genomic Alteration  TP53 p.(M237I) c.711G>A tumor protein p53 Allele Frequency: 39.92% Locus: chr17:7577570 Transcript: NM_000546.6	Relevant Therapies (In this cancer type) None*	Relevant Therapies (In other cancer type) None*	Clinical Trials 6
IIC	CDKN2A deletion  cyclin dependent kinase inhibitor 2A  Locus: chr9:21968178	None*	None*	3
IIC	CDKN2B deletion cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	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

GNAS amplification, MLH1 p.(V384D) c.1151T>A, MSH3 p.(A65Sfs\*17) c.192\_199delAGCGCCCC, Microsatellite stable, PPP2R2A deletion, UGT1A1 p.(G71R) c.211G>A, FOXA1 amplification, DSC1 deletion, PRKACA amplification, PTPRT deletion, RBM10 p.(Q310\*) c.928C>T, Tumor Mutational Burden

### **Variant Details**

DNA S	Sequence Varian	ts					
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
EGFR	p.(L747_P753delinsS)	c.2240_2257delTAAGA GAAGCAACATCTC	COSM12370	chr7:55242469	37.68%	NM_005228.5	nonframeshift Deletion
TP53	p.(M237I)	c.711G>A	COSM10834	chr17:7577570	39.92%	NM_000546.6	missense
MLH1	p.(V384D)	c.1151T>A		chr3:37067240	99.50%	NM_000249.4	missense
MSH3	p.(A65Sfs*17)	c.192_199delAGCGCC CC		chr5:79950733	6.43%	NM_002439.5	frameshift Deletion
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	99.65%	NM_000463.3	missense
RBM10	p.(Q310*)	c.928C>T		chrX:47038726	19.00%	NM_001204468.1	nonsense
PIK3R1	p.(F487C)	c.1460T>G		chr5:67590398	18.20%	NM_181523.3	missense
SMARCA4	p.(Y795S)	c.2384A>C		chr19:11123734	61.80%	NM_001128849.3	missense

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

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

# **Variant Details (continued)**

Copy Number V	Copy Number Variations						
Gene	Locus	Copy Number	CNV Ratio				
CDKN2A	chr9:21968178	0	0.49				
CDKN2B	chr9:22005728	0	0.55				
GNAS	chr20:57415551	5.64	1.8				
PPP2R2A	chr8:26149298	0.5	0.67				
FOXA1	chr14:38060550	9.86	2.73				
DSC1	chr18:28710424	0.41	0.65				
PRKACA	chr19:14204349	6.73	2.04				
PTPRT	chr20:40710527	0.55	0.68				
KEAP1	chr19:10597314	6.16	1.92				
KMT2B	chr19:36209128	5.48	1.76				
USP9X	chrX:40982869	5.36	1.74				
KDM6A	chrX:44732715	7	2.1				
RBM10	chrX:47006798	8.32	2.39				

# **Biomarker Descriptions**

#### EGFR exon 19 deletion

epidermal growth factor receptor

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR), a member of the ERBB/human epidermal growth factor receptor (HER) tyrosine kinase family<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>125</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>126</sup>. Activation of these pathways promotes cell proliferation, differentiation, and survival<sup>127,128</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>6,7,129,130</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 21131. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer<sup>131</sup>. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20<sup>132,133,134,135</sup>. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations<sup>136</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>131,137</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>6,7,90,130,137</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>138,139,140</sup>. Alterations in EGFR are rare in pediatric cancers<sup>6,7</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)<sup>6,7</sup>. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)6,7.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib<sup>141</sup> (2004) and gefitinib<sup>142</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

# **Biomarker Descriptions (continued)**

first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations<sup>143</sup>. Second-generation TKIs afatinib<sup>144</sup> (2013) and dacomitinib<sup>145</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<sup>146,147,148,149</sup>. However, BDTX-189<sup>150</sup> 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)<sup>151</sup> and sunvozertinib<sup>152</sup>, for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance<sup>153</sup>. The primary resistance mutation that emerges following treatment with firstgeneration TKI is T790M, accounting for 50-60% of resistant cases<sup>131</sup>. Third generation TKIs were developed to maintain sensitivity in the presence of T790M<sup>153</sup>. Osimertinib<sup>154</sup> (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>153</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>155</sup>. T790M and C797S can occur in either cis or trans allelic orientation<sup>155</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 TKIs<sup>155</sup>. 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>155,156</sup>. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs<sup>155</sup>. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535<sup>157</sup> (2024), a CNS-penetrating small molecule inhibitor, that received fast track designation from the FDA for the treatment of patients with EGFR C797S-positive NSCLC who have disease progression on or after a third-generation EGFR TKI. EGFR-targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations<sup>158</sup>. The bispecific antibody, amivantamab<sup>159</sup> (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib160 (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-801161 received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42162, 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. CPO301163 (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 ozeplasmid164 (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<sup>42,83,165</sup>.

#### TP53 p.(M237I) c.711G>A

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 repair<sup>1</sup>. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis<sup>85</sup>. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential<sup>86</sup>. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers<sup>87,88</sup>.

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%)<sup>6,7,89,90,91,92</sup>. 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<sup>6,7</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>93,94,95,96</sup>. Alterations in TP53 are also observed in pediatric cancers<sup>6,7</sup>. 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)<sup>6,7</sup>. 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)<sup>6,7</sup>.

Potential relevance: The small molecule p53 reactivator, PC14586<sup>97</sup> (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, eprenetapopt<sup>98</sup>, (2019)

# **Biomarker Descriptions (continued)**

and breakthrough designation<sup>99</sup> (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<sup>100,101</sup>. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma<sup>102</sup>. 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)<sup>103,104,105,106,107,108</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>109</sup>. 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 system<sup>110</sup>.

#### **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)²9. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb³0,31,32. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions³3. 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 degradation¹,33,34. CDKN2A aberrations commonly co-occur with CDKN2B²9. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation³5. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer³6,37.

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>38</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>6,7</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>6,7</sup>. Alterations in CDKN2A are also observed in pediatric cancers<sup>7</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>7</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>7</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>39,40,41</sup>. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma<sup>42</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>43,44,45</sup>. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme<sup>46</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>47,48,49,50</sup>.

### CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression<sup>1,29</sup>. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)<sup>29</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>30,31,32</sup>. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A<sup>29</sup>. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma<sup>1,51,52</sup>.

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous

# **Biomarker Descriptions (continued)**

cell carcinoma, 25% of diffuse large B -cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe<sup>6,7</sup>. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma<sup>6,7</sup>. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers<sup>6,7</sup>. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)<sup>6,7</sup>.

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma<sup>42</sup>.

#### **GNAS** amplification

**GNAS** complex locus

<u>Background:</u> GNAS encodes the stimulatory alpha subunit of the guanine nucleotide-binding protein (G-protein). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNAS links receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses.

Alterations and prevalence: Recurrent somatic mutations at amino acid positions R201 and Q227 lead to constitutive activation of GNAS and are observed in pancreatic cancer (3%) as well as lung adenocarcinoma, colorectal, and gastric cancers (approximately 1%)6,7,166,167. In colorectal cancer, GNAS mutations were enriched in right-sided tumors 168. In lung adenocarcinoma, GNAS mutations were enriched in female patients with invasive mucinous adenocarcinoma 167. Specifically, GNAS mutations in these patients were exclusively observed at R201C/H, along with concurrent mutations in KRAS or BRAF. 167.

Potential relevance: Currently, no therapies are approved for GNAS aberrations. A case study of a patient with appendiceal adenocarcinoma harboring a GNAS R201H mutation reported a progression-free survival (PFS) of 4 months when treated with the MEK inhibitor trametinib<sup>169</sup>.

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

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein¹. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex²4. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2²4,65. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia66,67. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway²4. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication²4. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes68. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue69,70,71. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes69,72. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>70,72,73,74</sup>. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer<sup>75,76,77,78</sup>.

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma<sup>6,7</sup>. Alterations in MLH1 are observed in pediatric cancers<sup>6,7</sup>. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)<sup>6,7</sup>.

Potential relevance: The PARP inhibitor, talazoparib<sup>79</sup> in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies<sup>80</sup>. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment<sup>81,82</sup>. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas<sup>83,84</sup>.

# **Biomarker Descriptions (continued)**

MSH3 p.(A65Sfs\*17) c.192\_199delAGCGCCCC

mutS homolog 3

<u>Background</u>: The MSH3 gene encodes the mutS homolog 3 protein<sup>1</sup>. MSH3 heterodimerizes with MSH2 to form the MutS $\beta$  complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair<sup>24,25</sup>. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutS $\beta$  localization to DNA mispairs<sup>24,25</sup>. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer<sup>26</sup>.

<u>Alterations and prevalence:</u> Somatic mutations in MSH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, and 3% of skin cutaneous melanoma<sup>6,7</sup>. Biallelic deletion of MSH3 are observed in 3% of ovarian serous cystadenocarcinoma and 2% of prostate adenocarcinoma<sup>6,7</sup>.

Potential relevance: Currently, no therapies are approved for MSH3 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>111</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>70,72</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>71</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>112</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>112</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>73,113,114,115,116</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>72</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>70,72,73,74</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>70,72,117,118</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>117,118</sup>.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>80</sup> (2014) and nivolumab<sup>81</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>80</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>80</sup>. Dostarlimab<sup>119</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>114,120</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>82</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>114,121,122</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>122</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>123,124</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>123,124</sup>.

#### PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)<sup>17,18</sup>. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess proapoptotic activity through negative regulation of the PI3K/AKT pathway<sup>19</sup>. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway<sup>17</sup>.

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer<sup>17,18,20,21</sup>. Biallelic loss of PPP2R2A is

# **Biomarker Descriptions (continued)**

observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma<sup>6</sup>.

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>22</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib<sup>17</sup>. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit<sup>23</sup>.

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily<sup>1,53</sup>. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites<sup>53,54</sup>. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance<sup>55</sup>. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation<sup>55,56,57,58</sup>. Furthermore, UGT1A1 polymorphisms, such as UGT1A1\*28, UGT1A1\*93, and UGT1A1\*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38<sup>59</sup>.

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma<sup>6,7</sup>.

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

#### FOXA1 amplification

forkhead box A1

Background: The FOXA1 gene encodes forkhead box A1¹. FOXA1 is a member of the forkhead box (FOX) family of transcription factors and the FoxA subfamily, along with FOXA2 and FOXA3²². FOXA1 is known to interact and modulate estrogen receptor (ER) and androgen receptor (AR) function²²,²²². However, its specific role in hormone receptor signaling is unclear and has been suggested to exhibit both oncogenic and tumor suppressor roles²²,²²².

Alterations and prevalence: Somatic mutations in FOXA1 are observed in 6% of prostate adenocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of bladder urothelial carcinoma and breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and skin cutaneous melanoma<sup>6,7</sup>. FOXA1 amplification is observed in 10% of lung adenocarcinoma and 3% of esophageal adenocarcinoma, lung squamous cell carcinoma, and prostate adenocarcinoma<sup>6,7</sup>.

Potential relevance: Currently, no therapies are approved for FOXA1 aberrations.

#### **DSC1** deletion

desmocollin 1

Background: The DSC1 gene encodes desmocollin 1, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC2 and DSC3 $^1$ . DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes $^8$ . Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion $^9$ . Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC1 in tumorigenesis $^{8,10,11,12}$ .

Alterations and prevalence: Somatic mutations in DSC1 are observed in 17% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, and 3% of lung adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma<sup>6,7</sup>. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma<sup>6,7</sup>.

Potential relevance: Currently, no therapies are approved for DSC1 aberrations.

# **Biomarker Descriptions (continued)**

#### **PRKACA** amplification

protein kinase cAMP-activated catalytic subunit alpha

Background: The PRKACA gene encodes the protein kinase cAMP-activated catalytic subunit alpha (C-alpha) of protein kinase A (PKA), an inactive tetrameric holoenzyme with two regulatory (R) subunits and two catalytic (C) subunits (namely PRKACA and PRKACB)<sup>1</sup>. PKA is a cAMP-dependent protein kinase involved in the phosphorylation of several downstream targets and an essential regulator of several cell signaling pathways including differentiation, proliferation, and apoptosis<sup>1,60,61</sup>. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins<sup>1,60</sup>. Aberrations in PRKACA are oncogenic, as they are predicted to abolish the interaction with R subunits leading to cAMP-independent activation of PKA<sup>62</sup>. Germline amplification and somatic mutation of PRKACA are associated with the development and pathogenesis of benign adrenal tumors leading to Cushing syndrome, which is characterized by overproduction of cortisol resulting in metabolic abnormalities<sup>62,63</sup>.

Alterations and prevalence: Somatic mutations in PRKACA are predominantly missense and occur in about 2-3% of melanoma, diffuse large B-cell lymphoma, and uterine cancer<sup>6,7</sup>. PRKACA fusions have also been observed in 2% of liver cancer<sup>6,7</sup>. Specifically, PRKACA fusion with DNAJB1 has been observed to be recurrent in fibrolamellar hepatocellular carcinoma, which results in the retention of a functional PRKACA catalytic domain and increased protein levels<sup>60,64</sup>. PRKACA amplification is observed in about 11% of ovarian cancer and 2-3% of adrenocortical carcinoma, sarcoma, and uterine cancer<sup>60,64</sup>.

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

#### PTPRT deletion

protein tyrosine phosphatase, receptor type T

<u>Background:</u> PTPRT encodes protein tyrosine phosphatase receptor type T, part of the protein tyrosine phosphatase (PTP) family which consists of 125 members<sup>1,2,3</sup>. PTPs are responsible for protein dephosphorylation of tyrosine residues and are involved in several cellular processes including proliferation, differentiation, adhesion, and survival<sup>4,5</sup>. Aberrant tyrosine phosphorylation resulting from PTP dysfunction has been linked to cancer progression<sup>4,5</sup>.

Alterations and prevalence: Somatic mutations in PTPRT are observed in 29% of skin cutaneous melanoma, 12% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 10% of colorectal adenocarcinoma and lung adenocarcinoma, 7% of esophageal adenocarcinoma and lung squamous cell carcinoma, 5% of uterine carcinosarcoma and bladder urothelial carcinoma, 4% of head and neck squamous cell carcinoma and cervical squamous cell carcinoma, 3% of glioblastoma multiforme and liver hepatocellular carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, and ovarian serous cystadenocarcinoma<sup>6,7</sup>. Biallelic loss of PTPRT is observed in about 1% of mesothelioma, prostate adenocarcinoma, and acute myeloid leukemia.<sup>6,7</sup>.

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

#### RBM10 p.(Q310\*) c.928C>T

RNA binding motif protein 10

<u>Background:</u> RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family<sup>1,13</sup>. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA<sup>13,14</sup>. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression<sup>13</sup>. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10<sup>15,16</sup>.

Alterations and prevalence: Somatic mutations in RBM10 are observed in 7% of lung adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma, 3% of colorectal adenocarcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, and kidney chromophobe<sup>6,7</sup>. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma<sup>6,7</sup>. Amplification of RBM10 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma<sup>6,7</sup>.

Potential relevance: Currently, no therapies are approved for RBM10 aberrations.

Report Date: 23 Sep 2025 10 of 24

# Alerts Informed By Public Data Sources

#### **Current FDA Information**

Contraindicated

Not recommended



Resistance



Breakthrough



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, FANCI, 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,

Report Date: 23 Sep 2025 11 of 24

# **Genes Assayed (continued)**

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

TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

# Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, 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, 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, FANCH, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

# **Relevant Therapy Summary**

In this cancer type In other	er cancer type	er type and other cancer types 💢 No evid	dence
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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.

12 of 24

# **Relevant Therapy Summary (continued)**

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib + carboplatin + pemetrexed	×		×	×	×
osimertinib + cisplatin + pemetrexed	×	•	×	×	×
BAT1706 + erlotinib	×	×		×	×
bevacizumab (Allergan) + erlotinib	×	×		×	×
bevacizumab (Biocon) + erlotinib	×	×	•	×	×
bevacizumab (Celltrion) + erlotinib	×	×	•	×	×
bevacizumab (Mabxience) + erlotinib	×	×	•	×	×
bevacizumab (Pfizer) + erlotinib	×	×	•	×	×
bevacizumab (Samsung Bioepis) + erlotinib	×	×	•	×	×
bevacizumab (Stada) + erlotinib	×	×	•	×	×
atezolizumab + bevacizumab + carboplatin + paclitaxel	×	×	×	•	×
gefitinib + carboplatin + pemetrexed	×	×	×	•	×
adebrelimab, bevacizumab, chemotherapy	×	×	×	×	(IV)
afatinib, bevacizumab, chemotherapy	×	×	×	×	(IV)
befotertinib	×	×	×	×	(IV)
bevacizumab, almonertinib, chemotherapy	×	×	×	×	(IV)
catequentinib, toripalimab	×	×	×	×	(IV)
EGFR tyrosine kinase inhibitor	×	×	×	×	(IV)
gefitinib, chemotherapy	×	×	×	×	(IV)
gefitinib, endostatin	×	×	×	×	(IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	×	×	×	×	<b>●</b> (IV)
almonertinib, apatinib	×	×	×	×	<b>(III)</b>
almonertinib, catequentinib	×	×	×	×	<b>(III)</b>
almonertinib, chemotherapy	×	×	×	×	<b>(III)</b>
almonertinib, radiation therapy	×	×	×	×	<b>(III)</b>
almonertinib, radiation therapy, chemotherapy	×	×	×	×	<b>(III)</b>
befotertinib, icotinib hydrochloride	×	×	×	×	(III)
bevacizumab, osimertinib	×	×	×	×	<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	FDA	NCCN	EMA	ESMO	Clinical Trials*
BL-B01D1	×	×	×	×	<b>(III)</b>
BL-B01D1, osimertinib	×	×	×	×	<b>(III)</b>
CK-101, gefitinib	×	×	×	×	<b>(III)</b>
datopotamab deruxtecan, osimertinib	×	×	×	×	<b>(III)</b>
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	×	×	×	×	<b>(III)</b>
TY-9591, osimertinib	×	×	×	×	<b>(III)</b>
SCTB-14, chemotherapy	×	×	×	×	<b>(II/III)</b>
ABSK-043, furmonertinib	×	×	×	×	<b>(II)</b>
almonertinib	×	×	×	×	(II)
almonertinib, adebrelimab, chemotherapy	×	×	×	×	(II)
almonertinib, bevacizumab	×	×	×	×	<b>(II)</b>
almonertinib, chemoradiation therapy	×	×	×	×	(II)
almonertinib, dacomitinib	×	×	×	×	(II)
amivantamab, 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	FDA	NCCN	EMA	ESMO	Clinical Trials*
amivantamab, lazertinib, chemotherapy	×	×	×	×	<b>(II)</b>
atezolizumab, bevacizumab, tiragolumab	×	×	×	×	<b>(II)</b>
pefotertinib, bevacizumab, chemotherapy	×	×	×	×	<b>(II)</b>
pevacizumab, afatinib	×	×	×	×	<b>(II)</b>
oevacizumab, 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>(II)</b>
dacomitinib, osimertinib	×	×	×	×	(II)
EGFR tyrosine kinase inhibitor, osimertinib, chemotherapy	×	×	×	×	<b>●</b> (II)
EGFR tyrosine kinase inhibitor, radiation therapy	×	×	×	×	<b>(II)</b>
erlotinib, chemotherapy	×	×	×	×	<b>(II)</b>
erlotinib, OBI-833	×	×	×	×	<b>(II)</b>
furmonertinib, bevacizumab	×	×	×	×	(II)
furmonertinib, bevacizumab, chemotherapy	×	×	×	×	(II)
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>●</b> (II)
gefitinib, icotinib hydrochloride	×	×	×	×	<b>(II)</b>
gefitinib, thalidomide	×	×	×	×	(II)
cotinib hydrochloride	×	×	×	×	(II)
cotinib hydrochloride, autologous RAK cell	×	×	×	×	(II)
cotinib hydrochloride, osimertinib	×	×	×	×	(II)
vonescimab, chemotherapy	×	×	×	×	(II)
azertinib	×	×	×	×	(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	FDA	NCCN	EMA	ESMO	Clinical Trials*
lazertinib, bevacizumab	×	×	×	×	<b>(II)</b>
lazertinib, chemotherapy	×	×	×	×	<b>(II)</b>
lenvatinib, pembrolizumab	×	×	×	×	<b>(II)</b>
osimertinib, bevacizumab, chemotherapy	×	×	×	×	<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	×	×	×	×	(II)
sunvozertinib, catequentinib	×	×	×	×	<b>(II)</b>
sunvozertinib, golidocitinib	×	×	×	×	(II)
tislelizumab, chemotherapy, bevacizumab	×	×	×	×	<b>(II)</b>
toripalimab	×	×	×	×	(II)
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> (I/II)
almonertinib, icotinib hydrochloride	×	×	×	×	<b>(</b> I/II)
benmelstobart, catequentinib	×	×	×	×	(I/II)
BH-30643	×	×	×	×	<b>●</b> (I/II)
bozitinib, osimertinib	×	×	×	×	<b>●</b> (I/II)
BPI-361175	×	×	×	×	<b>(</b> I/II)
cetrelimab, amivantamab	×	×	×	×	<b>(</b>  /  )
dacomitinib, catequentinib	×	×	×	×	<b>(</b>  /  )
DAJH-1050766	×	×	×	×	<b>●</b> (I/II)
DB-1310, osimertinib	×	×	×	×	(I/II)

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dositinib	×	×	×	×	<b>(</b>  /  )
FWD-1509	×	×	×	×	<b>(</b> 1/11)
H-002	×	×	×	×	<b>(</b> 1/11)
ifebemtinib, furmonertinib	×	×	×	×	<b>(</b> 1/11)
MRTX0902	×	×	×	×	<b>(</b> 1/11)
necitumumab, osimertinib	×	×	×	×	<b>(</b> 1/11)
quaratusugene ozeplasmid, osimertinib	×	×	×	×	<b>(</b> 1/11)
RC-108, furmonertinib, toripalimab	×	×	×	×	<b>(</b> 1/11)
sotiburafusp alfa, HB-0030	×	×	×	×	<b>(</b> 1/11)
sunvozertinib, chemotherapy	×	×	×	×	<b>(</b> 1/11)
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> 1)
almonertinib, midazolam	×	×	×	×	<b>(</b> 1)
ASKC-202	×	×	×	×	<b>(</b> I)
AZD-9592	×	×	×	×	<b>(</b> 1)
BG-60366	×	×	×	×	<b>(</b> 1)
BPI-1178, osimertinib	×	×	×	×	<b>(</b> 1)
catequentinib, gefitinib, metformin hydrochloride	×	×	×	×	<b>(</b> 1)
DZD-6008	×	×	×	×	<b>(</b> 1)
EGFR tyrosine kinase inhibitor, catequentinib	×	×	×	×	(I)
genolimzumab, fruquintinib	×	×	×	×	(I)
IBI-318, lenvatinib	×	×	×	×	(I)
KQB-198, osimertinib	×	×	×	×	(I)
LAVA-1223	×	×	×	×	(I)
MRX-2843, osimertinib	×	×	×	×	(I)
osimertinib, carotuximab	×	×	×	×	(I)

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

17 of 24

Report Date: 23 Sep 2025

# **Relevant Therapy Summary (continued)**

In this cancer type

O In other cancer type

• In this cancer type and other cancer types

X No evidence

# EGFR exon 19 deletion (continued)

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

# TP53 p.(M237I) c.711G>A

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

# **CDKN2A** deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	<b>(II)</b>
palbociclib, abemaciclib	×	×	×	×	<b>(II)</b>
AMG 193	×	×	×	×	(I/II)

# **CDKN2B** deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	×	×	×	×	(II)

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

Report Date: 23 Sep 2025 18 of 24

#### **HRR Details**

Gene/Genomic Alteration	Finding
LOH percentage	33.97%
Not Detected	Not Applicable

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

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

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21 of 24

Report Date: 23 Sep 2025

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Report Date: 23 Sep 2025 24 of 24

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