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Patient Name: 이순애
Gender: F
Sample ID: N25-167

Primary Tumor Site: lung
Collection Date: 2025.08.07

Sample Cancer Type: Unknown Primary Origin

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Report Highlights

4 Relevant Biomarkers
17 Therapies Available
220 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*EGFR exon 19 deletion* epidermal growth factor receptor Allele Frequency: 74.08% Locus: chr7:55242465 Transcript: NM_005228.5	None*	**afatinib** [1, 2 / I, II+] **amivantamab + lazertinib** [1, 2 / I, II+] **bevacizumab† + erlotinib** [2 / I, II+] **dacomitinib** [1, 2 / I, II+] **erlotinib** [2 / I, II+] **erlotinib + ramucirumab** [1, 2 / I, II+] **gefitinib** [1, 2 / I, II+] **osimertinib** [1, 2 / I, II+] **osimertinib + chemotherapy** [1, 2 / I] **amivantamab + chemotherapy** [1, 2 / II+] **BAT1706 + erlotinib** [2] gefitinib + chemotherapy [I] atezolizumab + bevacizumab + chemotherapy [II+]	197
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	13
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	11
IIC	*CTNNB1 p.(S37Y) c.110C>A* catenin beta 1 Allele Frequency: 22.65% Locus: chr3:41266113 Transcript: NM_001904.4	None*	None*	2

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
† Includes biosimilars/generics
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

MLH1 p.(V384D) c.1151T>A, MSH2 p.(M688I) c.2064G>A, Microsatellite stable, PARP4 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
EGFR	p.(E746_A750del)	c.2236_2250delGAATTAAGAGAAGCA	COSM6225	chr7:55242465	74.08%	NM_005228.5	nonframeshift Deletion
CTNNB1	p.(S37Y)	c.110C>A	COSM5666	chr3:41266113	22.65%	NM_001904.4	missense
MLH1	p.(V384D)	c.1151T>A	.	chr3:37067240	31.30%	NM_000249.4	missense
MSH2	p.(M688I)	c.2064G>A	.	chr2:47703564	49.80%	NM_000251.3	missense
PARP1	p.(E12K)	c.34G>A	.	chr1:226595597	3.20%	NM_001618.4	missense
NFE2L2	p.(S234*)	c.701C>A	.	chr2:178096630	4.25%	NM_006164.5	nonsense
BARD1	p.(P654S)	c.1960C>T	.	chr2:215595176	4.53%	NM_000465.4	missense
PRDM1	p.(E821K)	c.2461G>A	.	chr6:106555344	13.00%	NM_001198.4	missense
ARID1B	p.(Q855H)	c.2565G>T	.	chr6:157431640	5.60%	NM_001371656.1	missense
KMT2C	p.(E336Q)	c.1006G>C	.	chr7:151970796	3.00%	NM_170606.3	missense
KMT2D	p.(Y5349C)	c.16046A>G	.	chr12:49418367	49.78%	NM_003482.4	missense
CNTNAP4	p.(A1186S)	c.3556G>T	.	chr16:76592428	5.25%	NM_138994.5	missense
RTEL1	p.(S658*)	c.1973C>G	.	chr20:62320877	4.94%	NM_032957.5	nonsense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2A	chr9:21968178	0	0.37
MTAP	chr9:21802646	0.05	0.61
PARP4	chr13:25000551	0.4	0.68
SETBP1	chr18:42281265	0	0.53

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[21]. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[65]. 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[66]. Activation of these pathways promotes cell proliferation, differentiation, and survival[67,68].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[15,16,69,70]. 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 21[71]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer[71]. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[72,73,74,75]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[76]. In contrast, a different set of recurrent activating EGFR mutations in

Biomarker Descriptions (continued)

the extracellular domain includes R108K, A289V and G598V and are primarily observed in glioblastoma[71,77]. Amplification of EGFR is observed in several cancer types including 44% of glioblastoma multiforme, 12% of esophageal adenocarcinoma, 10% of head and neck squamous cell carcinoma, 8% of brain lower grade glioma, 6% of lung squamous cell carcinoma, 5% of bladder urothelial carcinoma cancer, lung adenocarcinoma, and stomach adenocarcinoma, 3% of cholangiocarcinoma, and 2% of cervical squamous cell carcinoma, sarcoma, and breast invasive carcinoma[15,16,70,77,78]. 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[79,80,81]. Alterations in EGFR are rare in pediatric cancers[15,16]. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)[15,16]. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)[15,16].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[82] (2004) and gefitinib[83] (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[84]. Second-generation TKIs afatinib[85] (2013) and dacomitinib[86] (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[87,88,89,90]. However, BDTX-189[91] 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)[92] and sunvozertinib[93], 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[94]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[71]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M[94]. Osimertinib[95] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases[94]. 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[96]. T790M and C797S can occur in either cis or trans allelic orientation[96]. 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[96]. 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[96,97]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[96]. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535[98] (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[99]. The bispecific antibody, amivantamab[100] (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib[101] (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-801[102] received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42[103], 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. CPO301[104] (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[105] (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[41,106,107].

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[21]. 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)[111]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[112,113,114]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[115]. Specifically, the CDKN2A/p16 transcript inhibits cell

Biomarker Descriptions (continued)

cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[21,115,116]. CDKN2A aberrations commonly co-occur with CDKN2B[111]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[117]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[118,119].

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[120]. 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[15,16]. 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[15,16]. Alterations in CDKN2A are also observed in pediatric cancers[16]. 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[16]. 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)[16].

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[18,121,122]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[107]. 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[123,124,125]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[126]. 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[127,128,129,130].

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[21]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[108,109]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[109].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[109,110]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[15,16]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[15,16].

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

CTNNB1 p.(S37Y) c.110C>A

catenin beta 1

Background: The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions, which are involved in maintaining adhesion and regulating the growth of epithelial cell layers[1]. CTNNB1 binds to the APC protein in the cytoplasm and interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling[2]. Steady-state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis[3,4,5]. CTNNB1 exon 3 mutations can lead to persistent activation of the WNT/β-catenin pathway and alter downstream nuclear transcription[6].

Alterations and prevalence: Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-3β and inhibit CTNNB1 degradation[6,7,8,9]. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in

Biomarker Descriptions (continued)

hepatocellular carcinoma, 20% in uterine carcinoma, and 15% in adrenocortical carcinoma[10,11,12,13,14,15,16]. Alterations in CTNNB1 are also observed in pediatric cancers[15,16]. Somatic mutations are observed in 36% of hepatobiliary cancer (4 in 11 cases), 6% of embryonal tumor (21 in 332 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of Wilms tumor (11 in 710 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and bone cancer (1 in 327 cases)[15,16].

Potential relevance: Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer[17]. Mutation of CTNNB1 is considered an ancillary diagnostic biomarker for desmoid fibromatosis and WNT-activated medulloblastoma[18,19,20].

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

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[21]. 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 complex[22]. 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 PMS2[22,23]. 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 hyperplasia[24,25]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[22]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[22]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[26]. 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 tissue[27,28,29]. 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 genes[27,30]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[28,30,31,32]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[33,34,35,36].

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

Potential relevance: The PARP inhibitor, talazoparib[37] 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[38]. 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[39,40]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[41,42].

MSH2 p.(M688I) c.2064G>A

mutS homolog 2

Background: The MSH2 gene encodes the mutS homolog 2 protein[21]. MSH2 is a tumor suppressor gene that heterodimerizes with MSH6 to form the MutSα complex or with MSH3 to form the MutSβ complex[22]. Both MutS complexes function in DNA damage recognition of base-base mismatches or insertion/deletion (indels) mispairs[22]. Specifically, the MutSα complex recognizes 1-2 nucleotide indels while MutSβ recognizes longer indel mispairs[22]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication[22]. Mutations in MSH2 result in the degradation of MSH6[23]. Loss of MSH2 protein expression correlates with mutations in the genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[24]. MSH2, along with MLH1, MSH6, and PMS2, form the core components of the MMR pathway[27]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[26]. 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 tissue[27,28,29]. 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 genes[27,30]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer.[28,30,31,32]. Specifically, MSH2 mutations are associated with an increased risk of ovarian and pancreatic cancer[33,34,35,36].

Alterations and prevalence: Somatic mutations in MSH2 are observed in 8% of uterine corpus endometrial carcinoma, as well as 2-3% of bladder urothelial carcinoma, melanoma, and colorectal adenocarcinoma[15,16]. Alterations in MSH2 are observed in pediatric cancers[15,16]. Somatic mutations are observed in 3% of soft tissue sarcoma, 1% of embryonal tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), and peripheral nervous system tumors (1 in 1158 cases)[15,16].

Biomarker Descriptions (continued)

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[38]. 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[39,40]. MSH2 mutations are consistent with high grade in pediatric diffuse gliomas[41,42].

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[51]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[28,30]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[29]. 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[52]. 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)[52]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[31,53,54,55,56]. 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[30]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[28,30,31,32].

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[28,30,57,58]. 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[57,58].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[38] (2014) and nivolumab[39] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[38] 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[38]. Dostarlimab[59] (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[54,60]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[40] (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[54,61,62]. 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[62]. 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[63,64]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[63,64].

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein[21]. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3[43]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[43,44]. PARP enzymes are involved in several DNA repair pathways[43,44]. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins[45].

Alterations and prevalence: Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma[15,16]. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)[15,16].

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (HRR) deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[46,47]. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[48] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the

Biomarker Descriptions (continued)

maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[48] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[49] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[37] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[50] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-05-14. For the most up-to-date information, search www.fda.gov.

EGFR exon 19 deletion

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion or EGFRi sensitizing mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to a potential first-in-class HER3 directed antibody-drug conjugate, patritumab deruxtecan, for metastatic or locally advanced, EGFR-mutant non-small cell lung cancer.

Reference:

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

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, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, 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, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, 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, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, 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 cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	○	○	○	○	○ (III)
afatinib	○	○	○	○	○ (II)
dacomitinib	○	○	○	○	○ (II)
gefitinib	○	○	○	○	○ (II)
erlotinib + ramucirumab	○	○	○	○	✖
amivantamab + carboplatin + pemetrexed	○	○	○	✖	✖
amivantamab + lazertinib	○	○	○	✖	✖
osimertinib + chemotherapy + pemetrexed	○	✖	○	✖	✖
bevacizumab + erlotinib	✖	○	○	○	✖
erlotinib	✖	○	○	○	✖

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib + carboplatin + pemetrexed	✖	○	✖	✖	✖
osimertinib + cisplatin + pemetrexed	✖	○	✖	✖	✖
BAT1706 + erlotinib	✖	✖	○	✖	✖
bevacizumab (Allergan) + erlotinib	✖	✖	○	✖	✖
bevacizumab (Biocon) + erlotinib	✖	✖	○	✖	✖
bevacizumab (Celltrion) + erlotinib	✖	✖	○	✖	✖
bevacizumab (Mabxience) + erlotinib	✖	✖	○	✖	✖
bevacizumab (Pfizer) + erlotinib	✖	✖	○	✖	✖
bevacizumab (Samsung Bioepis) + erlotinib	✖	✖	○	✖	✖
bevacizumab (Stada) + erlotinib	✖	✖	○	✖	✖
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	○	✖
gefitinib + carboplatin + pemetrexed	✖	✖	✖	○	✖
WSD-0922	✖	✖	✖	✖	◑ (I/II)
almonertinib, dacomitinib	✖	✖	✖	✖	● (II)
MRTX0902	✖	✖	✖	✖	● (I/II)
KQB-198, osimertinib	✖	✖	✖	✖	● (I)
adebrelimab, bevacizumab, chemotherapy	✖	✖	✖	✖	○ (IV)
afatinib, bevacizumab, chemotherapy	✖	✖	✖	✖	○ (IV)
befotertinib	✖	✖	✖	✖	○ (IV)
bevacizumab, almonertinib, chemotherapy	✖	✖	✖	✖	○ (IV)
catequentinib, toripalimab	✖	✖	✖	✖	○ (IV)
EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	○ (IV)
gefitinib, chemotherapy	✖	✖	✖	✖	○ (IV)
gefitinib, endostatin	✖	✖	✖	✖	○ (IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	✖	✖	✖	✖	○ (IV)
almonertinib, apatinib	✖	✖	✖	✖	○ (III)
almonertinib, chemotherapy	✖	✖	✖	✖	○ (III)
almonertinib, radiation therapy	✖	✖	✖	✖	○ (III)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion (continued)

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

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
almonertinib, chemoradiation therapy	✖	✖	✖	✖	○ (II)
amivantamab, chemotherapy	✖	✖	✖	✖	○ (II)
amivantamab, lazertinib, chemotherapy	✖	✖	✖	✖	○ (II)
atezolizumab, bevacizumab, tiragolumab	✖	✖	✖	✖	○ (II)
befotertinib, bevacizumab, chemotherapy	✖	✖	✖	✖	○ (II)
bevacizumab, afatinib	✖	✖	✖	✖	○ (II)
bevacizumab, furmonertinib	✖	✖	✖	✖	○ (II)
cadonilimab, chemotherapy, catequentinib	✖	✖	✖	✖	○ (II)
camrelizumab, apatinib	✖	✖	✖	✖	○ (II)
capmatinib, osimertinib, ramucirumab	✖	✖	✖	✖	○ (II)
catequentinib, almonertinib	✖	✖	✖	✖	○ (II)
chemotherapy, atezolizumab, bevacizumab	✖	✖	✖	✖	○ (II)
dacomitinib, osimertinib	✖	✖	✖	✖	○ (II)
EGFR tyrosine kinase inhibitor, osimertinib, chemotherapy	✖	✖	✖	✖	○ (II)
EGFR tyrosine kinase inhibitor, radiation therapy	✖	✖	✖	✖	○ (II)
erlotinib, chemotherapy	✖	✖	✖	✖	○ (II)
erlotinib, OBI-833	✖	✖	✖	✖	○ (II)
furmonertinib, bevacizumab	✖	✖	✖	✖	○ (II)
furmonertinib, bevacizumab, chemotherapy	✖	✖	✖	✖	○ (II)
furmonertinib, catequentinib	✖	✖	✖	✖	○ (II)
furmonertinib, chemotherapy	✖	✖	✖	✖	○ (II)
furmonertinib, chemotherapy, bevacizumab	✖	✖	✖	✖	○ (II)
furmonertinib, icotinib hydrochloride	✖	✖	✖	✖	○ (II)
gefitinib, bevacizumab, chemotherapy	✖	✖	✖	✖	○ (II)
gefitinib, icotinib hydrochloride	✖	✖	✖	✖	○ (II)
gefitinib, thalidomide	✖	✖	✖	✖	○ (II)
icotinib hydrochloride	✖	✖	✖	✖	○ (II)
icotinib hydrochloride, autologous RAK cell	✖	✖	✖	✖	○ (II)
icotinib hydrochloride, osimertinib	✖	✖	✖	✖	○ (II)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion (continued)

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

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
DB-1310, osimertinib	✖	✖	✖	✖	○ (I/II)
dositinib	✖	✖	✖	✖	○ (I/II)
EMB01	✖	✖	✖	✖	○ (I/II)
FWD-1509	✖	✖	✖	✖	○ (I/II)
H-002	✖	✖	✖	✖	○ (I/II)
ifebemtinib, furmonertinib	✖	✖	✖	✖	○ (I/II)
necitumumab, osimertinib	✖	✖	✖	✖	○ (I/II)
quaratusugene ozeplasmid, osimertinib	✖	✖	✖	✖	○ (I/II)
RC-108, furmonertinib, toripalimab	✖	✖	✖	✖	○ (I/II)
sotiburafusp alfa, HB-0030	✖	✖	✖	✖	○ (I/II)
sunvozertinib, chemotherapy	✖	✖	✖	✖	○ (I/II)
TAS-3351	✖	✖	✖	✖	○ (I/II)
TQ-B3525, osimertinib	✖	✖	✖	✖	○ (I/II)
TRX-221	✖	✖	✖	✖	○ (I/II)
afatinib, chemotherapy	✖	✖	✖	✖	○ (I)
alisertib, osimertinib	✖	✖	✖	✖	○ (I)
almonertinib, midazolam	✖	✖	✖	✖	○ (I)
ASKC-202	✖	✖	✖	✖	○ (I)
AZD-9592	✖	✖	✖	✖	○ (I)
BG-60366	✖	✖	✖	✖	○ (I)
BPI-1178, osimertinib	✖	✖	✖	✖	○ (I)
catequentinib, gefitinib, metformin hydrochloride	✖	✖	✖	✖	○ (I)
DZD-6008	✖	✖	✖	✖	○ (I)
EGFR tyrosine kinase inhibitor, catequentinib	✖	✖	✖	✖	○ (I)
genolimzumab, fruquintinib	✖	✖	✖	✖	○ (I)
IBI-318, lenvatinib	✖	✖	✖	✖	○ (I)
LAVA-1223	✖	✖	✖	✖	○ (I)
MRX-2843, osimertinib	✖	✖	✖	✖	○ (I)
osimertinib, carotuximab	✖	✖	✖	✖	○ (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

EGFR exon 19 deletion (continued)

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

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)
ficlatuzumab, cetuximab	✖	✖	✖	✖	○ (III)
palbociclib, cetuximab	✖	✖	✖	✖	○ (III)
chemotherapy, cetuximab, radiation therapy	✖	✖	✖	✖	○ (II/III)
abemaciclib	✖	✖	✖	✖	○ (II)
niraparib, dostarlimab	✖	✖	✖	✖	○ (II)
ribociclib, everolimus	✖	✖	✖	✖	○ (II)
tiragolumab, atezolizumab	✖	✖	✖	✖	○ (II)
tislelizumab, palbociclib	✖	✖	✖	✖	○ (I/II)
ipatasertib, chemotherapy, radiation therapy	✖	✖	✖	✖	○ (I)

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
MRTX-1719	✖	✖	✖	✖	◑ (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

MTAP deletion (continued)

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

CTNNB1 p.(S37Y) c.110C>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sunvozertinib, catequentinib	✖	✖	✖	✖	○ (II)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***27.7%***
BRCA2	***LOH, 13q13.1(32890491-32972932)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 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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