

Patient Name: 전태철
Gender: M
Sample ID: N25-75

Primary Tumor Site: Lung
Collection Date: 2025.06.09

Sample Cancer Type: Lung Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	4 Relevant Biomarkers
Biomarker Descriptions	3	26 Therapies Available
Alert Details	10	208 Clinical Trials
Relevant Therapy Summary	11	

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	EGFR p.(L858R) c.2573T>G	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	5.69 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	EGFR p.(L858R) c.2573T>G epidermal growth factor receptor Allele Frequency: 13.36% Locus: chr7:55259515 Transcript: NM_005228.5	afatinib ^{1, 2 / I, II+} amivantamab + lazertinib ^{1, 2 / I, II+} bevacizumab† + erlotinib ^{2 / I, II+} dacomitinib ^{1, 2 / I, II+} erlotinib ^{2 / I, II+} erlotinib + ramucirumab ^{1, 2 / I, II+} gefitinib ^{1, 2 / I, II+} osimertinib ^{1, 2 / I, II+} osimertinib + chemotherapy ^{1, 2 / I} amivantamab + chemotherapy ^{1, 2 / II+} BAT1706 + erlotinib ² gefitinib + chemotherapy ^I atezolizumab + bevacizumab + chemotherapy ^{II+}	None*	195

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

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

† Includes biosimilars/generics

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

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	BRCA1 p.(Q310*) c.928C>T BRCA1, DNA repair associated Allele Frequency: 48.62% Locus: chr17:41246620 Transcript: NM_007294.4	None*	abiraterone + niraparib ^{1, 2 / II+} bevacizumab + olaparib ^{1, 2 / II+} olaparib ^{1, 2 / II+} rucaparib ^{1 / II+} talazoparib + hormone therapy ^{1 / II+} bevacizumab + niraparib ^{II+} niraparib ^{II+} olaparib + hormone therapy ^{II+} talazoparib ^{II+}	13
IIC	STK11 deletion serine/threonine kinase 11 Locus: chr19:1206847	None*	None*	1
IIC	TSC2 deletion tuberous sclerosis 2 Locus: chr16:2098579	None*	None*	1

* Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
† Includes biosimilars/generics
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

 Alerts informed by public data sources:  Contraindicated,  Resistance,  Breakthrough,  Fast Track

EGFR p.(L858R) c.2573T>G  patritumab deruxtecan ¹

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

Prevalent cancer biomarkers without relevant evidence based on included data sources
MAP2K7 deletion, Microsatellite stable, ERAP2 deletion, HLA-A deletion, RECQL4 deletion, NOTCH1 deletion, NQO1 p.(P187S) c.559C>T, CIC deletion, RBM10 p.(L600Pfs*169) c.1799delT, Tumor Mutational Burden

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
EGFR	p.(L858R)	c.2573T>G	COSM6224	chr7:55259515	13.36%	NM_005228.5	missense
BRCA1	p.(Q310*)	c.928C>T	.	chr17:41246620	48.62%	NM_007294.4	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.70%	NM_000903.3	missense
RBM10	p.(L600Pfs*169)	c.1799delT	.	chrX:47041175	28.72%	NM_001204468.1	frameshift Deletion
JAK1	p.(Q834R)	c.2501A>G	.	chr1:65307187	54.40%	NM_002227.4	missense
MAML3	p.(Q489Tfs*29)	c.1455_1506delACAGC . AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACAGA CAGCCAGCAGCAGCA GCAGCAGCAGCAA	.	chr4:140811084	44.38%	NM_018717.5	frameshift Block Substitution

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGC . AACAGCAACAGCAGC AGCAGCAGCAGCAGC AGCAGCAGCAGCAGC AGinsGCAGCAACAGC AACAGCCAGCAGCAG CAGCAGCAGCAGCAA		chr4:140811084	54.79%	NM_018717.5	frameshift Block Substitution
MSH3	p.(A57_A62del)	c.162_179delTGCAGC . GGCCGCAGCGGC		chr5:79950707	58.04%	NM_002439.5	nonframeshift Deletion
LATS1	p.(I288L)	c.862A>C		chr6:150005363	50.65%	NM_004690.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
STK11	chr19:1206847	0.58	0.57
TSC2	chr16:2098579	0.7	0.61
MAP2K7	chr19:7968792	0.07	0.42
ERAP2	chr5:96219500	0.3	0.49
HLA-A	chr6:29910229	0.33	0.5
RECQL4	chr8:145736758	0.88	0.67
NOTCH1	chr9:139390441	0.33	0.5
CIC	chr19:42775916	1	0.7
FGFR3	chr4:1801456	0.03	0.41
FLT4	chr5:180030092	0.68	0.6
HRAS	chr11:532637	0	0.37
CCND1	chr11:69455949	0.42	0.52
FOXA1	chr14:38060550	0.05	0.42
AKT1	chr14:105236628	0.45	0.54
SOCS1	chr16:11348676	0.22	0.46
CYLD	chr16:50783549	5.18	1.96
SOX9	chr17:70117435	0.67	0.6

Biomarker Descriptions

EGFR p.(L858R) c.2573T>G

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 family¹². In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4⁸⁵. EGFR ligand-induced dimerization results in kinase activation and leads to stimulation

Biomarker Descriptions (continued)

of oncogenic signaling pathways, including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways⁸⁶. Activation of these pathways promotes cell proliferation, differentiation, and survival^{87,88}.

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^{5,6,7,89}. 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 21⁹⁰. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer⁹⁰. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{91,92,93,94}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations⁹⁵. 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^{90,96}. 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^{5,6,7,96,97}. 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^{98,99,100}. Alterations in EGFR are rare in pediatric cancers^{6,7}. 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)^{6,7}. 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 erlotinib¹⁰¹ (2004) and gefitinib¹⁰² (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 mutations¹⁰³. Second-generation TKIs afatinib¹⁰⁴ (2013) and dacomitinib¹⁰⁵ (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^{106,107,108,109}. However, BDTX-189¹¹⁰ 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)¹¹¹ and sunvozertinib¹¹², 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 resistance¹¹³. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases⁹⁰. Third generation TKIs were developed to maintain sensitivity in the presence of T790M¹¹³. Osimertinib¹¹⁴ (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 cases¹¹³. 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 versa¹¹⁵. T790M and C797S can occur in either cis or trans allelic orientation¹¹⁵. 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 TKIs¹¹⁵. 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^{115,116}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs¹¹⁵. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535¹¹⁷ (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 mutations¹¹⁸. The bispecific antibody, amivantamab¹¹⁹ (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib¹²⁰ (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-801¹²¹ received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42¹²², an anti-EGFR-antibody-drug conjugate (ADC) consisting of an anti-EGFR monoclonal antibody conjugated with a novel high potency DNA topoisomerase I (topo I) inhibitor, also received fast track designation (2024) for the treatment of patients with advanced or metastatic EGFR-mutated non-small cell lung cancer whose disease has progressed on a third-generation EGFR tyrosine kinase inhibitor. CPO301¹²³ (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 ozeplasmid¹²⁴ (2020), in combination with osimertinib, received fast track designation from the FDA for NSCLC tumors harboring EGFR

Biomarker Descriptions (continued)

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^{125,126,127}.

BRCA1 p.(Q310*) c.928C>T

BRCA1, DNA repair associated

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{59,60}. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{59,60}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{61,62,63}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{61,64}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{65,66,67,68,69,70,71,72}. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme^{6,7}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)⁷³. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{74,75}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁷⁶ (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib⁷⁶ 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. Rucaparib⁷⁷ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib⁷⁸ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib⁷⁸ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib⁷⁹ (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. Niraparib in combination with abiraterone acetate⁸⁰ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁸¹. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁸². In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁸³, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348⁸⁴, a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression¹. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development^{2,3}.

Alterations and prevalence: Somatic mutations in STK11 have been reported in 10% of lung cancer, 4% of cervical cancer, and up to 3% of cholangiocarcinoma and uterine cancer^{4,5,6,7}. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer^{6,7}. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others^{2,5,6,7,8}.

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription),

Biomarker Descriptions (continued)

TNG-260⁹ in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors¹⁰. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)¹¹.

TSC2 deletion

tuberous sclerosis 2

Background: The TSC2 gene encodes the tuberlin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains¹⁴⁴. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis¹⁴⁵. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway^{144,146}. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs¹⁴⁴.

Alterations and prevalence: Somatic mutations are observed in up to 8% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for TSC2 aberrations.

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7¹². MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10^{128,129,130}. Activation of MAPK proteins occurs through a kinase signaling cascade^{128,129,131}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{128,129,131}. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation^{128,129,131}.

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma^{6,7}. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma^{6,7}.

Potential relevance: Currently, no therapies are approved for MAP2K7 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 genome³⁷. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{38,39}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁴⁰. 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 D17S250⁴¹. 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)⁴¹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{42,43,44,45,46}. 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 genes³⁹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{38,39,43,47}.

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endometrial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma^{38,39,48,49}. 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^{48,49}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁵⁰ (2014) and nivolumab⁵¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁵⁰ 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

Biomarker Descriptions (continued)

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 indication⁵⁰. Dostarlimab⁵² (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^{44,53}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁵⁴ (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^{44,55,56}. 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 patients⁵⁶. 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^{57,58}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{57,58}.

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway^{132,133}. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules^{132,134}. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic¹³².

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma^{6,7}. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for ERAP2 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A¹². MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells¹³. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M¹⁴. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self^{15,16,17}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A¹⁸.

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma^{6,7}. Biallelic loss of HLA-A is observed in 4% of DLBCL^{6,7}.

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

RECQL4 deletion

RecQ like helicase 4

Background: RECQL4 encodes RecQ like helicase 4 and is member of the RecQ family of DNA helicases, which also includes RECQL1, WRN, BLM, and RECQL5^{12,19,20}. RECQL4 plays an important role in DNA replication, telomere maintenance, homologous recombination, and genomic stability^{20,21,22}. Mutations in RECQL4 can lead to several developmental syndromes including, Rothmund-Thomson syndrome (RTS), Baller-Gerold syndrome (BGS), and RAPADILINO syndrome, which confer predisposition to the development of several cancer types including skin cancer, osteosarcoma, lymphoma, and leukemia^{23,24,25}. Although widely considered a tumor suppressor gene, amplification and overexpression of RECQL4 has been observed to promote tumor growth in some cancer types^{26,27,28}.

Alterations and prevalence: Somatic mutations in RECQL4 are observed in 5% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of lung squamous cell carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, liver hepatocellular carcinoma, esophageal adenocarcinoma, and head and neck squamous cell carcinoma^{6,7}. Amplification of RECQL4 is observed in 27% of ovarian serous cystadenocarcinoma, 11% of breast

Biomarker Descriptions (continued)

invasive carcinoma, 10% of esophageal adenocarcinoma and liver hepatocellular carcinoma, 9% of pancreatic adenocarcinoma and uterine carcinosarcoma, 8% of head and neck squamous cell carcinoma, 6% of prostate adenocarcinoma, 5% of lung adenocarcinoma, stomach adenocarcinoma, and lung squamous cell carcinoma, 4% of skin cutaneous melanoma and brain lower grade glioma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and diffuse large B-cell lymphoma^{6,7}. Biallelic loss of RECQL4 is observed in 4% of diffuse large B-cell lymphoma and 2% of brain lower grade glioma^{6,7}.

Potential relevance: Currently, no therapies are approved for RECQL4 aberrations.

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling¹³⁵. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism^{136,137}. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members^{138,139,140,141}.

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers^{6,7,97}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{142,143}.

Potential relevance: Currently, no therapies are approved for NOTCH1 aberrations.

CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily^{12,29}. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes^{12,29}. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5²⁹. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC²⁹.

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma^{6,7}. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)^{6,7}. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma^{29,30}.

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma^{31,32}.

RBM10 p.(L600Pfs*169) c.1799delT

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family^{12,33}. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA^{33,34}. 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 expression³³. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10^{35,36}.

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^{6,7}. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma^{6,7}. Amplification of RBM10 is observed in 5% of

Biomarker Descriptions (continued)

ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma^{6,7}.

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-04-16. For the most up-to-date information, search www.fda.gov.

EGFR p.(L858R) c.2573T>G

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer Variant class: EGFR L858R mutation or EGFRi sensitizing mutation

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

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBF1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERFFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBF2,

Genes Assayed (continued)

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

TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSP02, RSP03, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBF3, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERFF1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

Relevant Therapy Summary

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

EGFR p.(L858R) c.2573T>G

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 p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib + carboplatin + pemetrexed	✕	●	✕	✕	✕
osimertinib + cisplatin + pemetrexed	✕	●	✕	✕	✕
BAT1706 + erlotinib	✕	✕	●	✕	✕
bevacizumab (Allergan) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Biocon) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Celltrion) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Mabxience) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Pfizer) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Samsung Bioepis) + erlotinib	✕	✕	●	✕	✕
bevacizumab (Stada) + erlotinib	✕	✕	●	✕	✕
atezolizumab + bevacizumab + carboplatin + paclitaxel	✕	✕	✕	●	✕
gefitinib + carboplatin + pemetrexed	✕	✕	✕	●	✕
adebreliumab, bevacizumab, chemotherapy	✕	✕	✕	✕	● (IV)
afatinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (IV)
befotertinib	✕	✕	✕	✕	● (IV)
bevacizumab, almonertinib, chemotherapy	✕	✕	✕	✕	● (IV)
catequentinib, toripalimab	✕	✕	✕	✕	● (IV)
EGFR tyrosine kinase inhibitor	✕	✕	✕	✕	● (IV)
gefitinib, chemotherapy	✕	✕	✕	✕	● (IV)
gefitinib, endostatin	✕	✕	✕	✕	● (IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	✕	✕	✕	✕	● (IV)
almonertinib, apatinib	✕	✕	✕	✕	● (III)
almonertinib, chemotherapy	✕	✕	✕	✕	● (III)
almonertinib, radiation therapy	✕	✕	✕	✕	● (III)
almonertinib, radiation therapy, chemotherapy	✕	✕	✕	✕	● (III)
befotertinib, icotinib hydrochloride	✕	✕	✕	✕	● (III)
bevacizumab, osimertinib	✕	✕	✕	✕	● (III)
BL-B01D1	✕	✕	✕	✕	● (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
 ① In this cancer type and other cancer types
 ✕ No evidence

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BL-B01D1, osimertinib	✕	✕	✕	✕	● (III)
CK-101, gefitinib	✕	✕	✕	✕	● (III)
datopotamab deruxtecan, osimertinib	✕	✕	✕	✕	● (III)
FHND9041, afatinib	✕	✕	✕	✕	● (III)
furmonertinib	✕	✕	✕	✕	● (III)
furmonertinib, osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
gefitinib, afatinib, erlotinib, metformin hydrochloride	✕	✕	✕	✕	● (III)
icotinib hydrochloride, catequentinib	✕	✕	✕	✕	● (III)
icotinib hydrochloride, chemotherapy	✕	✕	✕	✕	● (III)
icotinib hydrochloride, radiation therapy	✕	✕	✕	✕	● (III)
JMT-101, osimertinib	✕	✕	✕	✕	● (III)
osimertinib, bevacizumab	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, datopotamab deruxtecan	✕	✕	✕	✕	● (III)
sacituzumab tirumotecan	✕	✕	✕	✕	● (III)
sacituzumab tirumotecan, osimertinib	✕	✕	✕	✕	● (III)
savolitinib, osimertinib	✕	✕	✕	✕	● (III)
SH-1028	✕	✕	✕	✕	● (III)
targeted therapy	✕	✕	✕	✕	● (III)
TY-9591, osimertinib	✕	✕	✕	✕	● (III)
ABSK-043, furmonertinib	✕	✕	✕	✕	● (II)
almonertinib	✕	✕	✕	✕	● (II)
almonertinib, adabrelimab, chemotherapy	✕	✕	✕	✕	● (II)
almonertinib, bevacizumab	✕	✕	✕	✕	● (II)
almonertinib, chemoradiation therapy	✕	✕	✕	✕	● (II)
almonertinib, dacomitinib	✕	✕	✕	✕	● (II)
amivantamab, chemotherapy	✕	✕	✕	✕	● (II)
amivantamab, lazertinib, chemotherapy	✕	✕	✕	✕	● (II)
atezolizumab, bevacizumab, tiragolumab	✕	✕	✕	✕	● (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 p.(L858R) c.2573T>G (continued)

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

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

Relevant Therapy Summary (continued)

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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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)
zorifertinib, pirotinib	✕	✕	✕	✕	● (II)
AFM-24_I, atezolizumab	✕	✕	✕	✕	● (I/II)
almonertinib, icotinib hydrochloride	✕	✕	✕	✕	● (I/II)
BDTX-1535	✕	✕	✕	✕	● (I/II)
BEBT-908, BEBT-109	✕	✕	✕	✕	● (I/II)
benmelstobart, catequentinib	✕	✕	✕	✕	● (I/II)
BH-30643	✕	✕	✕	✕	● (I/II)
bozitinib, osimertinib	✕	✕	✕	✕	● (I/II)
bozitinib, PLB-1004	✕	✕	✕	✕	● (I/II)
BPI-361175	✕	✕	✕	✕	● (I/II)
cetrelimab, amivantamab	✕	✕	✕	✕	● (I/II)
dacomitinib, catequentinib	✕	✕	✕	✕	● (I/II)
DAJH-1050766	✕	✕	✕	✕	● (I/II)
DB-1310, osimertinib	✕	✕	✕	✕	● (I/II)
dositinib	✕	✕	✕	✕	● (I/II)

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

Relevant Therapy Summary (continued)

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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
FWD-1509	×	×	×	×	● (I/II)
H-002	×	×	×	×	● (I/II)
ifebemtinib, furmonertinib	×	×	×	×	● (I/II)
MRTX0902	×	×	×	×	● (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)
WSD-0922	×	×	×	×	● (I/II)
afatinib, chemotherapy	×	×	×	×	● (I)
alisertib, osimertinib	×	×	×	×	● (I)
AZD-9592	×	×	×	×	● (I)
BG-60366	×	×	×	×	● (I)
BPI-1178, osimertinib	×	×	×	×	● (I)
catequentinib, gefitinib, metformin hydrochloride	×	×	×	×	● (I)
cemiplimab, sarilumab	×	×	×	×	● (I)
DZD-6008	×	×	×	×	● (I)
EGFR tyrosine kinase inhibitor, catequentinib	×	×	×	×	● (I)
genolimzumab, fruquintinib	×	×	×	×	● (I)
IBI-318, lenvatinib	×	×	×	×	● (I)
KQB-198, osimertinib	×	×	×	×	● (I)
LAVA-1223	×	×	×	×	● (I)
MRX-2843, osimertinib	×	×	×	×	● (I)
osimertinib, carotuximab	×	×	×	×	● (I)
osimertinib, Minnelide	×	×	×	×	● (I)

* 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 p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib, tegatrabetan	✕	✕	✕	✕	● (I)
patritumab deruxtecan	✕	✕	✕	✕	● (I)
repotrectinib, osimertinib	✕	✕	✕	✕	● (I)
VIC-1911, osimertinib	✕	✕	✕	✕	● (I)
WJ13404	✕	✕	✕	✕	● (I)
WTS-004	✕	✕	✕	✕	● (I)
YH-013	✕	✕	✕	✕	● (I)
YL-202	✕	✕	✕	✕	● (I)

BRCA1 p.(Q310*) c.928C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	○	○	○	○	● (II)
bevacizumab + olaparib	○	○	○	○	✕
abiraterone + niraparib	○	○	○	✕	✕
rucaparib	○	○	✕	○	✕
talazoparib + enzalutamide	○	○	✕	✕	✕
niraparib	✕	○	✕	○	● (II)
bevacizumab + niraparib	✕	○	✕	✕	✕
olaparib + abiraterone acetate	✕	○	✕	✕	✕
talazoparib	✕	✕	✕	○	● (II)
niraparib, dostarlimab	✕	✕	✕	✕	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✕	✕	✕	✕	● (II)
pamiparib, tislelizumab	✕	✕	✕	✕	● (II)
ZEN-3694, talazoparib	✕	✕	✕	✕	● (II)
AMXI-5001	✕	✕	✕	✕	● (I/II)
sacituzumab govitecan, berzosertib	✕	✕	✕	✕	● (I/II)
HS-10502	✕	✕	✕	✕	● (I)
niraparib, chemotherapy	✕	✕	✕	✕	● (I)
novobiocin	✕	✕	✕	✕	● (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

BRCA1 p.(Q310*) c.928C>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, chemotherapy	×	×	×	×	<div></div> (I)

STK11 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TQ-B3525, osimertinib	×	×	×	×	<div></div> (I/II)

TSC2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TQ-B3525, osimertinib	×	×	×	×	<div></div> (I/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	0.0%
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 2025.05(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-04-16. NCCN information was sourced from www.nccn.org and is current as of 2025-04-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-04-16. ESMO information was sourced from www.esmo.org and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

References

1. Li et al. Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells (Review). *Oncol. Rep.* 2015 Dec;34(6):2821-6. PMID: 26398719
2. Zhou et al. LKB1 Tumor Suppressor: Therapeutic Opportunities Knock when LKB1 Is Inactivated. *Genes Dis.* 2014 Sep 1;1(1):64-74. PMID: 25679014
3. Hemminki et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* 1998 Jan 8;391(6663):184-7. PMID: 9428765
4. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat. Genet.* 2016 Jun;48(6):607-16. PMID: 27158780
5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature.* 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
8. Sanchez-Cespedes et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res.* 2002 Jul 1;62(13):3659-62. PMID: 12097271
9. <https://ir.tangotx.com/news-releases/news-release-details/tango-therapeutics-announces-first-patient-dosed-tng260-phase-12>
10. Koyama et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. *Cancer Res.* 2016 Mar 1;76(5):999-1008. PMID: 26833127
11. Skoulidis et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discov.* 2018 Jul;8(7):822-835. PMID: 29773717
12. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
13. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
14. Adams et al. The adaptable major histocompatibility complex (MHC) fold: structure and function of nonclassical and MHC class I-like molecules. *Annu Rev Immunol.* 2013;31:529-61. PMID: 23298204
15. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
16. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
17. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
18. Cornel et al. MHC Class I Downregulation in Cancer: Underlying Mechanisms and Potential Targets for Cancer Immunotherapy. *Cancers (Basel).* 2020 Jul 2;12(7). PMID: 32630675
19. Croteau et al. RECQL4 in genomic instability and aging. *Trends Genet.* 2012 Dec;28(12):624-31. PMID: 22940096
20. Arora et al. RECQL4 helicase has oncogenic potential in sporadic breast cancers. *J Pathol.* 2016 Mar;238(4):495-501. PMID: 26690729
21. Chi et al. RecQL4 cytoplasmic localization: implications in mitochondrial DNA oxidative damage repair. *Int J Biochem Cell Biol.* 2012 Nov;44(11):1942-51. PMID: 22824301
22. Singh et al. The human RecQ helicases BLM and RECQL4 cooperate to preserve genome stability. *Nucleic Acids Res.* 2012 Aug;40(14):6632-48. PMID: 22544709
23. Guo et al. RECQL4, Negatively Regulated by miR-10a-5p, Facilitates Cell Proliferation and Invasion via MAFB in Ovarian Cancer. *Front Oncol.* 2020;10:524128. PMID: 33014878
24. Lu et al. RECQ DNA Helicases and Osteosarcoma. *Adv Exp Med Biol.* 2020;1258:37-54. PMID: 32767233
25. Balajee. Human RecQL4 as a Novel Molecular Target for Cancer Therapy. *Cytogenet Genome Res.* 2021;161(6-7):305-327. PMID: 34474412
26. Fang et al. RecQL4 helicase amplification is involved in human breast tumorigenesis. *PLoS One.* 2013;8(7):e69600. PMID: 23894508
27. Su et al. Human RecQL4 helicase plays critical roles in prostate carcinogenesis. *Cancer Res.* 2010 Nov 15;70(22):9207-17. PMID: 21045146
28. Chen et al. Overexpression of RECQL4 is associated with poor prognosis in patients with gastric cancer. *Oncol Lett.* 2018 Oct;16(4):5419-5425. PMID: 30250613

References (continued)

29. Wong et al. Making heads or tails - the emergence of capicua (CIC) as an important multifunctional tumour suppressor. *J Pathol.* 2020 Apr;250(5):532-540. PMID: 32073140
30. Huang et al. Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations. *Am J Surg Pathol.* 2016 May;40(5):645-55. PMID: 26735859
31. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 5.2024]
32. NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2025]
33. Cao et al. RBM10 Regulates Tumor Apoptosis, Proliferation, and Metastasis. *Front Oncol.* 2021;11:603932. PMID: 33718153
34. Zhang et al. RNA binding motif protein 10 suppresses lung cancer progression by controlling alternative splicing of eukaryotic translation initiation factor 4H. *EBioMedicine.* 2020 Nov;61:103067. PMID: 33130397
35. Sun et al. Functional role of RBM10 in lung adenocarcinoma proliferation. *Int J Oncol.* 2019 Feb;54(2):467-478. PMID: 30483773
36. Loiselle et al. RBM10 promotes transformation-associated processes in small cell lung cancer and is directly regulated by RBM5. *PLoS One.* 2017;12(6):e0180258. PMID: 28662214
37. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
38. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. *Front Oncol.* 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
39. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
40. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. *Front Microbiol.* 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
41. Boland et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998 Nov 15;58(22):5248-57. PMID: 9823339
42. Halford et al. Low-level microsatellite instability occurs in most colorectal cancers and is a nonrandomly distributed quantitative trait. *Cancer Res.* 2002 Jan 1;62(1):53-7. PMID: 11782358
43. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
44. NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2025]
45. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
46. Lee et al. Low-Level Microsatellite Instability as a Potential Prognostic Factor in Sporadic Colorectal Cancer. *Medicine (Baltimore).* 2015 Dec;94(50):e2260. PMID: 26683947
47. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J. Clin. Oncol.* 2019 Feb 1;37(4):286-295. PMID: 30376427
48. Cortes-Ciriano et al. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun.* 2017 Jun 6;8:15180. doi: 10.1038/ncomms15180. PMID: 28585546
49. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
51. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125554s127lbl.pdf
52. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
53. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
54. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s132lbl.pdf
55. Ribic et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N. Engl. J. Med.* 2003 Jul 17;349(3):247-57. PMID: 12867608
56. Klingbiel et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann. Oncol.* 2015 Jan;26(1):126-32. PMID: 25361982
57. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
58. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
59. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. *Breast Cancer Res.* 2002;4(1):9-13. PMID: 11879553

References (continued)

60. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene*. 2002 Dec 16;21(58):8981-93. PMID: 12483514
61. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017 Jun 20;317(23):2402-2416. PMID: 28632866
62. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J. Natl. Cancer Inst.* 2007 Dec 5;99(23):1811-4. PMID: 18042939
63. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br. J. Cancer*. 2007 Jan 15;96(1):11-5. PMID: 17213823
64. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. *JNCI Cancer Spectr.* 2020 Aug;4(4):pkaa029. PMID: 32676552
65. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. *GeneReviews®* [Internet]. PMID: 20301425
66. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin. Proc.* 2010 Dec;85(12):1111-20. PMID: 21123638
67. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc. Natl. Acad. Sci. U.S.A.* 2011 Nov 1;108(44):18032-7. PMID: 22006311
68. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J. Clin. Oncol.* 2012 Jul 20;30(21):2654-63. PMID: 22711857
69. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiol. Biomarkers Prev.* 2004 Dec;13(12):2078-83. PMID: 15598764
70. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003 Oct 24;302(5645):643-6. PMID: 14576434
71. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br. J. Cancer*. 2000 Nov;83(10):1301-8. PMID: 11044354
72. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. *Environ Mol Mutagen.* 2022 Jul;63(6):308-316. PMID: 36054589
73. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. *Br. J. Cancer*. 2018 Nov;119(11):1401-1409. PMID: 30353044
74. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005 Apr 14;434(7035):913-7. PMID: 15829966
75. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005 Apr 14;434(7035):917-21. PMID: 15829967
76. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
77. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
78. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
79. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf
80. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
81. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. *J. Pathol.* 2013 Feb;229(3):422-9. PMID: 23165508
82. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst.)*. 2018 Nov;71:172-176. PMID: 30177437
83. <https://www.senhwbio.com/en/news/20220125>
84. <https://ir.tangotx.com/news-releases/news-release-details/tango-therapeutics-reports-third-quarter-2023-financial-results>
85. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science*. 1985 Sep 6;229(4717):974-6. PMID: 2992089
86. Liu et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. *Mol Cancer*. 2018 Feb 19;17(1):53. PMID: 29455669
87. Zhixiang. ErbB Receptors and Cancer. *Methods Mol. Biol.* 2017;1652:3-35. PMID: 28791631
88. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
89. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. *FEBS Lett.* 2010 Jun 18;584(12):2699-706. PMID: 20388509

References (continued)

90. da et al. EGFR mutations and lung cancer. *Annu Rev Pathol.* 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
91. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol. Cancer Ther.* 2013 Feb;12(2):220-9. PMID: 23371856
92. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. *Clin Cancer Res.* 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867
93. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med.* 2013 Dec 18;5(216):216ra177. PMID: 24353160
94. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. *J Thorac Oncol.* 2015 May;10(5):793-9. PMID: 25668120
95. Karachaliou et al. KRAS mutations in lung cancer. *Clin Lung Cancer.* 2013 May;14(3):205-14. PMID: 23122493
96. Brennan et al. The somatic genomic landscape of glioblastoma. *Cell.* 2013 Oct 10;155(2):462-77. PMID: 24120142
97. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
98. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J.* 2010 Jan;277(2):301-8. PMID: 19922469
99. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene.* 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293
100. Gan et al. The EGFRvIII variant in glioblastoma multiforme. *J Clin Neurosci.* 2009 Jun;16(6):748-54. PMID: 19324552
101. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
102. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
103. Riely et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. *Clin Cancer Res.* 2006 Feb 1;12(3 Pt 1):839-44. PMID: 16467097
104. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf
105. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
106. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2025]
107. Naidoo et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. *Cancer.* 2015 Sep 15;121(18):3212-3220. PMID: 26096453
108. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther.* 2019;4:5. PMID: 30854234
109. Yi et al. A comparison of epidermal growth factor receptor mutation testing methods in different tissue types in non-small cell lung cancer. *Int J Mol Med.* 2014 Aug;34(2):464-74. PMID: 24891042
110. <https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda>
111. <https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncology>
112. <https://www.prnewswire.com/news-releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceuticals-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion-301469692.html>
113. Madic et al. EGFR C797S, EGFR T790M and EGFR sensitizing mutations in non-small cell lung cancer revealed by six-color crystal digital PCR. *Oncotarget.* 2018 Dec 21;9(100):37393-37406. PMID: 30647840
114. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208065s033lbl.pdf
115. Niederst et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. *Clin. Cancer Res.* 2015 Sep 1;21(17):3924-33. PMID: 25964297
116. Wang et al. Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance. *J Thorac Oncol.* 2017 Nov;12(11):1723-1727. PMID: 28662863
117. <https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-announces-corporate-update-and>
118. Ciardiello et al. The role of anti-EGFR therapies in EGFR-TKI-resistant advanced non-small cell lung cancer. *Cancer Treat Rev.* 2024 Jan;122:102664. PMID: 38064878

References (continued)

119. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s007lbl.pdf
120. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000bledt.pdf
121. <https://investors.erasca.com//news-releases/news-release-details/erasca-granted-fda-fast-track-designation-cns-penetrant-egfr>
122. <https://iis.aastocks.com/20231227/11015917-0.PDF>
123. <http://iis.aastocks.com/20230612/10770455-0.PDF>
124. <https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>
125. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 2.2025]
126. Buccoliero et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. *Genes (Basel)*. 2022 Mar 31;13(4). PMID: 35456430
127. Louis et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol*. 2020 Jul;30(4):844-856. PMID: 32307792
128. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. *Clin. Cancer Res*. 2013 May 1;19(9):2301-9. PMID: 23406774
129. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. *Br J Pharmacol*. 2014 Jan;171(1):24-37. PMID: 24117156
130. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev*. 2011 Mar;75(1):50-83. PMID: 21372320
131. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *Int J Mol Sci*. 2020 Feb 7;21(3). PMID: 32046099
132. Stratikos et al. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer predisposition. *Front Oncol*. 2014;4:363. PMID: 25566501
133. López. How ERAP1 and ERAP2 Shape the Peptidomes of Disease-Associated MHC-I Proteins. *Front Immunol*. 2018;9:2463. PMID: 30425713
134. Serwold et al. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. *Nature*. 2002 Oct 3;419(6906):480-3. PMID: 12368856
135. Sakamoto et al. Distinct roles of EGF repeats for the Notch signaling system. *Exp. Cell Res*. 2005 Jan 15;302(2):281-91. PMID: 15561108
136. Bray. Notch signalling in context. *Nat. Rev. Mol. Cell Biol*. 2016 Nov;17(11):722-735. PMID: 27507209
137. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. *Cell*. 2009 Apr 17;137(2):216-33. PMID: 19379690
138. Lobry et al. Oncogenic and tumor suppressor functions of Notch in cancer: it's NOTCH what you think. *J. Exp. Med*. 2011 Sep 26;208(10):1931-5. PMID: 21948802
139. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. *Nat Rev Urol*. 2018 Jun;15(6):345-357. PMID: 29643502
140. Wang et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. *Proc. Natl. Acad. Sci. U.S.A*. 2011 Oct 25;108(43):17761-6. PMID: 22006338
141. Xiu et al. The role of oncogenic Notch2 signaling in cancer: a novel therapeutic target. *Am J Cancer Res*. 2019;9(5):837-854. PMID: 31218097
142. Weng et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science*. 2004 Oct 8;306(5694):269-71. PMID: 15472075
143. Breit et al. Activating NOTCH1 mutations predict favorable early treatment response and long-term outcome in childhood precursor T-cell lymphoblastic leukemia. *Blood*. 2006 Aug 15;108(4):1151-7. PMID: 16614245
144. Rosset et al. TSC1 and TSC2 gene mutations and their implications for treatment in Tuberous Sclerosis Complex: a review. *Genet Mol Biol*. 2017 Jan-Mar;40(1):69-79. PMID: 28222202
145. Henske et al. Tuberous sclerosis complex. *Nat Rev Dis Primers*. 2016 May 26;2:16035. PMID: 27226234
146. Santiago et al. Identification of regions critical for the integrity of the TSC1-TSC2-TBC1D7 complex. *PLoS ONE*. 2014;9(4):e93940. PMID: 24714658