

**Patient Name:** 천복실  
**Gender:** F  
**Sample ID:** N25-118

**Primary Tumor Site:** lung  
**Collection Date:** 2025.07.11

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	4 Relevant Biomarkers
Biomarker Descriptions	3	20 Therapies Available
Alert Details	9	200 Clinical Trials
Relevant Therapy Summary	10	

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	MET	None detected
BRAF	None detected	NRG1	None detected
EGFR	<b>EGFR p.(L858R) c.2573T&gt;G</b>	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	ROS1	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	<b>4.79 Mut/Mb measured</b>

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<b>EGFR p.(L858R) c.2573T&gt;G</b> epidermal growth factor receptor Allele Frequency: 19.89% Locus: chr7:55259515 Transcript: NM_005228.5	<b>afatinib</b> <sup>1, 2 / I, II+</sup> <b>amivantamab + lazertinib</b> <sup>1, 2 / I, II+</sup> <b>bevacizumab† + erlotinib</b> <sup>2 / I, II+</sup> <b>dacomitinib</b> <sup>1, 2 / I, II+</sup> <b>erlotinib</b> <sup>2 / I, II+</sup> <b>erlotinib + ramucirumab</b> <sup>1, 2 / I, II+</sup> <b>gefitinib</b> <sup>1, 2 / I, II+</sup> <b>osimertinib</b> <sup>1, 2 / I, II+</sup> <b>osimertinib + chemotherapy</b> <sup>1, 2 / I</sup> <b>amivantamab + chemotherapy</b> <sup>1, 2 / II+</sup> <b>BAT1706 + erlotinib</b> <sup>2</sup> <b>gefitinib + chemotherapy</b> <sup>I</sup>	None*	196

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		atezolizumab + bevacizumab + chemotherapy <sup>II+</sup>		
IIC	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib <sup>II+</sup> olaparib <sup>II+</sup> rucaparib <sup>II+</sup>	2
IIC	PTEN deletion phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	2
IIC	NBN p.(E736*) c.2206G>T nibrin Allele Frequency: 57.64% Locus: chr8:90949282 Transcript: NM_002485.5	None*	None*	1

\* Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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 <sup>1</sup>

Public data sources included in alerts: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources  
Microsatellite stable, UGT1A1 p.(G71R) c.211G>A, CDH10 p.(R472C) c.1414C>T, HLA-A deletion, NOTCH4 p.(G349Afs\*49) c.1044delC, LARP4B p.(R716G) c.2146C>G, NQO1 p.(P187S) c.559C>T, RBM10 p.(R830\*) c.2488C>T, 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	19.89%	NM_005228.5	missense
NBN	p.(E736*)	c.2206G>T	.	chr8:90949282	57.64%	NM_002485.5	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.18%	NM_000463.3	missense
CDH10	p.(R472C)	c.1414C>T	COSM337943	chr5:24498608	33.04%	NM_006727.5	missense
NOTCH4	p.(G349Afs*49)	c.1044delC	.	chr6:32188296	35.34%	NM_004557.4	frameshift Deletion
LARP4B	p.(R716G)	c.2146C>G	COSM4333217	chr10:858937	3.57%	NM_015155.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.30%	NM_000903.3	missense
RBM10	p.(R830*)	c.2488C>T	.	chrX:47044967	14.51%	NM_001204468.1	nonsense
PSMB10	p.(G134R)	c.400G>C	.	chr16:67969584	45.91%	NM_002801.4	missense
PLCG1	p.(G11C)	c.31G>T	.	chr20:39766312	52.98%	NM_002660.3	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KDM6A	p.(Q435H)	c.1305G>T	.	chrX:44919377	12.05%	NM_021140.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.91
PTEN	chr10:89623659	0.33	0.66
HLA-A	chr6:29910229	0	0.29

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 family<sup>1</sup>. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4<sup>96</sup>. EGFR ligand-induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways, including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways<sup>97</sup>. Activation of these pathways promotes cell proliferation, differentiation, and survival<sup>98,99</sup>.

**Alterations and prevalence:** Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations<sup>5,6,100,101</sup>. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21<sup>102</sup>. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer<sup>102</sup>. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20<sup>103,104,105,106</sup>. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations<sup>107</sup>. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain includes R108K, A289V and G598V and are primarily observed in glioblastoma<sup>102,108</sup>. Amplification of EGFR is observed in several cancer types including 44% of glioblastoma multiforme, 12% of esophageal adenocarcinoma, 10% of head and neck squamous cell carcinoma, 8% of brain lower grade glioma, 6% of lung squamous cell carcinoma, 5% of bladder urothelial carcinoma cancer, lung adenocarcinoma, and stomach adenocarcinoma, 3% of cholangiocarcinoma, and 2% of cervical squamous cell carcinoma, sarcoma, and breast invasive carcinoma<sup>5,6,101,108,109</sup>. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma<sup>110,111,112</sup>. Alterations in EGFR are rare in pediatric cancers<sup>5,6</sup>. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)<sup>5,6</sup>. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)<sup>5,6</sup>.

**Potential relevance:** Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib<sup>113</sup> (2004) and gefitinib<sup>114</sup> (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations<sup>115</sup>. Second-generation TKIs afatinib<sup>116</sup> (2013) and dacomitinib<sup>117</sup> (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763\_Y764insFQEA, confer resistance to the same therapies<sup>118,119,120,121</sup>. However, BDTX-189<sup>122</sup> was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutations. In 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)<sup>123</sup> and sunvozertinib<sup>124</sup>, for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance<sup>125</sup>. The primary resistance mutation that emerges following treatment with first-

## Biomarker Descriptions (continued)

generation TKI is T790M, accounting for 50-60% of resistant cases<sup>102</sup>. Third generation TKIs were developed to maintain sensitivity in the presence of T790M<sup>125</sup>. Osimertinib<sup>126</sup> (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases<sup>125</sup>. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa<sup>127</sup>. T790M and C797S can occur in either cis or trans allelic orientation<sup>127</sup>. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs<sup>127</sup>. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone<sup>127,128</sup>. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs<sup>127</sup>. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535<sup>129</sup> (2024), a CNS-penetrating small molecule inhibitor, that received fast track designation from the FDA for the treatment of patients with EGFR C797S-positive NSCLC who have disease progression on or after a third-generation EGFR TKI. EGFR-targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations<sup>130</sup>. The bispecific antibody, amivantamab<sup>131</sup> (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib<sup>132</sup> (2024), was approved in combination with amivantamab as a first-line treatment for adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations. In 2024, a CNS penetrating small molecule, ERAS-801<sup>133</sup> received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42<sup>134</sup>, 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. CPO301<sup>135</sup> (2023) received a fast track designation from the FDA for the treatment of EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors, including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid<sup>136</sup> (2020), in combination with osimertinib, received fast track designation from the FDA for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. Amplification and mutations of EGFR commonly occur in H3-wild type IDH-wild type diffuse pediatric high-grade glioma<sup>137,138,139</sup>.

### BRCA2 deletion

#### *BRCA2, DNA repair associated*

**Background:** The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity<sup>27,28</sup>. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer<sup>29</sup> and in men for breast and prostate cancer<sup>30,31</sup>. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer<sup>32</sup>. 테스트입니다.

**Alterations and prevalence:** Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer<sup>33,34,35,36,37,38,39</sup>. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers<sup>5,6</sup>.

**Potential clinical relevance:** Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)<sup>40</sup>. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells<sup>41,42</sup>. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib<sup>43</sup> (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Rucaparib<sup>44</sup> (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with two or more chemotherapies. Talazoparib<sup>45</sup> (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Due to efficacy in both gBRCAm and non-gBRCAm patients, Niraparib (2017) is another PARPi approved for maintenance of epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of BRCA status<sup>43</sup>. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported<sup>44</sup>. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality<sup>45</sup>.

## Biomarker Descriptions (continued)

### PTEN deletion

*phosphatase and tensin homolog*

**Background:** The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities<sup>13</sup>. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT<sup>14,15</sup>. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency<sup>16</sup>. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation<sup>17</sup>. PTEN germline mutations are also associated with inherited cancer risk in several cancer types<sup>18</sup>.

**Alterations and prevalence:** PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer<sup>5,6</sup>. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN<sup>15,19,20,21,22</sup>. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer<sup>5,6</sup>.

**Potential relevance:** Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors<sup>23,24</sup>. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>25</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib<sup>26</sup> in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

### NBN p.(E736\*) c.2206G>T

*nibrin*

**Background:** The NBN gene encodes nibrin, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) protein complex, which is necessary for the maintenance of genomic stability<sup>81,82</sup>. The MRN complex is involved in repair of double-stranded breaks (DSB) by homologous recombination repair (HRR) and non-homologous end joining (NHEJ)<sup>83,84,85</sup>. Specifically, NBN contains a nuclear localization signaling motif responsible for translocation of the MRN complex into the nucleus and contributes to DNA repair by mediating protein-protein interactions at the site of DNA damage<sup>81</sup>. NBN is a tumor suppressor gene. Loss of function mutations in NBN are implicated in the BRCAness phenotype, which is characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss<sup>86,87</sup>. Germline mutations in NBN are associated with Nijmegen breakage syndrome, an autosomal recessive disorder resulting in microcephaly at birth, immunodeficiency, radiosensitivity, and cancer predisposition<sup>88,89</sup>.

**Alterations and prevalence:** Somatic mutations in NBN are observed in 7-8% of uterine cancer and 2-4% of melanoma, colorectal, esophageal, bladder and stomach cancers<sup>5</sup>.

**Potential relevance:** The PARP inhibitor, talazoparib<sup>90</sup> in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Loss of function mutations in one or more HRR genes, including NBN, may confer sensitivity to platinum agents and PARP inhibitors<sup>86,87,91</sup>. NBN overexpression has been shown to be associated with poor prognosis in uveal melanoma, head and neck cancer, and ovarian cancer<sup>92,93,94,95</sup>.

### Microsatellite stable

**Background:** Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome<sup>59</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>60,61</sup>. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2<sup>62</sup>. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250<sup>63</sup>. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)<sup>63</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>64,65,66,67,68</sup>. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes<sup>61</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>60,61,65,69</sup>.

## Biomarker Descriptions (continued)

**Alterations and prevalence:** The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma<sup>60,61,70,71</sup>. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers<sup>70,71</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>72</sup> (2014) and nivolumab<sup>73</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>72</sup> is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication<sup>72</sup>. Dostarlimab<sup>74</sup> (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer<sup>66,75</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>76</sup> (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location<sup>66,77,78</sup>. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients<sup>78</sup>. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors<sup>79,80</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>79,80</sup>.

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

*UDP glucuronosyltransferase family 1 member A1*

**Background:** The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily<sup>1,140</sup>. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites<sup>140,141</sup>. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance<sup>142</sup>. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation<sup>142,143,144,145</sup>. Furthermore, UGT1A1 polymorphisms, such as UGT1A1\*28, UGT1A1\*93, and UGT1A1\*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38<sup>146</sup>.

**Alterations and prevalence:** Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma<sup>5,6</sup>.

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

### CDH10 p.(R472C) c.1414C>T

*cadherin 10*

**Background:** The CDH10 gene encodes cadherin 10, a type II classical cadherin and member of the cadherin superfamily<sup>1</sup>. Cadherins are important in calcium-dependent cell-cell adhesion, and are known to mediate cell recognition, cell movement, and maintain structural and functional cell and tissue polarity<sup>2</sup>. CDH10 is classified as an atypical type II cadherin due to its lack of a histidine-alanine-valine (HAV) cell adhesion recognition motif, a hallmark characteristic to type I cadherins<sup>1,2</sup>. Abnormal expression of cadherins results in increased tumor cell invasion, which precedes metastasis of tumors<sup>3,4</sup>.

**Alterations and prevalence:** Somatic mutations of CDH10 are observed in 20% of lung squamous cell carcinoma, 16% of lung adenocarcinoma, 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 8% of stomach adenocarcinoma, and colorectal adenocarcinoma, 6% of head and neck squamous cell carcinoma, 4% of bladder urothelial carcinoma and esophageal adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of pancreatic adenocarcinoma, ovarian serous cystadenocarcinoma, uterine carcinosarcoma, and sarcoma<sup>5,6</sup>. Amplification of CDH10 is observed in 10% of lung squamous cell carcinoma, 7% of lung adenocarcinoma and esophageal adenocarcinoma, 6% of bladder urothelial carcinoma, 5% of ovarian serous cystadenocarcinoma and cervical squamous cell carcinoma, 4% of sarcoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% uterine corpus endometrial carcinoma<sup>5,6</sup>.

**Potential relevance:** Currently, no therapies are approved for CDH10 aberrations.

## Biomarker Descriptions (continued)

### HLA-A deletion

*major histocompatibility complex, class I, A*

**Background:** The HLA-A gene encodes the major histocompatibility complex, class I, A<sup>1</sup>. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells<sup>7</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>8</sup>. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the  $\alpha$  polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self<sup>9,10,11</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A<sup>12</sup>.

**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<sup>5,6</sup>. Biallelic loss of HLA-A is observed in 4% of DLBCL<sup>5,6</sup>.

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

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

*notch 4*

**Background:** The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling<sup>52</sup>. 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<sup>53,54</sup>. 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<sup>55,56,57,58</sup>.

**Alterations and prevalence:** Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers<sup>5</sup>.

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

### LARP4B p.(R716G) c.2146C>G

*La ribonucleoprotein domain family member 4B*

**Background:** The LARP4B gene encodes the La ribonucleoprotein 4B protein<sup>1</sup>. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7<sup>46</sup>. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs<sup>46</sup>. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B<sup>47</sup>.

**Alterations and prevalence:** Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma<sup>5,6</sup>. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma<sup>5,6</sup>.

**Potential relevance:** Currently, no therapies are approved for LARP4B aberrations.

### RBM10 p.(R830\*) c.2488C>T

*RNA binding motif protein 10*

**Background:** RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family<sup>1,48</sup>. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA<sup>48,49</sup>. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression<sup>48</sup>. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10<sup>50,51</sup>.

## Biomarker Descriptions (continued)

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

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 2025-05-14. For the most up-to-date information, search [www.fda.gov](https://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, ERF1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBF2

Genes Assayed (continued)

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

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

EGFR 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    
 ● 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)
SCTB-14, chemotherapy	✕	✕	✕	✕	● (II/III)
ABSK-043, furmonertinib	✕	✕	✕	✕	● (II)
almonertinib	✕	✕	✕	✕	● (II)
almonertinib, adbrelimab, chemotherapy	✕	✕	✕	✕	● (II)
almonertinib, bevacizumab	✕	✕	✕	✕	● (II)
almonertinib, chemoradiation therapy	✕	✕	✕	✕	● (II)
almonertinib, dacomitinib	✕	✕	✕	✕	● (II)
amivantamab, chemotherapy	✕	✕	✕	✕	● (II)
amivantamab, 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*
atezolizumab, bevacizumab, tiragolumab	✕	✕	✕	✕	● (II)
befotertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
bevacizumab, afatinib	✕	✕	✕	✕	● (II)
bevacizumab, furmonertinib	✕	✕	✕	✕	● (II)
cadonilimab, chemotherapy, catequentinib	✕	✕	✕	✕	● (II)
camrelizumab, apatinib	✕	✕	✕	✕	● (II)
capmatinib, osimertinib, ramucirumab	✕	✕	✕	✕	● (II)
catequentinib, almonertinib	✕	✕	✕	✕	● (II)
chemotherapy, atezolizumab, bevacizumab	✕	✕	✕	✕	● (II)
dacomitinib, osimertinib	✕	✕	✕	✕	● (II)
EGFR tyrosine kinase inhibitor, osimertinib, chemotherapy	✕	✕	✕	✕	● (II)
EGFR tyrosine kinase inhibitor, radiation therapy	✕	✕	✕	✕	● (II)
erlotinib, chemotherapy	✕	✕	✕	✕	● (II)
erlotinib, OBI-833	✕	✕	✕	✕	● (II)
furmonertinib, bevacizumab	✕	✕	✕	✕	● (II)
furmonertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
furmonertinib, catequentinib	✕	✕	✕	✕	● (II)
furmonertinib, chemotherapy	✕	✕	✕	✕	● (II)
furmonertinib, chemotherapy, bevacizumab	✕	✕	✕	✕	● (II)
furmonertinib, icotinib hydrochloride	✕	✕	✕	✕	● (II)
gefitinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
gefitinib, icotinib hydrochloride	✕	✕	✕	✕	● (II)
gefitinib, thalidomide	✕	✕	✕	✕	● (II)
icotinib hydrochloride	✕	✕	✕	✕	● (II)
icotinib hydrochloride, autologous RAK cell	✕	✕	✕	✕	● (II)
icotinib hydrochloride, osimertinib	✕	✕	✕	✕	● (II)
ivonescimab, chemotherapy	✕	✕	✕	✕	● (II)
lazertinib	✕	✕	✕	✕	● (II)
lazertinib, 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 p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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)
BDTX-1535	✕	✕	✕	✕	● (I/II)
benmelstobart, catequentinib	✕	✕	✕	✕	● (I/II)
BH-30643	✕	✕	✕	✕	● (I/II)
bozitinib, osimertinib	✕	✕	✕	✕	● (I/II)
BPI-361175	✕	✕	✕	✕	● (I/II)
cetrelimab, amivantamab	✕	✕	✕	✕	● (I/II)
dacomitinib, catequentinib	✕	✕	✕	✕	● (I/II)
DAJH-1050766	✕	✕	✕	✕	● (I/II)
DB-1310, osimertinib	✕	✕	✕	✕	● (I/II)
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)
ifebemt看inib, 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)
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)
KQB-198, osimertinib	×	×	×	×	● (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 p.(L858R) c.2573T>G (continued)

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

### BRCA2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✕	○	✕	✕	● (II)
niraparib	✕	○	✕	✕	✕
rucaparib	✕	○	✕	✕	✕
pamiparib, tislelizumab	✕	✕	✕	✕	● (II)

### PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TQ-B3525, osimertinib	✕	✕	✕	✕	● (I/II)
palbociclib, gedatolisib	✕	✕	✕	✕	● (I)

### NBN p.(E736\*) c.2206G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✕	✕	✕	✕	● (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	15.53%
BRCA2	CNV, CN:1.0
BRCA2	LOH, 13q13.1(32890491-32972932)x1

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

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from [www.fda.gov](http://www.fda.gov) and is current as of 2025-05-14. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-05-01. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-05-14. ESMO information was sourced from [www.esmo.org](http://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](http://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. 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
2. Jinawath et al. Alterations of type II classical cadherin, cadherin-10 (CDH10), is associated with pancreatic ductal adenocarcinomas. *Genes Chromosomes Cancer.* 2017 May;56(5):427-435. PMID: 28124395
3. Paredes et al. Epithelial E- and P-cadherins: role and clinical significance in cancer. *Biochim Biophys Acta.* 2012 Dec;1826(2):297-311. PMID: 22613680
4. Cavallaro et al. Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. *Nat Rev Cancer.* 2004 Feb;4(2):118-32. PMID: 14964308
5. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
6. 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
7. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
8. 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
9. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
10. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
11. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
12. 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
13. Milella et al. PTEN: Multiple Functions in Human Malignant Tumors. *Front Oncol.* 2015 Feb 16;5:24. doi: 10.3389/fonc.2015.00024. eCollection 2015. PMID: 25763354
14. Song et al. The functions and regulation of the PTEN tumour suppressor. *Nat. Rev. Mol. Cell Biol.* 2012 Apr 4;13(5):283-96. PMID: 22473468
15. Chalhoub et al. PTEN and the PI3-kinase pathway in cancer. *Annu Rev Pathol.* 2009;4:127-50. PMID: 18767981
16. Mansour et al. Loss of PTEN-assisted G2/M checkpoint impedes homologous recombination repair and enhances radio-curability and PARP inhibitor treatment response in prostate cancer. *Sci Rep.* 2018 Mar 2;8(1):3947. PMID: 29500400
17. Leslie et al. Inherited PTEN mutations and the prediction of phenotype. *Semin. Cell Dev. Biol.* 2016 Apr;52:30-8. PMID: 26827793
18. Tan et al. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin. Cancer Res.* 2012 Jan 15;18(2):400-7. PMID: 22252256
19. Dillon et al. Therapeutic targeting of cancers with loss of PTEN function. *Curr Drug Targets.* 2014 Jan;15(1):65-79. PMID: 24387334
20. Papa et al. Cancer-associated PTEN mutants act in a dominant-negative manner to suppress PTEN protein function. *Cell.* 2014 Apr 24;157(3):595-610. PMID: 24766807
21. Kato et al. Functional evaluation of p53 and PTEN gene mutations in gliomas. *Clin. Cancer Res.* 2000 Oct;6(10):3937-43. PMID: 11051241
22. Han et al. Functional evaluation of PTEN missense mutations using in vitro phosphoinositide phosphatase assay. *Cancer Res.* 2000 Jun 15;60(12):3147-51. PMID: 10866302
23. Mendes-Pereira et al. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. *EMBO Mol Med.* 2009 Sep;1(6-7):315-22. PMID: 20049735
24. Bian et al. PTEN deficiency sensitizes endometrioid endometrial cancer to compound PARP-PI3K inhibition but not PARP inhibition as monotherapy. *Oncogene.* 2018 Jan 18;37(3):341-351. PMID: 28945226
25. <https://www.senhwbio.com/en/news/20220125>
26. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/218197s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf)
27. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. *Breast Cancer Res.* 2002;4(1):9-13. PMID: 11879553
28. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene.* 2002 Dec 16;21(58):8981-93. PMID: 12483514
29. 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

## References (continued)

30. 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
31. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br. J. Cancer.* 2007 Jan 15;96(1):11-5. PMID: 17213823
32. NCCN Guidelines® - NCCN-Genetic/Familial High-Risk Assessment: Breast and Ovarian [Version 1.2018]. NCCN-Genetic/Familial High-Risk Assessment: Breast and Ovarian
33. ARUP Laboratories University of Utah Department of Pathology.. <https://arupconsult.com/ati/hereditary-breast-and-ovarian-cancer>
34. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. *GeneReviews®* [Internet]. PMID: 20301425
35. 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
36. 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
37. 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
38. 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
39. 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
40. 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
41. 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
42. 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
43. Ison et al. FDA Approval Summary: Niraparib for the Maintenance Treatment of Patients with Recurrent Ovarian Cancer in Response to Platinum-Based Chemotherapy. *Clin. Cancer Res.* 2018 Sep 1;24(17):4066-4071. PMID: 29650751
44. 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
45. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst.).* 2018 Nov;71:172-176. PMID: 30177437
46. Seetharaman et al. The RNA-binding protein LARP4 regulates cancer cell migration and invasion. *Cytoskeleton (Hoboken).* 2016 Nov;73(11):680-690. PMID: 27615744
47. Koso et al. Identification of RNA-Binding Protein LARP4B as a Tumor Suppressor in Glioma. *Cancer Res.* 2016 Apr 15;76(8):2254-64. PMID: 26933087
48. Cao et al. RBM10 Regulates Tumor Apoptosis, Proliferation, and Metastasis. *Front Oncol.* 2021;11:603932. PMID: 33718153
49. 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
50. Sun et al. Functional role of RBM10 in lung adenocarcinoma proliferation. *Int J Oncol.* 2019 Feb;54(2):467-478. PMID: 30483773
51. 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
52. 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
53. Bray. Notch signalling in context. *Nat. Rev. Mol. Cell Biol.* 2016 Nov;17(11):722-735. PMID: 27507209
54. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. *Cell.* 2009 Apr 17;137(2):216-33. PMID: 19379690
55. 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
56. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. *Nat Rev Urol.* 2018 Jun;15(6):345-357. PMID: 29643502
57. 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

## References (continued)

58. 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
59. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
60. 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
61. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
62. 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
63. 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
64. 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
65. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
66. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
67. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
68. 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
69. 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
70. 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
71. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
72. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125514s174lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf)
73. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125554s129lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf)
74. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/761174s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf)
75. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
76. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/125377s133lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf)
77. 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
78. 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
79. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
80. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
81. Lamarche et al. The MRN complex in double-strand break repair and telomere maintenance. *FEBS Lett.* 2010 Sep 10;584(17):3682-95. PMID: 20655309
82. Stracker et al. The MRE11 complex: starting from the ends. *Nat. Rev. Mol. Cell Biol.* 2011 Feb;12(2):90-103. PMID: 21252998
83. Bartkova et al. Aberrations of the MRE11-RAD50-NBS1 DNA damage sensor complex in human breast cancer: MRE11 as a candidate familial cancer-predisposing gene. *Mol Oncol.* 2008 Dec;2(4):296-316. PMID: 19383352
84. Rupnik et al. The MRN complex. *Curr. Biol.* 2008 Jun 3;18(11):R455-7. PMID: 18522810
85. Assenmacher et al. MRE11/RAD50/NBS1: complex activities. *Chromosoma.* 2004 Oct;113(4):157-66. PMID: 15309560
86. Lim et al. Evaluation of the methods to identify patients who may benefit from PARP inhibitor use. *Endocr. Relat. Cancer.* 2016 Jun;23(6):R267-85. PMID: 27226207
87. Lord et al. BRCAness revisited. *Nat. Rev. Cancer.* 2016 Feb;16(2):110-20. PMID: 26775620
88. Chrzanowska et al. Nijmegen breakage syndrome (NBS). *Orphanet J Rare Dis.* 2012 Feb 28;7:13. doi: 10.1186/1750-1172-7-13. PMID: 22373003

## References (continued)

89. Watanabe et al. Mutational inactivation of the nijmegen breakage syndrome gene (NBS1) in glioblastomas is associated with multiple TP53 mutations. *J. Neuropathol. Exp. Neurol.* 2009 Feb;68(2):210-5. PMID: 19151620
90. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/217439s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf)
91. Pennington et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin. Cancer Res.* 2014 Feb 1;20(3):764-75. PMID: 24240112
92. Ehlers et al. NBS1 expression as a prognostic marker in uveal melanoma. *Clin. Cancer Res.* 2005 Mar 1;11(5):1849-53. PMID: 15756009
93. Hsu et al. Identification of increased NBS1 expression as a prognostic marker of squamous cell carcinoma of the oral cavity. *Cancer Sci.* 2010 Apr;101(4):1029-37. PMID: 20175780
94. Yang et al. Increased NBS1 expression is a marker of aggressive head and neck cancer and overexpression of NBS1 contributes to transformation. *Clin. Cancer Res.* 2006 Jan 15;12(2):507-15. PMID: 16428493
95. Lee et al. Clinicopathological values of NBS1 and DNA damage response genes in epithelial ovarian cancers. *Exp. Mol. Med.* 2015 Nov 20;47:e195. PMID: 26584681
96. 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
97. Liu et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. *Mol Cancer.* 2018 Feb 19;17(1):53. PMID: 29455669
98. Zhixiang. ErbB Receptors and Cancer. *Methods Mol. Biol.* 2017;1652:3-35. PMID: 28791631
99. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
100. 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
101. 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
102. da et al. EGFR mutations and lung cancer. *Annu Rev Pathol.* 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
103. 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
104. 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
105. 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
106. 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
107. Karachaliou et al. KRAS mutations in lung cancer. *Clin Lung Cancer.* 2013 May;14(3):205-14. PMID: 23122493
108. Brennan et al. The somatic genomic landscape of glioblastoma. *Cell.* 2013 Oct 10;155(2):462-77. PMID: 24120142
109. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
110. 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
111. 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
112. Gan et al. The EGFRvIII variant in glioblastoma multiforme. *J Clin Neurosci.* 2009 Jun;16(6):748-54. PMID: 19324552
113. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021743s025lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf)
114. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/206995s004lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf)
115. 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
116. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/201292s017lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf)
117. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/211288s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf)
118. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2025]

## References (continued)

119. 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
120. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther*. 2019;4:5. PMID: 30854234
121. 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
122. <https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda>
123. <https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncology>
124. <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>
125. 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
126. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/208065s033lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208065s033lbl.pdf)
127. 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
128. 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
129. <https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-announces-corporate-update-and>
130. 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
131. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/761210s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s007lbl.pdf)
132. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/219008s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000lbl.pdf)
133. <https://investors.erasca.com/news-releases/news-release-details/erasca-granted-fda-fast-track-designation-cns-penetrant-egfr>
134. <https://iis.aastocks.com/20231227/11015917-0.PDF>
135. <http://iis.aastocks.com/20230612/10770455-0.PDF>
136. <https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>
137. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 2.2025]
138. 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
139. 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
140. Ouzzine et al. The UDP-glucuronosyltransferases of the blood-brain barrier: their role in drug metabolism and detoxication. *Front Cell Neurosci*. 2014;8:349. PMID: 25389387
141. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene*. 2006 Mar 13;25(11):1659-72. PMID: 16550166
142. Allain et al. Emerging roles for UDP-glucuronosyltransferases in drug resistance and cancer progression. *Br J Cancer*. 2020 Apr;122(9):1277-1287. PMID: 32047295
143. Izumi et al. Expression of UDP-glucuronosyltransferase 1A in bladder cancer: association with prognosis and regulation by estrogen. *Mol Carcinog*. 2014 Apr;53(4):314-24. PMID: 23143693
144. Sundararaghavan et al. Glucuronidation and UGT isozymes in bladder: new targets for the treatment of uroepithelial carcinomas?. *Oncotarget*. 2017 Jan 10;8(2):3640-3648. PMID: 27690298
145. Lu et al. Drug-Metabolizing Activity, Protein and Gene Expression of UDP-Glucuronosyltransferases Are Significantly Altered in Hepatocellular Carcinoma Patients. *PLoS One*. 2015;10(5):e0127524. PMID: 26010150
146. Karas et al. *JCO Oncol Pract*. 2021 Dec 3;OP2100624. PMID: 34860573