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Patient Name: 류진환
Gender: M
Sample ID: N25-261

Primary Tumor Site: lung
Collection Date: 2025.09.24

Sample Cancer Type: Lung Cancer

Table of Contents

Report Highlights

3 Relevant Biomarkers
17 Therapies Available
196 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	***EGFR exon 19 deletion***	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***0.95 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EGFR exon 19 deletion* epidermal growth factor receptor Allele Frequency: 40.80% Locus: chr7:55242465 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*	194

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	*DDR2 amplification* discoidin domain receptor tyrosine kinase 2 Locus: chr1:162724523	None*	None*	1

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

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

EGFR exon 19 deletion	**patritumab deruxtecan** [1]

Public data sources included in alerts: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

*MLH1 p.(V384D) c.1151T>A, Microsatellite stable, NOTCH1 p.(P935Sfs*242) c.2803_2809delCCCGGCT, SF3B1 p.(K700E) c.2098A>G, MCL1 amplification, RIT1 amplification, HLA-B deletion, NQO1 p.(P187S) c.559C>T, DDX3X deletion, PHF6 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
EGFR	p.(E746_A750del)	c.2236_2250delGAATTAAGAGAAGCA	COSM6225	chr7:55242465	40.80%	NM_005228.5	nonframeshift Deletion
MLH1	p.(V384D)	c.1151T>A	.	chr3:37067240	51.73%	NM_000249.4	missense
NOTCH1	p.(P935Sfs*242)	c.2803_2809delCCCGGCT	.	chr9:139404344	20.69%	NM_017617.5	frameshift Deletion
SF3B1	p.(K700E)	c.2098A>G	COSM84677	chr2:198266834	3.33%	NM_012433.4	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	47.87%	NM_000903.3	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
MTUS2	p.(A919V)	c.2756C>T	.	chr13:29855952	3.50%	NM_001033602.4	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CHEK2	chr22:29083868	1	0.79
DDR2	chr1:162724523	5.44	1.78
MCL1	chr1:150549846	5.13	1.71
RIT1	chr1:155870154	7.87	2.32

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
HLA-B	chr6:31322252	0	0.48
DDX3X	chrX:41193501	0.67	0.7
PHF6	chrX:133511628	0.64	0.69

Biomarker Descriptions

EGFR exon 19 deletion

epidermal growth factor receptor

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR), a member of the ERBB/human epidermal growth factor receptor (HER) tyrosine kinase family[1]. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[79]. 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[80]. Activation of these pathways promotes cell proliferation, differentiation, and survival[81,82].

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[8,9,49,83]. 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[84]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer[84]. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[85,86,87,88]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[89]. 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[84,90]. 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[8,9,49,90,91]. 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[92,93,94]. Alterations in EGFR are rare in pediatric cancers[8,9]. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)[8,9]. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)[8,9].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[95] (2004) and gefitinib[96] (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[97]. Second-generation TKIs afatinib[98] (2013) and dacomitinib[99] (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[100,101,102,103]. However, BDTX-189[104] 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)[105] and sunvozertinib[106], 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[107]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[84]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M[107]. Osimertinib[108] (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[107]. 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[109]. T790M and C797S can occur in either cis or trans allelic orientation[109]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to

Biomarker Descriptions (continued)

first-generation TKIs[109]. 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[109,110]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[109]. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535[111] (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[112]. The bispecific antibody, amivantamab[113] (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib[114] (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[115] received fast track designation for the treatment of adult patients with EGFR altered glioblastoma. HLX-42[116], an anti-EFGR-antibody-drug conjugate (ADC) consisting of an anti-EGFR monoclonal antibody conjugated with a novel high potency DNA topoisomerase I (topo I) inhibitor, also received fast track designation (2024) for the treatment of patients with advanced or metastatic EGFR-mutated non-small cell lung cancer whose disease has progressed on a third-generation EGFR tyrosine kinase inhibitor. CPO301[117] (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[118] (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[40,119,120].

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[136]. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)[137,138,139]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[140,141,142].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[8,9]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[8,9].

Potential relevance: The PARP inhibitor, olaparib[143] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[144], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

DDR2 amplification

discoidin domain receptor tyrosine kinase 2

Background: The DDR2 gene encodes the discoidin domain receptor tyrosine kinase 2 protein. In comparison to receptor tyrosine kinases (RTKs) such as EGFR and FGFR that display rapid and transient activation, DDR2 exhibits delayed and continued receptor activation[42]. DDR2 binds to collagen and can impact cell adhesion and migration through extracellular matrix (ECM) remodeling[43,44]. DDR2 activation stimulates oncogenic signaling including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways thereby promoting cell proliferation and metastasis[44].

Alterations and prevalence: Somatic mutations are observed in up to 7% of uterine cancer, and up to 4% of melanoma, non-small lung cell carcinoma, stomach cancer, and colorectal cancer[8,45,46]. DDR2 mutations have been found along the kinase and discoidin domains but do not appear to occur in hotspot fashion and are not mutually exclusive with other driver mutations[9,44,47]. Amplification of DDR2 is found to occur in up to 15% of bladder cancer and 10-14% of cholangiocarcinoma, breast, lung adenocarcinoma, and liver cancers[8,9,48,49].

Potential relevance: Currently, no therapies are approved for DDR2 aberrations. Various pre-clinical studies have demonstrated the efficacy of dasatinib (an approved multi-targeted tyrosine kinase inhibitor) in DDR2 mutated cancers[47,50,51]. However, clinical data is limited. In an early phase clinical trial, one squamous cell carcinoma patient with a DDR2 S768R mutation and without an EGFR mutation demonstrated a radiographic response to treatment with dasatinib and erlotinib[52].

Biomarker Descriptions (continued)

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

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[21]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[21,22]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[23,24]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[21]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[21]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[25]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[26,27,28]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[26,29]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[27,29,30,31]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[32,33,34,35].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[8,9]. Alterations in MLH1 are observed in pediatric cancers[8,9]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[8,9].

Potential relevance: The PARP inhibitor, talazoparib[36] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[37]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[38,39]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[40,41].

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[65]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[27,29]. 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[28]. 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[66]. 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)[66]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[30,67,68,69,70]. 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[29]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[27,29,30,31].

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[27,29,71,72]. 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[71,72].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[37] (2014) and nivolumab[38] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[37] 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[37]. Dostarlimab[73] (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[68,74]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[39] (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[68,75,76]. 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[76]. 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

Biomarker Descriptions (continued)

with MSI-H tumors[77,78]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[77,78].

NOTCH1 p.(P935Sfs*242) c.2803_2809delCCCGGCT

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 signaling[127]. 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[128,129]. 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[130,131,132,133].

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[8,9,91]. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia[134,135].

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

SF3B1 p.(K700E) c.2098A>G

splicing factor 3b subunit 1

Background: The SF3B1 gene encodes the splicing factor 3b subunit 1 protein, a core component of the U2 small nuclear ribonucleoprotein (snRNP) complex of the spliceosome responsible for RNA splicing[1]. SF3B1 is involved in recognition of the branch point sequence during selection of the 3' splice site[1]. Recurrent somatic mutations in SF3B1 and other components of the splicing machinery including SRSF2, U2AF1, and ZRSR2, are common in myelodysplasia[145]. These components experience mutations in a mutually exclusive manner suggesting a common impact on RNA splicing and the pathogenesis of myelodysplasia[145]. SF3B1 mutations are believed to contribute to aberrant post-translational inactivation of the regulatory complex PPP2R5A of protein phosphatase 2A (PP2A), leading to the activation and stabilization of MYC activation and impairing apoptosis[146].

Alterations and prevalence: SF3B1 mutations occur in the majority (70-80%) of myelodysplastic syndromes (MDS) with ring sideroblasts (RS) and at lower frequency in other myeloid neoplasms including MDS without RS (7%), chronic myelomonocytic leukemia (5-6%), therapy-related acute myeloid leukemia (AML) or AML with MDS features (5%), and de novo AML (3%)[145,147,148]. Recurrent somatic SF3B1 mutations are also common in certain solid cancers including uveal melanoma (20-30%) and breast cancer (2%) and at lower frequencies in diverse cancer types[8,9,149,150,151,152,153,154]. Cancer-associated recurrent missense mutations in SF3B1 occur within the HEAT repeat domains 5-9 at codon positions R625, K666, K700, G742, and D781[155]. The functional significance of recurrent SF3B1 mutations is to alter branch point selection thus inducing cryptic 3' splice site selection[155,156,157]

Potential relevance: Currently, no therapies are approved for SF3B1 aberrations. SF3B1 mutations are associated with poor/adverse risk in AML, intermediate risk of distant metastasis in uveal melanoma, and aggressive disease and shorter survival in patients diagnosed with chronic lymphocytic leukemia (CLL)[158,159,160,161]. Somatic mutations in SF3B1 at positions E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, and D781 are independently associated with favorable risk in myelodysplastic syndrome[162]. Investigational inhibitors of the spliceosome are in early clinical development[163,164].

MCL1 amplification

MCL1, BCL2 family apoptosis regulator

Background: MCL1 encodes the MCL1 apoptosis regulator and is a member of the BCL2 family[1,2]. The BCL2 family of proteins includes anti-apoptotic proteins, such as MCL1, BCL-2, BCL-W, BCL-B, BCL-XL, and BFL-1/A1, and pro-apoptotic proteins, such as BAX, BAK, BIM, BID, BAD, NOXA, and PUMA. MCL1 blocks apoptosis by sequestering pro-apoptotic proteins such as BAK and BAX, thereby preventing the release of cytochrome c from mitochondria, which is responsible for macromolecular degradation during apoptosis[3]. High levels of MCL1 expression sustain cancer cell survival and promote chemotherapy resistance[4,5,6,7].

Alterations and prevalence: Somatic mutations in MCL1 are observed in 2% of skin cutaneous melanoma[8,9]. Amplification of MCL1 are observed in 11% of Liver Hepatocellular Carcinoma and Bladder Urothelial Carcinoma, 10% of Lung Adenocarcinoma and Breast Invasive Carcinoma, 8% of Cholangiocarcinoma and Ovarian Serous Cystadenocarcinoma, 7% of Uterine Corpus Endometrial Carcinoma, and 5% of Uterine Carcinosarcoma, Sarcoma, and Lung Squamous Cell Carcinoma[8,9].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for MCL1 aberrations.

RIT1 amplification

Ras like without CAAX 1

Background: The RIT1 gene encodes the ras-like without CAAX1 protein[1]. RIT1 is a member of the Ras family, possessing intrinsic GTP hydrolysis activity[10]. Specifically, RIT1 is ubiquitously expressed and plays a role in neuron survival following oxidative stress and dendritic cell retraction[10,11,12]. RIT1 mutations have been shown to activate PI3K and MEK signaling pathways and likely promotes tumorigenesis[13]. Hereditary mutations in RIT1 lead to constitutive activation of RAS and MAPK pathways resulting in Noonan syndrome, a type of RASopathy[13,14].

Alterations and prevalence: Somatic mutations in RIT1 are observed in 3% of cholangiocarcinoma, 2% of uterine corpus endometrial carcinoma and lung adenocarcinoma, and 1% of cervical squamous cell carcinoma, skin cutaneous melanoma, and acute myeloid leukemia (AML)[8,9]. Amplifications in RIT1 are observed in 14% of uterine carcinosarcoma, 11% of liver hepatocellular and cholangiocarcinoma, 8% of lung adenocarcinoma, breast invasive carcinoma, uterine corpus endometrial carcinoma, and 6% of ovarian serous cystadenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for RIT1 aberrations.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. 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[15]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[16]. 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[17,18,19]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[20].

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

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

DDX3X deletion

DEAD-box helicase 3, X-linked

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II[1,53]. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)[53,54,55,56]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[53]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[57,58,59,60,61,62,63,64]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[57].

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma[8,9]. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for DDX3X aberrations.

PHF6 deletion

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling

Biomarker Descriptions (continued)

deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[121,122].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[121,123,124,125]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[123,125]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[123]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[121,123].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[126].

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

EGFR exon 19 deletion

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion or EGFRi sensitizing mutation

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

Reference:

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

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2,

Genes Assayed (continued)

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

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

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

EGFR exon 19 deletion

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

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

Relevant Therapy Summary (continued)

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

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib + carboplatin + pemetrexed	✖	●	✖	✖	✖
osimertinib + cisplatin + pemetrexed	✖	●	✖	✖	✖
BAT1706 + erlotinib	✖	✖	●	✖	✖
bevacizumab (Allergan) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Biocon) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Celltrion) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Mabxience) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Pfizer) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Samsung Bioepis) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Stada) + erlotinib	✖	✖	●	✖	✖
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
gefitinib + carboplatin + pemetrexed	✖	✖	✖	●	✖
adebrelimab, bevacizumab, chemotherapy	✖	✖	✖	✖	● (IV)
afatinib, bevacizumab, chemotherapy	✖	✖	✖	✖	● (IV)
befotertinib	✖	✖	✖	✖	● (IV)
bevacizumab, almonertinib, chemotherapy	✖	✖	✖	✖	● (IV)
catequentinib, toripalimab	✖	✖	✖	✖	● (IV)
EGFR tyrosine kinase inhibitor	✖	✖	✖	✖	● (IV)
gefitinib, chemotherapy	✖	✖	✖	✖	● (IV)
gefitinib, endostatin	✖	✖	✖	✖	● (IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	✖	✖	✖	✖	● (IV)
almonertinib, apatinib	✖	✖	✖	✖	● (III)
almonertinib, chemotherapy	✖	✖	✖	✖	● (III)
almonertinib, radiation therapy	✖	✖	✖	✖	● (III)
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 exon 19 deletion (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, adebrelimab, 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 exon 19 deletion (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 exon 19 deletion (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)
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)
FWD-1509	✖	✖	✖	✖	● (I/II)

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

Relevant Therapy Summary (continued)

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

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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)
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)
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 exon 19 deletion (continued)

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

CHEK2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)

DDR2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib	✖	✖	✖	✖	● (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	***20.64%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x2***
ATM	***LOH, 11q22.3(108098341-108236285)x2***
CHEK1	***LOH, 11q24.2(125496639-125525271)x2***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130729)x1***
RAD51B	***LOH, 14q24.1(68290164-69061406)x2***
RAD54L	***LOH, 1p34.1(46714017-46743978)x2***

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

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

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. Kozopas et al. MCL1, a gene expressed in programmed myeloid cell differentiation, has sequence similarity to BCL2. Proc Natl Acad Sci U S A. 1993 Apr 15;90(8):3516-20. PMID: 7682708
3. Thomas et al. Mcl-1; the molecular regulation of protein function. FEBS Lett. 2010 Jul 16;584(14):2981-9. PMID: 20540941
4. Zhang et al. Mcl-1 is critical for survival in a subgroup of non-small-cell lung cancer cell lines. Oncogene. 2011 Apr 21;30(16):1963-8. PMID: 21132008
5. Grabow et al. MCL-1 but not BCL-XL is critical for the development and sustained expansion of thymic lymphoma in p53-deficient mice. Blood. 2014 Dec 18;124(26):3939-46. PMID: 25368374
6. Xiang et al. Mcl1 haploinsufficiency protects mice from Myc-induced acute myeloid leukemia. J Clin Invest. 2010 Jun;120(6):2109-18. PMID: 20484815
7. Wu et al. Ubiquitination and deubiquitination of MCL1 in cancer: deciphering chemoresistance mechanisms and providing potential therapeutic options. Cell Death Dis. 2020 Jul 22;11(7):556. PMID: 32699213
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. 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
10. Feng et al. RIT1 suppresses esophageal squamous cell carcinoma growth and metastasis and predicts good prognosis. Cell Death Dis. 2018 Oct 22;9(11):1085. PMID: 30348939
11. Andres et al. Rit signaling contributes to interferon-gamma-induced dendritic retraction via p38 mitogen-activated protein kinase activation. J Neurochem. 2008 Dec;107(5):1436-47. PMID: 18957053
12. Cai et al. Rit GTPase regulates a p38 MAPK-dependent neuronal survival pathway. Neurosci Lett. 2012 Dec 7;531(2):125-30. PMID: 23123784
13. Berger et al. Oncogenic RIT1 mutations in lung adenocarcinoma. Oncogene. 2014 Aug 28;33(35):4418-23. PMID: 24469055
14. Aoki et al. Gain-of-function mutations in RIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. Am J Hum Genet. 2013 Jul 11;93(1):173-80. PMID: 23791108
15. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem Sci. PMID: 23849087
16. 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
17. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. Annu Rev Immunol. 2015;33:169-200. PMID: 25493333
18. Parham. MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol. 2005 Mar;5(3):201-14. PMID: 15719024
19. Sidney et al. HLA class I supertypes: a revised and updated classification. BMC Immunol. 2008 Jan 22;9:1. PMID: 18211710
20. 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
21. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
22. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
23. Berends et al. MLH1 and MSH2 protein expression as a pre-screening marker in hereditary and non-hereditary endometrial hyperplasia and cancer. Int. J. Cancer. 2001 May 1;92(3):398-403. PMID: 11291077
24. Gausachs et al. MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: a cost-effectiveness study. Eur. J. Hum. Genet. 2012 Jul;20(7):762-8. PMID: 22274583
25. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. Clin Cancer Res. 2010 Nov 1;16(21):5107-13. PMID: 20823149
26. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
27. 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
28. 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
29. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854

References (continued)

30. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
31. 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
32. Bonadona et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun 8;305(22):2304-10. PMID: 21642682
33. Engel et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012 Dec 10;30(35):4409-15. PMID: 23091106
34. Grant et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015 Mar;148(3):556-64. PMID: 25479140
35. Hu et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018 Jun 19;319(23):2401-2409. PMID: 29922827
36. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
37. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
38. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
39. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
40. 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
41. Friker et al. MSH2, MSH6, MLH1, and PMS2 immunohistochemistry as highly sensitive screening method for DNA mismatch repair deficiency syndromes in pediatric high-grade glioma. Acta Neuropathol. 2025 Feb 2;149(1):11. PMID: 39894875
42. Rammal et al. Discoidin Domain Receptors: Potential Actors and Targets in Cancer. Front Pharmacol. 2016 Mar 14;7:55. doi: 10.3389/fphar.2016.00055. eCollection 2016. PMID: 27014069
43. Olaso et al. Discoidin domain receptor 2 regulates fibroblast proliferation and migration through the extracellular matrix in association with transcriptional activation of matrix metalloproteinase-2. J. Biol. Chem. 2002 Feb 1;277(5):3606-13. PMID: 11723120
44. Payne et al. Discoidin domain receptor 2 signaling networks and therapy in lung cancer. J Thorac Oncol. 2014 Jun;9(6):900-4. PMID: 24828669
45. 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
46. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
47. Ricordel et al. Mutational Landscape of DDR2 Gene in Lung Squamous Cell Carcinoma Using Next-generation Sequencing. Clin Lung Cancer. 2018 Mar;19(2):163-169.e4. PMID: 29129434
48. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
49. 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
50. Terai et al. Characterization of DDR2 Inhibitors for the Treatment of DDR2 Mutated Nonsmall Cell Lung Cancer. ACS Chem. Biol. 2015 Dec 18;10(12):2687-96. PMID: 26390252
51. von et al. Targeting DDR2 in head and neck squamous cell carcinoma with dasatinib. Int. J. Cancer. 2016 Nov 15;139(10):2359-69. PMID: 27434411
52. Hammerman et al. Mutations in the DDR2 kinase gene identify a novel therapeutic target in squamous cell lung cancer. Cancer Discov. 2011 Jun;1(1):78-89. PMID: 22328973
53. Rocak et al. DEAD-box proteins: the driving forces behind RNA metabolism. Nat Rev Mol Cell Biol. 2004 Mar;5(3):232-41. PMID: 14991003
54. Fuller-Pace. The DEAD box proteins DDX5 (p68) and DDX17 (p72): multi-tasking transcriptional regulators. Biochim Biophys Acta. 2013 Aug;1829(8):756-63. PMID: 23523990
55. Ali. DEAD-box RNA helicases: The driving forces behind RNA metabolism at the crossroad of viral replication and antiviral innate immunity. Virus Res. 2021 Apr 15;296:198352. PMID: 33640359
56. Linder et al. Looking back on the birth of DEAD-box RNA helicases. Biochim Biophys Acta. 2013 Aug;1829(8):750-5. PMID: 23542735

References (continued)

57. Lin. DDX3X Multifunctionally Modulates Tumor Progression and Serves as a Prognostic Indicator to Predict Cancer Outcomes. Int J Mol Sci. 2019 Dec 31;21(1). PMID: 31906196
58. Song et al. The mechanism of RNA duplex recognition and unwinding by DEAD-box helicase DDX3X. Nat Commun. 2019 Jul 12;10(1):3085. PMID: 31300642
59. Zhou et al. Comprehensive proteomic analysis of the human spliceosome. Nature. 2002 Sep 12;419(6903):182-5. PMID: 12226669
60. Yedavalli et al. Requirement of DDX3 DEAD box RNA helicase for HIV-1 Rev-RRE export function. Cell. 2004 Oct 29;119(3):381-92. PMID: 15507209
61. Chao et al. DDX3, a DEAD box RNA helicase with tumor growth-suppressive property and transcriptional regulation activity of the p21waf1/cip1 promoter, is a candidate tumor suppressor. Cancer Res. 2006 Jul 1;66(13):6579-88. PMID: 16818630
62. Chuang et al. Requirement of the DEAD-Box protein ded1p for messenger RNA translation. Science. 1997 Mar 7;275(5305):1468-71. PMID: 9045610
63. Shih et al. Candidate tumor suppressor DDX3 RNA helicase specifically represses cap-dependent translation by acting as an eIF4E inhibitory protein. Oncogene. 2008 Jan 24;27(5):700-14. PMID: 17667941
64. Lee et al. Human DDX3 functions in translation and interacts with the translation initiation factor eIF3. Nucleic Acids Res. 2008 Aug;36(14):4708-18. PMID: 18628297
65. Lander et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. PMID: 11237011
66. 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
67. 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
68. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
69. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis. Markers. 2004;20(4-5):199-206. PMID: 15528785
70. 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
71. 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
72. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
73. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
74. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
75. 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
76. 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
77. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. J Pers Med. 2019 Jan 16;9(1). PMID: 30654522
78. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat. Rev. 2019 Jun;76:22-32. PMID: 31079031
79. 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
80. Liu et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. Mol Cancer. 2018 Feb 19;17(1):53. PMID: 29455669
81. Zhixiang. ErbB Receptors and Cancer. Methods Mol. Biol. 2017;1652:3-35. PMID: 28791631
82. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711
83. 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
84. da et al. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
85. 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

References (continued)

86. 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
87. 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
88. 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
89. Karachaliou et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013 May;14(3):205-14. PMID: 23122493
90. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
91. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
92. 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
93. 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
94. Gan et al. The EGFRvIII variant in glioblastoma multiforme. J Clin Neurosci. 2009 Jun;16(6):748-54. PMID: 19324552
95. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
96. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
97. 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
98. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf
99. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
100. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2025]
101. 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
102. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5. PMID: 30854234
103. 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
104. https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda
105. https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys
106. 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
107. 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
108. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208065s033lbl.pdf
109. 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
110. 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
111. https://investors.blackdiamondtherapeutics.com//news-releases/news-release-details/black-diamond-therapeutics-announces-corporate-update-and
112. 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
113. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s007lbl.pdf
114. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219008s000lbledt.pdf
115. https://investors.erasca.com//news-releases/news-release-details/erasca-granted-fda-fast-track-designation-cns-penetrant-egfr

References (continued)

116. https://iis.aastocks.com/20231227/11015917-0.PDF
117. http://iis.aastocks.com/20230612/10770455-0.PDF
118. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/
119. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 2.2025]
120. 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
121. Wendorff et al. Phf6 Loss Enhances HSC Self-Renewal Driving Tumor Initiation and Leukemia Stem Cell Activity in T-ALL. Cancer Discov. 2019 Mar;9(3):436-451. PMID: 30567843
122. Lower et al. Mutations in PHF6 are associated with Börjeson-Forssman-Lehmann syndrome. Nat. Genet. 2002 Dec;32(4):661-5. PMID: 12415272
123. Van et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. Nat. Genet. 2010 Apr;42(4):338-42. PMID: 20228800
124. Van et al. PHF6 mutations in adult acute myeloid leukemia. Leukemia. 2011 Jan;25(1):130-4. PMID: 21030981
125. Yoo et al. Somatic mutation of PHF6 gene in T-cell acute lymphoblatic leukemia, acute myelogenous leukemia and hepatocellular carcinoma. Acta Oncol. 2012 Jan;51(1):107-11. PMID: 21736506
126. Patel et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N. Engl. J. Med. 2012 Mar 22;366(12):1079-89. PMID: 22417203
127. 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
128. Bray. Notch signalling in context. Nat. Rev. Mol. Cell Biol. 2016 Nov;17(11):722-735. PMID: 27507209
129. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. Cell. 2009 Apr 17;137(2):216-33. PMID: 19379690
130. 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
131. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. Nat Rev Urol. 2018 Jun;15(6):345-357. PMID: 29643502
132. 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
133. 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
134. Weng et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science. 2004 Oct 8;306(5694):269-71. PMID: 15472075
135. 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
136. Matsuoka et al. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. Science. 1998 Dec 4;282(5395):1893-7. PMID: 9836640
137. Cai et al. Structure and activation mechanism of the CHK2 DNA damage checkpoint kinase. Mol. Cell. 2009 Sep 24;35(6):818-29. PMID: 19782031
138. Zhang et al. Chk2 phosphorylation of BRCA1 regulates DNA double-strand break repair. Mol. Cell. Biol. 2004 Jan;24(2):708-18. PMID: 14701743
139. Huang et al. Chk1 and Chk2 are differentially involved in homologous recombination repair and cell cycle arrest in response to DNA double-strand breaks induced by camptothecins. Mol. Cancer Ther. 2008 Jun;7(6):1440-9. PMID: 18566216
140. Apostolou et al. Current perspectives on CHEK2 mutations in breast cancer. Breast Cancer (Dove Med Press). 2017;9:331-335. PMID: 28553140
141. Nevanlinna et al. The CHEK2 gene and inherited breast cancer susceptibility. Oncogene. 2006 Sep 25;25(43):5912-9. PMID: 16998506
142. Näslund-Koch et al. Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. J. Clin. Oncol. 2016 Apr 10;34(11):1208-16. PMID: 26884562
143. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
144. https://www.senhwabio.com//en/news/20220125
145. Yoshida et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. 2011 Sep 11;478(7367):64-9. PMID: 21909114

References (continued)

146. Liu et al. Mutations in the RNA Splicing Factor SF3B1 Promote Tumorigenesis through MYC Stabilization. Cancer Discov. 2020 Mar 18. PMID: 32188705
147. Patnaik et al. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management. Am. J. Hematol. 2017 Mar;92(3):297-310. PMID: 28188970
148. Patnaik et al. Spliceosome mutations involving SRSF2, SF3B1, and U2AF35 in chronic myelomonocytic leukemia: prevalence, clinical correlates, and prognostic relevance. Am. J. Hematol. 2013 Mar;88(3):201-6. PMID: 23335386
149. Ellis et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. Nature. 2012 Jun 10;486(7403):353-60. PMID: 22722193
150. Maguire et al. SF3B1 mutations constitute a novel therapeutic target in breast cancer. J. Pathol. 2015 Mar;235(4):571-80. PMID: 25424858
151. Harbour et al. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. Nat. Genet. 2013 Feb;45(2):133-5. PMID: 23313955
152. Martin et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. Nat. Genet. 2013 Aug;45(8):933-6. PMID: 23793026
153. Furney et al. SF3B1 mutations are associated with alternative splicing in uveal melanoma. Cancer Discov. 2013 Oct;3(10):1122-1129. PMID: 23861464
154. Dono et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: detection of an activating mutation in the TERT gene promoter in a single case of uveal melanoma. Br. J. Cancer. 2014 Feb 18;110(4):1058-65. PMID: 24423917
155. DeBoever et al. Transcriptome sequencing reveals potential mechanism of cryptic 3' splice site selection in SF3B1-mutated cancers. PLoS Comput. Biol. 2015 Mar;11(3):e1004105. PMID: 25768983
156. Darman et al. Cancer-Associated SF3B1 Hotspot Mutations Induce Cryptic 3' Splice Site Selection through Use of a Different Branch Point. Cell Rep. 2015 Nov 3;13(5):1033-45. PMID: 26565915
157. Alsafadi et al. Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage. Nat Commun. 2016 Feb 4;7:10615. doi: 10.1038/ncomms10615. PMID: 26842708
158. Wan et al. SF3B1 mutations in chronic lymphocytic leukemia. Blood. 2013 Jun 6;121(23):4627-34. PMID: 23568491
159. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
160. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
161. NCCN Guidelines® - NCCN-Uveal Melanoma [Version 1.2025]
162. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
163. Seiler et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. Nat. Med. 2018 May;24(4):497-504. PMID: 29457796
164. Lee et al. Therapeutic targeting of splicing in cancer. Nat. Med. 2016 Sep 7;22(9):976-86. PMID: 27603132