

Patient Name: 김기홍
Gender: Male
Sample ID: N26-93

Primary Tumor Site: lung
Collection Date: 2026.03.03

Sample Cancer Type: Lung Cancer

Table of Contents	Page	Report Highlights
Variant Details	2	6 Relevant Biomarkers
Biomarker Descriptions	4	18 Therapies Available
Alert Details	16	219 Clinical Trials
Relevant Therapy Summary	19	

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	3.8 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: 42.86% Locus: chr7:55242464 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+} datopotamab deruxtecán-dlnk ^{1 / II+} BAT1706 + erlotinib ² gefitinib + chemotherapy ^I atezolizumab + bevacizumab + chemotherapy ^{II+}	None*	203

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

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

† Includes biosimilars/generics

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

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	<i>CCNE1</i> amplification cyclin E1 Locus: chr19:30303647	None*	None*	11
IIC	<i>TP53</i> p.(S241C) c.722C>G tumor protein p53 Allele Frequency: 45.41% Locus: chr17:7577559 Transcript: NM_000546.6	None*	None*	6
IIC	<i>CDKN2A</i> deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5
IIC	<i>CDKN2B</i> deletion cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	2
IIC	<i>RAD50</i> deletion RAD50 double strand break repair protein Locus: chr5:131892978	None*	None*	1

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

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

† Includes biosimilars/generics

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

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

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

EGFR exon 19 deletion izarontamab brengitecan¹, patritumab deruxtecan¹, sacituzumab tirumotecan¹
 DB-1310¹, DB-1418¹

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

AKT2 amplification, *LATS2* deletion, *MAP2K7* deletion, *MLH1* deletion, *Microsatellite stable*, *PARP4* deletion, *PIK3R1* deletion, *PIK3R2* p.(G373R) c.1117G>A, *PPP2R2A* deletion, *RPA1* deletion, *SETD2* deletion, *UGT1A1* p.(G71R) c.211G>A, *DOCK3* deletion, *MAP3K1* deletion, *RASA1* deletion, *ERAP1* deletion, *ERAP2* deletion, *HLA-B* deletion, *NOTCH4* p.(L14Afs*46) c.40_41delCT, *PTCH1* deletion, *NOTCH1* deletion, *PDIA3* deletion, *NCOR1* deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele		Variant Effect
					Frequency	Transcript	
EGFR	p.(E746_A750del)	c.2235_2249delGGAAT TAAGAGAAGC	COSM6223	chr7:55242464	42.86%	NM_005228.5	nonframeshift Deletion
TP53	p.(S241C)	c.722C>G	COSM10709	chr17:7577559	45.41%	NM_000546.6	missense
PIK3R2	p.(G373R)	c.1117G>A	COSM993028	chr19:18273784	17.50%	NM_005027.4	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	49.52%	NM_000463.3	missense
NOTCH4	p.(L14Afs*46)	c.40_41delCT	.	chr6:32191664	99.76%	NM_004557.4	frameshift Deletion

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	58.02%	NM_002439.5	nonframeshift Insertion
HLA-B	p.([T118];L119])	c.353_355delCCCinsT CA	.	chr6:31324208	99.68%	NM_005514.8	missense, missense
KMT2C	p.(P860S)	c.2578C>T	.	chr7:151935866	29.75%	NM_170606.3	missense
OR5D18	p.(M229I)	c.687G>C	.	chr11:55587792	28.60%	NM_001001952.1	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CCNE1	chr19:30303647	7.26	3.11
CDKN2A	chr9:21968178	0.3	0.32
CDKN2B	chr9:22005728	0.35	0.34
RAD50	chr5:131892978	1.19	0.67
AKT2	chr19:40739751	5.4	2.36
LATS2	chr13:21548922	1.21	0.68
MAP2K7	chr19:7968792	0.96	0.59
MLH1	chr3:37034957	1.24	0.69
PARP4	chr13:25000551	1.23	0.69
PIK3R1	chr5:67522468	1.24	0.69
PPP2R2A	chr8:26149298	1.23	0.69
RPA1	chr17:1733385	1.24	0.7
SETD2	chr3:47058542	1.23	0.69
DOCK3	chr3:51101879	1.14	0.66
MAP3K1	chr5:56111388	1.24	0.7
RASA1	chr5:86564256	1.25	0.7
ERAP1	chr5:96112128	1.15	0.66
ERAP2	chr5:96219500	0.49	0.4
HLA-B	chr6:31322252	0.84	0.54
PTCH1	chr9:98209140	1.16	0.66
NOTCH1	chr9:139390441	1.13	0.65
PDIA3	chr15:44038719	1.14	0.65
NCOR1	chr17:15935586	1.21	0.69
GATA2	chr3:128200046	1.15	0.66
PXDNL	chr8:52233342	1.1	0.64
CD276	chr15:73991923	0.89	0.56

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
KMT2B	chr19:36209128	5.18	2.27

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 family⁹. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4⁶⁵. 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 pathways⁶⁶. Activation of these pathways promotes cell proliferation, differentiation, and survival^{67,68}.

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations^{6,14,69,70}. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21⁷¹. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer⁷¹. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20^{72,73,74,75}. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations⁷⁶. 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^{71,77}. Amplification of EGFR is observed in several cancer types including 44% of glioblastoma multiforme, 12% of esophageal adenocarcinoma, 10% of head and neck squamous cell carcinoma, 8% of brain lower grade glioma, 6% of lung squamous cell carcinoma, 5% of bladder urothelial carcinoma cancer, lung adenocarcinoma, and stomach adenocarcinoma, 3% of cholangiocarcinoma, and 2% of cervical squamous cell carcinoma, sarcoma, and breast invasive carcinoma^{6,14,70,77,78}. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma^{79,80,81}. Alterations in EGFR are rare in pediatric cancers^{6,14}. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)^{6,14}. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)^{6,14}.

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib⁸² (2004) and gefitinib⁸³ (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 mutations⁸⁴. Second-generation TKIs afatinib⁸⁵ (2013) and dacomitinib⁸⁶ (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies^{87,88,89,90}. In 2025, the FDA approved the irreversible EGFR inhibitor, sunvozertinib⁹¹, for the treatment of locally advanced or metastatic non-small cell lung cancer in adult patients with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. In 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitor, CLN-081 (TPC-064)⁹² 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 resistance⁹³. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases⁷¹. Third generation TKIs were developed to maintain sensitivity in the presence of T790M⁹³. Osimertinib⁹⁴ (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 cases⁹³. 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 versa⁹⁵. T790M and C797S can occur in either cis or trans allelic orientation⁹⁵. 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 TKIs⁹⁵. 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^{95,96}. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs⁹⁵. Fourth-generation TKIs are in

Biomarker Descriptions (continued)

development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535⁹⁷ (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 mutations⁹⁸. The bispecific antibody, amivantamab⁹⁹ (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib¹⁰⁰ (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. HLX-42¹⁰¹, 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. CPO301¹⁰² (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 ozeplasmid¹⁰³ (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^{49,104,105}.

CCNE1 amplification

cyclin E1

Background: The CCNE1 gene encodes the cyclin E1 protein, a member of the highly conserved E-cyclin family which also includes CCNE2¹⁵⁶. CCNE1 facilitates progression from G1 to the S phase of the cell cycle by binding to cyclin dependent kinase 2 (CDK2) which results in phosphorylation and inactivation of the retinoblastoma (RB1) protein¹⁵⁶. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition resulting in cell cycle progression, a common event observed in tumorigenesis^{157,158,159}. Additionally, CCNE1 is often deregulated in a variety of cancer types supporting an oncogenic role for CCNE1^{156,160}.

Alterations and prevalence: CCNE1 amplification is observed in about 40% of uterine carcinosarcoma, 20% of ovarian cancer, 11% of stomach cancer, 7-8% sarcoma, uterine, and esophageal cancers, 5-6%, adrenocortical carcinoma, squamous lung, and bladder cancers⁶. Additionally, CCNE1 overexpression has been observed in many different tumor types including in 70-80% of Hodgkin's lymphoma.^{156,160,161}

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib¹⁶², in combination with camonsertib for the treatment of adult patients with CCNE1 amplified endometrial cancer and platinum resistant ovarian cancer. CCNE1 amplification and overexpression has been associated with poor prognosis in certain cancer types including lung and breast cancers^{163,164,165}.

TP53 p.(S241C) c.722C>G

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair⁹. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis²¹⁵. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential²¹⁶. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{217,218}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{6,14,78,219,220,221}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282^{6,14}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{222,223,224,225}. Alterations in TP53 are also observed in pediatric cancers^{6,14}. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)^{6,14}. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)^{6,14}.

Potential relevance: The small molecule p53 reactivator, PC14586²²⁶ (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53

Biomarker Descriptions (continued)

activity, compounds that induce synthetic lethality are also under clinical evaluation^{227,228}. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma²²⁹. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{230,231,232,233,234}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant²³⁵. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system²³⁶.

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression⁹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)¹⁶⁶. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{167,168,169}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions¹⁷⁰. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation^{9,170,171}. CDKN2A aberrations commonly co-occur with CDKN2B¹⁶⁶. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation¹⁷². Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{173,174}.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations¹⁷⁵. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma^{6,14}. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{6,14}. Alterations in CDKN2A are also observed in pediatric cancers¹⁴. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors¹⁴. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)¹⁴.

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors^{176,177,178}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma¹⁰⁵. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib^{179,180,181}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme¹⁸². CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer^{183,184,185,186}.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression^{9,166}. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)¹⁶⁶. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{167,168,169}. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A¹⁶⁶. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma^{9,187,188}.

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B-cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian

Biomarker Descriptions (continued)

serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe^{6,14}. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma^{6,14}. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers^{6,14}. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)^{6,14}.

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma¹⁰⁵.

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases^{189,190}. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability^{190,191}. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex^{191,192}. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)^{191,192}. RAD50 contains long coiled-coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response^{191,193}. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss^{194,195}. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer¹⁹⁶.

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer^{6,14}. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients¹⁹⁷.

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy¹⁹⁸. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression¹⁹⁸. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype¹⁹⁹.

AKT2 amplification

AKT serine/threonine kinase 2

Background: The AKT2 gene encodes a serine/threonine kinase that belongs to a family of closely related protein kinases that also includes AKT1 and AKT3⁹. Growth factor signaling leads to the activation of phosphatidylinositol 3-kinase (PI3K), recruitment of AKT to the plasma membrane, and subsequent activation of downstream effectors including MTOR¹¹⁹. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism^{119,120}. AKT2 is implicated in cancer cell invasion, survival, and metastasis in various cancers, including acute myeloid leukemia, neuroblastoma, bladder cancer, prostate cancer, and ovarian cancer^{121,122,123}.

Alterations and prevalence: Recurrent AKT2 activating mutations occur at E17K, L52R, and D324G/H¹²⁴. Somatic mutations in AKT2 are observed in 4% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, skin cutaneous melanoma, and cervical squamous cell carcinoma^{6,14}. AKT2 is amplified in 14% of uterine carcinosarcoma, 7% of pancreatic adenocarcinoma, 6% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 4% of sarcoma, 3% of cervical squamous cell carcinoma and uterine corpus endometrial carcinoma, and 2% of bladder urothelial carcinoma^{6,14}. A BCAM::AKT2 fusion has been identified in ovarian cancer¹²⁵. Alterations in AKT2 are also observed in pediatric cancers¹⁴. Somatic mutations in AKT2 are observed in less than 1% of Wilms tumors (1 in 710 cases). AKT2 amplification is observed in 2% of Wilms tumors (3 in 136 cases)¹⁴.

Potential relevance: Currently, no therapies are approved specifically for AKT2 aberrations. Although the pan-AKT inhibitor capivasertib (AZD5363) targets all AKT isoforms, clinical evidence of supporting its efficacy in AKT2-aberrant cancers remains limited¹²⁶.

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2⁹. LATS2 is a serine/threonine protein kinase and, along with LATS1, is a member of the AGC kinase family comprised of more than 60 members^{106,107}. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP

Biomarker Descriptions (continued)

and TAZ¹⁰⁸. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes¹⁰⁸. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1¹⁰⁹.

Alterations and prevalence: Somatic mutations in LATS2 are observed in 9% of mesothelioma, 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% stomach adenocarcinoma, and 3% of colorectal adenocarcinoma^{6,14}. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma^{6,14}.

Potential relevance: Currently, no therapies are approved for LATS2 aberrations.

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7⁹. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10^{141,142,143}. Activation of MAPK proteins occurs through a kinase signaling cascade^{141,142,144}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{141,142,144}. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation^{141,142,144}.

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma^{6,14}. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma^{6,14}.

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein⁹. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutL α complex, PMS1 to form the MutL β complex, and MLH3 to form the MutL γ complex³⁰. The MutL α complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutL α and degradation of PMS2^{30,31}. 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^{32,33}. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway³⁰. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication³⁰. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes³⁴. 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^{35,36,37}. 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^{35,38}. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{36,38,39,40}. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer^{41,42,43,44}.

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^{6,14}. Alterations in MLH1 are observed in pediatric cancers^{6,14}. 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)^{6,14}.

Potential relevance: The PARP inhibitor, talazoparib⁴⁵ 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 therapies⁴⁶. 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^{47,48}. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas^{49,50}.

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 genome⁵¹. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{36,38}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2³⁷. 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

Biomarker Descriptions (continued)

five markers: BAT25, BAT26, D5S346, D2S123, and D17S250⁵². Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)⁵². Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{39,53,54,55,56}. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes³⁸. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{36,38,39,40}.

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^{36,38,57,58}. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers^{57,58}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab⁴⁶ (2014) and nivolumab⁴⁷ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab⁴⁶ 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 indication⁴⁶. Dostarlimab⁵⁹ (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer^{54,60}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab⁴⁸ (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location^{54,61,62}. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients⁶². The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors^{63,64}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{63,64}.

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein⁹. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3¹²⁷. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure^{127,128}. PARP enzymes are involved in several DNA repair pathways^{127,128}. Although the functional role of PARP4 is not well understood, PARP4 has been predicted to function in base excision repair (BER) due to its BRCA1 C Terminus (BRCT) domain which is found in other DNA repair pathway proteins¹²⁹.

Alterations and prevalence: Somatic mutations in PARP4 are observed in 9% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of bladder urothelial carcinoma, 4% of stomach adenocarcinoma, and 3% of lung squamous cell carcinoma^{6,14}. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)^{6,14}.

Potential relevance: Currently, no therapies are approved for PARP4 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are homologous recombination repair (HRR) deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death^{130,131}. Although not indicated for specific alterations in PARP4, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib¹³² (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib¹³² is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib¹³³ (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib⁴⁵ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib¹³⁴ (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

Biomarker Descriptions (continued)

PIK3R1 deletion

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme⁹. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit¹⁵². Specifically, PIK3R1 encodes the p85 α protein, one of five p85 isoforms¹⁵². p85 α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity¹⁵². PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction^{154,155}. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism^{154,155,209,210}. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability²¹¹. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1¹⁵².

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 10% of glioblastoma multiforme, 6% of colorectal adenocarcinoma, 4% of brain lower grade glioma, and skin cutaneous melanoma, 3% of cervical squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, and breast invasive carcinoma, and 2% of lung squamous cell carcinoma, bladder urothelial carcinoma, esophageal adenocarcinoma, thymoma, head and neck squamous cell carcinoma, and kidney chromophobe^{6,14}. Additionally, biallelic loss of PIK3R1 is observed in 4% of prostate adenocarcinoma and 3% of ovarian serous cystadenocarcinoma^{6,14}. Alterations in PIK3R1 are also observed in pediatric cancers¹⁴. Somatic mutations in PIK3R1 are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and leukemia (7 in 354 cases), 1% of glioma (3 in 297 cases) and bone cancer (3 in 327 cases), and less than 1% of embryonal tumors (2 in 332 cases) and peripheral nervous system tumors (1 in 1158 cases)¹⁴. Biallelic deletion of PIK3R1 is observed in 3% of leukemia (8 of 250 cases) and in less than 1% of B-lymphoblastic leukemia/lymphoma (4 of 731 cases), while structural alterations in PIK3R1 occur in fewer than 1% of leukemia (1 of 107 cases)¹⁴.

Potential relevance: Currently, no therapies are approved for PIK3R1 aberrations.

PIK3R2 p.(G373R) c.1117G>A

phosphoinositide-3-kinase regulatory subunit 2

Background: The PIK3R2 gene encodes the phosphoinositide-3-kinase regulatory subunit 2 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme^{9,152}. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit¹⁵². PIK3R2 encodes the p85 β protein, one of five p85 isoforms¹⁵². p85 β is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity¹⁵³. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3)^{154,155}. Increased PIK3R2 expression has been observed to correlate with elevated AKT activation and tumor stage, supporting an oncogenic role for PIK3R2¹⁵³.

Alterations and prevalence: Somatic mutations in PIK3R2 are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and colorectal adenocarcinoma^{6,14}. Amplification of PIK3R2 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, mesothelioma, and liver hepatocellular carcinoma^{6,14}.

Potential relevance: Currently, no therapies are approved for PIK3R2 aberrations.

PPP2R2A deletion

protein phosphatase 2 regulatory subunit B alpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPP2CA and PPP2CB)^{1,2}. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway³. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway¹.

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer^{1,2,4,5}. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma⁶.

Biomarker Descriptions (continued)

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁷, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib¹. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit⁸.

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1⁹. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)¹⁴⁰. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)¹⁴⁰. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair¹⁴⁰.

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma^{6,14}. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma^{6,14}.

Potential relevance: Currently, no therapies are approved for RPA1 aberrations.

SETD2 deletion

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)^{200,201}. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation²⁰². Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation^{203,204}. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery²⁰¹. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)²⁰⁵. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2^{201,206}.

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating^{6,206,207}. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity^{6,200}. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers²⁰⁰. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma²⁰⁰.

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)²⁰⁸.

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^{9,17}. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites^{17,18}. 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 resistance¹⁹. 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^{19,20,21,22}. 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-38²³.

Biomarker Descriptions (continued)

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^{6,14}.

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

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)⁹. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling²³⁷. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion^{9,238,239}. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β -catenin/WNT signaling^{240,241}. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3²³⁹.

Alterations and prevalence: Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe^{6,14}. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma^{6,14}.

Potential relevance: Currently, no therapies are approved for DOCK3 aberrations.

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1⁹. Activation of MAPK proteins occurs through a kinase signaling cascade^{141,142,144}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{141,142,144}. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation^{141,142,144}. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain¹⁴⁵. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis¹⁴⁵. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitinating c-JUN and MAPK1/MAPK3¹⁴⁵.

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma^{6,14}. MAP3K1 mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes¹⁴⁵. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma^{6,14}.

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

RASA1 deletion

RAS p21 protein activator 1

Background: The RASA1 gene encodes the Ras p21 protein activator 1⁹. RASA1 is a member of the RasGAP family, which includes RASA2^{15,16}. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form¹⁵. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis¹⁵. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways¹⁵. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types¹⁵.

Alterations and prevalence: Somatic mutations in RASA1 are observed in 11% of uterine corpus endometrial carcinoma, 6% of lung squamous cell carcinoma, 5% of stomach adenocarcinoma and of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, head and neck squamous cell carcinoma, colorectal carcinoma, and uterine carcinosarcoma, and 3% of esophageal adenocarcinoma^{6,14}. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma^{6,14}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for RASA1 aberrations.

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein⁹. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway^{146,147}. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules^{146,148}. ERAP1 has also been shown to be involved in the shedding of cytokine receptors (including TNFR1, IL6-Ra, and type II IL-II receptor) and is observed to be secreted by macrophages, which is believed to enhance phagocytosis^{146,149,150}. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma^{146,151}.

Alterations and prevalence: Somatic mutations in ERAP1 are observed in 7% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma^{6,14}. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma^{6,14}.

Potential relevance: Currently, no therapies are approved for ERAP1 aberrations.

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway^{146,147}. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules^{146,148}. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic¹⁴⁶.

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma^{6,14}. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma^{6,14}.

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B⁹. 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 cells²⁴. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M²⁵. 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^{26,27,28}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B²⁹.

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^{6,14}. Biallelic loss of HLA-B is observed in 5% of DLBCL^{6,14}.

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

NOTCH4 p.(L14Afs*46) c.40_41delCT

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

Biomarker Descriptions (continued)

(EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling¹¹⁰. 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^{111,112}. 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^{113,114,115,116}.

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 cancers⁶.

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

PTCH1 deletion

patched 1

Background: The PTCH1 gene encodes the patched 1 protein, a transmembrane protein that along with PTCH2, belongs to the patched gene family⁹. PTCH1 is involved in the Hedgehog (Hh) signaling pathway that plays a significant role in embryonic development, cell proliferation, and cell differentiation^{212,213}. PTCH1 is a tumor suppressor gene that inhibits the transmembrane receptor Smoothed (SMO) and prevents downstream Hh signaling pathway activation^{212,213}. The Hh pathway is activated when one of the Hh ligands including Sonic hedgehog (SHh), Indian hedgehog (IHh), or Desert Hedgehog (Dhh) bind to PTCH1 and disrupt SMO inhibition²¹³. Inactivating mutations in PTCH1 lead to ligand-independent signaling of Hh, as PTCH1 no longer prevents SMO activity²¹³. Germline mutations in PTCH1 are associated with basal cell nevus syndrome (BCNS) or Gorlin Syndrome with a predisposition to non-cancerous and cancerous tumors including basal cell carcinoma^{213,214}.

Alterations and prevalence: Inactivating mutations in PTCH1 are observed in 85% of sporadic basal cell carcinomas²¹⁴. Somatic mutations in PTCH1 are also observed in 11% of uterine corpus endometrial carcinoma and 4-5% of stomach adenocarcinoma, skin cutaneous melanoma, cholangiocarcinoma, esophagus adenocarcinoma, colorectal adenocarcinoma, and mesothelioma^{6,14}.

Potential relevance: Currently, no therapies are approved for PTCH1 aberrations.

NOTCH1 deletion

notch 1

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling¹¹⁰. 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^{111,112}. 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^{113,114,115,116}.

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers^{6,14,78}. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia^{117,118}.

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

PDIA3 deletion

protein disulfide isomerase family A member 3

Background: The PDIA3 gene encodes the protein disulfide isomerase family A member 3⁹. PDIA3 is a member of the protein disulfide isomerase (PDI) gene family, and acts as an enzymatic chaperone for reconstructing misfolded proteins¹⁰. PDIA3 has also been identified as being involved EGFR regulation, mTOR signaling, and associated with the major histocompatibility complex (MHC) protein loading complex (PLC)¹¹. Deregulation of PDIA3, including both overexpression and loss, has been observed in several cancer types, suggesting that PDIA3 may exhibit differing roles depending on the tumor type^{11,12,13}.

Alterations and prevalence: Somatic mutations in PDIA3 are observed in 5% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, skin cutaneous melanoma, and 1% of stomach adenocarcinoma, bladder urothelial carcinoma, lung adenocarcinoma,

Biomarker Descriptions (continued)

pancreatic adenocarcinoma, and glioblastoma multiforme^{6,14}. Deletions in PDIA3 are observed in 6% of diffuse large B-cell lymphoma 5% of mesothelioma, and 2% of lung adenocarcinoma, and ovarian serous cystadenocarcinoma^{6,14}.

Potential relevance: Currently, no therapies are approved for PDIA3 aberrations. Overexpression of PDIA3 in hepatocellular carcinoma and colon cancer is associated with advanced disease and poor prognosis¹⁰. Conversely, PDIA3 loss is correlated with aggressive disease and poor survival in gastric cancer and head and neck cancer^{12,13}.

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)^{9,135,136}. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability^{135,136,137,138}. NCOR1 has been shown to exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models¹³⁶. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types, including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer^{136,139}.

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma^{6,14}. Biallelic loss of NCOR1 is observed in 3% of liver hepatocellular carcinoma and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma^{6,14}. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma^{6,14}. Alterations in NCOR1 are also observed in pediatric cancer¹⁴. Somatic mutations in NCOR1 are observed in 3% of soft tissue sarcoma (1 in 38 cases), 2% of leukemia (6 in 354 cases), Hodgkin lymphoma (1 in 61 cases), B-lymphoblastic leukemia/lymphoma (4 in 252 cases), bone cancer (5 in 327 cases), and embryonal cancer (5 in 332 cases), and less than 1% of glioma (2 in 297 cases) and peripheral nervous system cancers (1 in 1158 cases)¹⁴. Biallelic deletion of NCOR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (6 in 731 cases) and leukemia (2 in 250 cases)¹⁴.

Potential relevance: Currently, no therapies are approved for NCOR1 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

EGFR exon 19 deletion

izationaltamab brengitecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Supporting Statement:

The FDA has granted Breakthrough designation to EGFR/HER3 targeting bispecific antibody-drug conjugate (ADC), izationaltamab brengitecan, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 L858R substitution mutations who experienced disease progression on or after treatment with an EGFR TKI and platinum-based chemotherapy.

Reference:

<https://www.onclive.com/view/fda-grants-breakthrough-therapy-designation-to-izationaltamab-brengitecan-in-egfr-nsclc>

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>

sacituzumab tirumotecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Supporting Statement:

The FDA has granted Breakthrough designation to the trophoblast cell-surface antigen 2 (TROP2)-directed antibody drug conjugate (ADC), sacituzumab tirumotecan, for the treatment of patients with advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations (exon 19 deletion [19del] or exon 21 L858R) whose disease progressed on or after tyrosine kinase inhibitor (TKI) and platinum-based chemotherapy.

Reference:

<https://www.merck.com/news/fda-grants-breakthrough-therapy-designation-to-sacituzumab-tirumotecan-sac-tmt-for-the-treatment-of-certain-patients-with-previously-treated-advanced-or-metastatic-nonsquamous-non-small-cell-lung-ca/>

EGFR exon 19 deletion (continued)

A DB-1310

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Supporting Statement:

The FDA has granted Fast Track designation to the HER3-targeting antibody-drug conjugate, DB-1310, for the treatment of adult patients with advanced, unresectable or metastatic non-squamous non-small cell lung cancer with EGFR exon 19 deletion or L858R mutation and who have progressed after treatment with a third-generation EGFR tyrosine kinase inhibitor and platinum-based chemotherapy.

Reference:

<https://www.targetedonc.com/view/novel-her3-adc-receives-fda-fast-track-for-refractory-nsclc>

A DB-1418

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR exon 19 deletion

Supporting Statement:

The FDA has granted Fast Track designation to the EGFR/HER3 bispecific antibody-drug conjugate (BsADC), AVZO-1418 (DB-1418), for the treatment of patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC) with an epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R mutation, whose disease has progressed on or after therapy with an EGFR tyrosine kinase inhibitor (TKI).

Reference:

<https://avenzotx.com/press-releases/avenzo-therapeutics-granted-fast-track-designation-for-avzo-1418-a-potential-best-in-class-egfr-her3-bispecific-adc-for-the-treatment-of-patients-with-egfr-mutated-tki-pretreated-nsclc/>

CCNE1 amplification

A camonsertib + lunresertib

Cancer type: Endometrial Carcinoma, Ovarian Cancer

Variant class: CCNE1 amplification

Supporting Statement:

- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated platinum resistant ovarian cancer.
- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated endometrial cancer.

Reference:

<https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda>

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,

Genes Assayed (continued)

Genes Assayed for the Detection of DNA Sequence Variants (continued)

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, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABC1, 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, CBF, 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, ERFF1, 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, IKK, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, 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, TGFB2, 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, PPAR, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, REL, 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, CBF, 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 ① 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	●	●	●	✕	✕
datopotamab deruxtecan-dlnk	●	●	✕	✕	✕
osimertinib + chemotherapy + pemetrexed	●	✕	●	✕	✕
bevacizumab + erlotinib	✕	●	●	●	✕
erlotinib	✕	●	●	●	✕
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)

* 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*
furmonertinib, chemotherapy	✕	✕	✕	✕	● (IV)
gefitinib, chemotherapy	✕	✕	✕	✕	● (IV)
gefitinib, endostatin	✕	✕	✕	✕	● (IV)
natural product, gefitinib, erlotinib, icotinib hydrochloride, osimertinib, almonertinib, furmonertinib	✕	✕	✕	✕	● (IV)
almonertinib, apatinib	✕	✕	✕	✕	● (III)
almonertinib, catequentinib	✕	✕	✕	✕	● (III)
almonertinib, chemotherapy	✕	✕	✕	✕	● (III)
almonertinib, radiation therapy	✕	✕	✕	✕	● (III)
asandeutertinib, osimertinib	✕	✕	✕	✕	● (III)
ASKC-202, limertinib	✕	✕	✕	✕	● (III)
befotertinib, icotinib hydrochloride	✕	✕	✕	✕	● (III)
bevacizumab, osimertinib	✕	✕	✕	✕	● (III)
CK-101, gefitinib	✕	✕	✕	✕	● (III)
furmonertinib	✕	✕	✕	✕	● (III)
furmonertinib, osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
gefitinib, afatinib, erlotinib, metformin hydrochloride	✕	✕	✕	✕	● (III)
glumetinib, osimertinib	✕	✕	✕	✕	● (III)
icotinib hydrochloride, catequentinib	✕	✕	✕	✕	● (III)
icotinib hydrochloride, chemotherapy	✕	✕	✕	✕	● (III)
icotinib hydrochloride, radiation therapy	✕	✕	✕	✕	● (III)
izalontamab brengitecan, osimertinib	✕	✕	✕	✕	● (III)
JMT-101, osimertinib	✕	✕	✕	✕	● (III)
osimertinib, bevacizumab	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, datopotamab deruxtecan-dlnk	✕	✕	✕	✕	● (III)
osimertinib, gefitinib, chemotherapy	✕	✕	✕	✕	● (III)
sacituzumab tirumotecan	✕	✕	✕	✕	● (III)
sacituzumab tirumotecan, osimertinib	✕	✕	✕	✕	● (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*
SH-1028	✕	✕	✕	✕	● (III)
PM-1080, almonertinib	✕	✕	✕	✕	● (II/III)
SCTB-14, chemotherapy	✕	✕	✕	✕	● (II/III)
ABSK-043, furmonertinib	✕	✕	✕	✕	● (II)
afatinib, chemotherapy	✕	✕	✕	✕	● (II)
almonertinib	✕	✕	✕	✕	● (II)
almonertinib, adabrelinab, chemotherapy	✕	✕	✕	✕	● (II)
almonertinib, bevacizumab	✕	✕	✕	✕	● (II)
almonertinib, chemoradiation therapy	✕	✕	✕	✕	● (II)
almonertinib, chemotherapy, radiation therapy	✕	✕	✕	✕	● (II)
almonertinib, dacomitinib	✕	✕	✕	✕	● (II)
amivantamab, chemotherapy	✕	✕	✕	✕	● (II)
amivantamab, lazertinib, chemotherapy	✕	✕	✕	✕	● (II)
asandeutertinib, chemotherapy	✕	✕	✕	✕	● (II)
befotertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
befotertinib, chemotherapy	✕	✕	✕	✕	● (II)
bevacizumab, afatinib	✕	✕	✕	✕	● (II)
bevacizumab, furmonertinib	✕	✕	✕	✕	● (II)
cadonilimab, chemotherapy, catequentinib	✕	✕	✕	✕	● (II)
camrelizumab, apatinib	✕	✕	✕	✕	● (II)
capmatinib, osimertinib, ramucirumab	✕	✕	✕	✕	● (II)
catequentinib, almonertinib	✕	✕	✕	✕	● (II)
catequentinib, chemotherapy	✕	✕	✕	✕	● (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)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ① In this cancer type and other cancer types ✕ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
furmonertinib, bevacizumab	✕	✕	✕	✕	● (II)
furmonertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
furmonertinib, catequentinib	✕	✕	✕	✕	● (II)
furmonertinib, chemotherapy, bevacizumab	✕	✕	✕	✕	● (II)
furmonertinib, icotinib hydrochloride	✕	✕	✕	✕	● (II)
gefitinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
gefitinib, icotinib hydrochloride	✕	✕	✕	✕	● (II)
gefitinib, thalidomide	✕	✕	✕	✕	● (II)
IBI-318, lenvatinib	✕	✕	✕	✕	● (II)
icotinib hydrochloride	✕	✕	✕	✕	● (II)
icotinib hydrochloride, autologous RAK cell	✕	✕	✕	✕	● (II)
icotinib hydrochloride, osimertinib	✕	✕	✕	✕	● (II)
ivonescimab, chemotherapy	✕	✕	✕	✕	● (II)
izalontamab brengitecan, almonertinib	✕	✕	✕	✕	● (II)
JS-207, chemotherapy	✕	✕	✕	✕	● (II)
JSKN-016	✕	✕	✕	✕	● (II)
lazertinib	✕	✕	✕	✕	● (II)
lazertinib, bevacizumab	✕	✕	✕	✕	● (II)
lazertinib, chemotherapy	✕	✕	✕	✕	● (II)
osimertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
osimertinib, radiation therapy	✕	✕	✕	✕	● (II)
PLB-1004, bozitinib, osimertinib	✕	✕	✕	✕	● (II)
ramucirumab, erlotinib	✕	✕	✕	✕	● (II)
sunvozertinib	✕	✕	✕	✕	● (II)
sunvozertinib, catequentinib	✕	✕	✕	✕	● (II)
sunvozertinib, golidocitinib	✕	✕	✕	✕	● (II)
tislelizumab, chemotherapy, bevacizumab	✕	✕	✕	✕	● (II)
toripalimab	✕	✕	✕	✕	● (II)
toripalimab, bevacizumab, Clostridium butyricum, 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*
toripalimab, chemotherapy	✕	✕	✕	✕	● (II)
vabametkib, lazertinib	✕	✕	✕	✕	● (II)
YL-202	✕	✕	✕	✕	● (II)
zipalertinib	✕	✕	✕	✕	● (II)
zorifertinib, pirotinib	✕	✕	✕	✕	● (II)
AP-L1898	✕	✕	✕	✕	● (I/II)
BH-30643	✕	✕	✕	✕	● (I/II)
bozitinib, osimertinib	✕	✕	✕	✕	● (I/II)
BPI-361175	✕	✕	✕	✕	● (I/II)
chemotherapy, DZD-6008	✕	✕	✕	✕	● (I/II)
dacomitinib, catequentinib	✕	✕	✕	✕	● (I/II)
DAJH-1050766	✕	✕	✕	✕	● (I/II)
DB-1310, osimertinib	✕	✕	✕	✕	● (I/II)
dositinib	✕	✕	✕	✕	● (I/II)
FWD-1509	✕	✕	✕	✕	● (I/II)
H-002	✕	✕	✕	✕	● (I/II)
ifebemtinib, furmonertinib	✕	✕	✕	✕	● (I/II)
necitumumab, osimertinib	✕	✕	✕	✕	● (I/II)
PLB-1004, chemotherapy	✕	✕	✕	✕	● (I/II)
quaratusugene ozeplasmid, osimertinib	✕	✕	✕	✕	● (I/II)
RC-108, furmonertinib, toripalimab	✕	✕	✕	✕	● (I/II)
sotiburafusp alfa, chemotherapy	✕	✕	✕	✕	● (I/II)
sotiburafusp alfa, HB-0030	✕	✕	✕	✕	● (I/II)
sunvozertinib, chemotherapy	✕	✕	✕	✕	● (I/II)
TRX-221	✕	✕	✕	✕	● (I/II)
WSD-0922	✕	✕	✕	✕	● (I/II)
YL-202, pumitamig	✕	✕	✕	✕	● (I/II)
almonertinib, midazolam	✕	✕	✕	✕	● (I)
ASKC-202	✕	✕	✕	✕	● (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 ① In this cancer type and other cancer types ✕ No evidence

EGFR exon 19 deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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)
izalontamab brengitecan	✕	✕	✕	✕	● (I)
KQB-198, osimertinib	✕	✕	✕	✕	● (I)
LAVA-1223	✕	✕	✕	✕	● (I)
MRX-2843, osimertinib	✕	✕	✕	✕	● (I)
osimertinib, carotuximab	✕	✕	✕	✕	● (I)
osimertinib, Minnelide	✕	✕	✕	✕	● (I)
osimertinib, tegatrabetan	✕	✕	✕	✕	● (I)
patritumab deruxtecan	✕	✕	✕	✕	● (I)
PB-101 (Precision Biotech Taiwan Corp), EGFR tyrosine kinase inhibitor	✕	✕	✕	✕	● (I)
reprotrectinib, osimertinib	✕	✕	✕	✕	● (I)
VIC-1911, osimertinib	✕	✕	✕	✕	● (I)
VT-3989, osimertinib, nivolumab, ipilimumab	✕	✕	✕	✕	● (I)
WTS-004	✕	✕	✕	✕	● (I)
YH-013	✕	✕	✕	✕	● (I)
zipalertinib, chemotherapy, glumetinib, pimitespi, quemliclustat	✕	✕	✕	✕	● (I)

CCNE1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✕	✕	✕	✕	● (II)
APR-1051	✕	✕	✕	✕	● (I/II)
ARTS-021	✕	✕	✕	✕	● (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

CCNE1 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ECI-830, hormone therapy, ribociclib	✕	✕	✕	✕	● (I/II)
INX-315, hormone therapy	✕	✕	✕	✕	● (I/II)
WJB-001	✕	✕	✕	✕	● (I/II)
ETX-197, hormone therapy	✕	✕	✕	✕	● (I)
lunresertib, camonsertib, Debio-0123	✕	✕	✕	✕	● (I)
nedisertib, tuvusertib	✕	✕	✕	✕	● (I)
NKT-3964	✕	✕	✕	✕	● (I)
NKT-5097	✕	✕	✕	✕	● (I)

TP53 p.(S241C) c.722C>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
almonertinib, catequentinib	✕	✕	✕	✕	● (III)
osimertinib, chemotherapy	✕	✕	✕	✕	● (III)
osimertinib, bevacizumab, chemotherapy	✕	✕	✕	✕	● (II)
sunvozertinib, catequentinib	✕	✕	✕	✕	● (II)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
AMG 193	✕	✕	✕	✕	● (I/II)
ABSK-131	✕	✕	✕	✕	● (I)
CID-078	✕	✕	✕	✕	● (I)

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
CID-078	✕	✕	✕	✕	● (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

RAD50 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✘	✘	✘	✘	● (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
Not Detected	Not Applicable

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

Thermo Fisher Scientific's Ion Torrent 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 (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. 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. Kaley et al. Loss of PPP2R2A inhibits homologous recombination DNA repair and predicts tumor sensitivity to PARP inhibition. *Cancer Res.* 2012 Dec 15;72(24):6414-24. PMID: 23087057
2. Álvarez-Fernández et al. Therapeutic relevance of the PP2A-B55 inhibitory kinase MASTL/Greatwall in breast cancer. *Cell Death Differ.* 2018 May;25(5):828-840. PMID: 29229993
3. Perrotti et al. Protein phosphatase 2A: a target for anticancer therapy. *Lancet Oncol.* 2013 May;14(6):e229-38. PMID: 23639323
4. Beca et al. Altered PPP2R2A and Cyclin D1 Expression Defines a Subgroup of Aggressive Luminal-Like Breast Cancer. *BMC Cancer.* 2015 Apr 15;15:285. doi: 10.1186/s12885-015-1266-1. PMID: 25879784
5. Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature.* 2012 Apr 18;486(7403):346-52. PMID: 22522925
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
7. <https://www.senhwabio.com/en/news/20220125>
8. NCCN Guidelines® - NCCN-Prostate Cancer [Version 2.2026]
9. 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
10. Zou et al. P4HB and PDIA3 are associated with tumor progression and therapeutic outcome of diffuse gliomas. *Oncol Rep.* 2018 Feb;39(2):501-510. PMID: 29207176
11. Zhang et al. PDIA3 correlates with clinical malignant features and immune signature in human gliomas. *Aging (Albany NY).* 2020 Aug 29;12(15):15392-15413. PMID: 32687065
12. Chung et al. Downregulation of ERp57 expression is associated with poor prognosis in early-stage cervical cancer. *Biomarkers.* 2013 Nov;18(7):573-9. PMID: 23957851
13. Leys et al. Expression and prognostic significance of prothymosin-alpha and ERp57 in human gastric cancer. *Surgery.* 2007 Jan;141(1):41-50. PMID: 17188166
14. 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
15. Zhang et al. Role of RASA1 in cancer: A review and update (Review). *Oncol Rep.* 2020 Dec;44(6):2386-2396. PMID: 33125148
16. King et al. Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. *Sci Signal.* 2013 Feb 26;6(264):re1. PMID: 23443682
17. 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
18. Nagar et al. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene.* 2006 Mar 13;25(11):1659-72. PMID: 16550166
19. 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
20. 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
21. 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
22. 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
23. Karas et al. *JCO Oncol Pract.* 2021 Dec 3:OP2100624. PMID: 34860573
24. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci.* PMID: 23849087
25. 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
26. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol.* 2015;33:169-200. PMID: 25493333
27. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol.* 2005 Mar;5(3):201-14. PMID: 15719024
28. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol.* 2008 Jan 22;9:1. PMID: 18211710
29. 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
30. Li. Mechanisms and functions of DNA mismatch repair. *Cell Res.* 2008 Jan;18(1):85-98. PMID: 18157157

References (continued)

31. 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
32. 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
33. 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
34. Martin et al. Therapeutic targeting of the DNA mismatch repair pathway. *Clin Cancer Res.* 2010 Nov 1;16(21):5107-13. PMID: 20823149
35. 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
36. 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
37. 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
38. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
39. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
40. 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
41. 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
42. 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
43. 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
44. 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
45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/217439s003lbl.pdf
46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s178lbl.pdf
47. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s131lbl.pdf
48. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s136lbl.pdf
49. 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
50. 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
51. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
52. 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
53. 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
54. NCCN Guidelines® - NCCN-Colon Cancer [Version 5.2025]
55. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
56. 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
57. 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
58. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
59. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
60. NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2025]

References (continued)

61. 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
62. 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
63. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
64. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
65. 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
66. Liu et al. EGFR-TKIs resistance via EGFR-independent signaling pathways. *Mol Cancer.* 2018 Feb 19;17(1):53. PMID: 29455669
67. Zhixiang. ErbB Receptors and Cancer. *Methods Mol. Biol.* 2017;1652:3-35. PMID: 28791631
68. Gutierrez et al. HER2: biology, detection, and clinical implications. *Arch. Pathol. Lab. Med.* 2011 Jan;135(1):55-62. PMID: 21204711
69. 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
70. 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
71. da Cunha Santos et al. EGFR mutations and lung cancer. *Annu Rev Pathol.* 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
72. 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
73. 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
74. 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
75. 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
76. Karachaliou et al. KRAS mutations in lung cancer. *Clin Lung Cancer.* 2013 May;14(3):205-14. PMID: 23122493
77. Brennan et al. The somatic genomic landscape of glioblastoma. *Cell.* 2013 Oct 10;155(2):462-77. PMID: 24120142
78. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015 Jan 29;517(7536):576-82. PMID: 25631445
79. 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
80. 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
81. Gan et al. The EGFRvIII variant in glioblastoma multiforme. *J Clin Neurosci.* 2009 Jun;16(6):748-54. PMID: 19324552
82. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
83. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
84. 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
85. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf
86. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
87. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2025]
88. 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
89. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther.* 2019;4:5. PMID: 30854234
90. 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

References (continued)

91. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219839s000lbl.pdf
92. <https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys>
93. 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
94. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208065s033lbl.pdf
95. 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
96. 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
97. <https://investors.blackdiamondtherapeutics.com//news-releases/news-release-details/black-diamond-therapeutics-announces-corporate-update-and>
98. 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
99. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s011lbl.pdf
100. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219008s003lbl.pdf
101. <https://iis.aastocks.com/20231227/11015917-0.PDF>
102. <https://www1.hkexnews.hk/listedco/listconews/sehk/2024/1008/2024100800433.pdf>
103. <https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/>
104. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 3.2025]
105. 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
106. Furth et al. The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway. *Cell Death Differ*. 2017 Sep;24(9):1488-1501. PMID: 28644436
107. Leroux et al. AGC kinases, mechanisms of regulation #and innovative drug development. *Semin Cancer Biol*. 2018 Feb;48:1-17. PMID: 28591657
108. Meng et al. Mechanisms of Hippo pathway regulation. *Genes Dev*. 2016 Jan 1;30(1):1-17. PMID: 26728553
109. Yu et al. Mutation analysis of large tumor suppressor genes LATS1 and LATS2 supports a tumor suppressor role in human cancer. *Protein Cell*. 2015 Jan;6(1):6-11. PMID: 25482410
110. 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
111. Bray. Notch signalling in context. *Nat. Rev. Mol. Cell Biol*. 2016 Nov;17(11):722-735. PMID: 27507209
112. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. *Cell*. 2009 Apr 17;137(2):216-33. PMID: 19379690
113. 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
114. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. *Nat Rev Urol*. 2018 Jun;15(6):345-357. PMID: 29643502
115. 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
116. 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
117. Weng et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science*. 2004 Oct 8;306(5694):269-71. PMID: 15472075
118. 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
119. Gonzalez et al. The Akt kinases: isoform specificity in metabolism and cancer. *Cell Cycle*. 2009 Aug 15;8(16):2502-8. PMID: 19597332
120. Porta et al. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front Oncol*. 2014 Apr 14;4:64. doi: 10.3389/fonc.2014.00064. eCollection 2014. PMID: 24782981

References (continued)

121. Honardoost et al. Triangle of AKT2, miRNA, and Tumorigenesis in Different Cancers. *Appl. Biochem. Biotechnol.* 2018 Jun;185(2):524-540. PMID: 29199386
122. Agarwal et al. Role of Akt2 in regulation of metastasis suppressor 1 expression and colorectal cancer metastasis. *Oncogene.* 2017 Jun 1;36(22):3104-3118. PMID: 28068324
123. Riggio et al. AKT1 and AKT2 isoforms play distinct roles during breast cancer progression through the regulation of specific downstream proteins. *Sci Rep.* 2017 Mar 13;7:44244. doi: 10.1038/srep44244. PMID: 28287129
124. Yi et al. Recurrent AKT mutations in human cancers: functional consequences and effects on drug sensitivity. *Oncotarget.* 2016 Jan 26;7(4):4241-51. PMID: 26701849
125. Kannan et al. Recurrent BCAM-AKT2 fusion gene leads to a constitutively activated AKT2 fusion kinase in high-grade serous ovarian carcinoma. *Proc. Natl. Acad. Sci. U.S.A.* 2015 Mar 17;112(11):E1272-7. PMID: 25733895
126. Davies et al. Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. *Mol. Cancer Ther.* 2012 Apr;11(4):873-87. PMID: 22294718
127. Amé et al. The PARP superfamily. *Bioessays.* 2004 Aug;26(8):882-93. PMID: 15273990
128. Morales et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. *Crit Rev Eukaryot Gene Expr.* 2014;24(1):15-28. PMID: 24579667
129. Prawira et al. Assessment of PARP4 as a candidate breast cancer susceptibility gene. *Breast Cancer Res Treat.* 2019 Aug;177(1):145-153. PMID: 31119570
130. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. *Clin Cancer Res.* 2019 Jul 1;25(13):3759-3771. PMID: 30760478
131. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. *Science.* 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
132. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208558s031lbl.pdf
133. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
134. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214876s003s004lbl.pdf
135. Geiger et al. Role of the Nuclear Receptor Corepressor 1 (NCOR1) in Atherosclerosis and Associated Immunometabolic Diseases. *Front Immunol.* 2020;11:569358. PMID: 33117357
136. Martínez-Iglesias et al. Tumor suppressive actions of the nuclear receptor corepressor 1. *Pharmacol Res.* 2016 Jun;108:75-79. PMID: 27149915
137. Bhaskara et al. Hdac3 is essential for the maintenance of chromatin structure and genome stability. *Cancer Cell.* 2010 Nov 16;18(5):436-47. PMID: 21075309
138. Mottis et al. Emerging roles of the corepressors NCoR1 and SMRT in homeostasis. *Genes Dev.* 2013 Apr 15;27(8):819-35. PMID: 23630073
139. Noblejas-López et al. Evaluation of transcriptionally regulated genes identifies NCOR1 in hormone receptor negative breast tumors and lung adenocarcinomas as a potential tumor suppressor gene. *PLoS One.* 2018;13(11):e0207776. PMID: 30485330
140. Binz et al. Replication Protein A phosphorylation and the cellular response to DNA damage. *DNA Repair.* 01 Aug 2004, 3(8-9):1015-1024. PMID: 15279788
141. Pritchard et al. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. *Clin. Cancer Res.* 2013 May 1;19(9):2301-9. PMID: 23406774
142. Bubici et al. JNK signalling in cancer: in need of new, smarter therapeutic targets. *Br J Pharmacol.* 2014 Jan;171(1):24-37. PMID: 24117156
143. Cargnello et al. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev.* 2011 Mar;75(1):50-83. PMID: 21372320
144. Lee et al. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *Int J Mol Sci.* 2020 Feb 7;21(3). PMID: 32046099
145. Pham et al. MAP3K1: Genomic Alterations in Cancer and Function in Promoting Cell Survival or Apoptosis. *Genes Cancer.* 2013 Nov;4(11-12):419-26. PMID: 24386504
146. Stratikos et al. A role for naturally occurring alleles of endoplasmic reticulum aminopeptidases in tumor immunity and cancer predisposition. *Front Oncol.* 2014;4:363. PMID: 25566501
147. López de Castro. How ERAP1 and ERAP2 Shape the Peptidomes of Disease-Associated MHC-I Proteins. *Front Immunol.* 2018;9:2463. PMID: 30425713
148. Serwold et al. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. *Nature.* 2002 Oct 3;419(6906):480-3. PMID: 12368856

References (continued)

149. Cui et al. Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding. *J Clin Invest.* 2002 Aug;110(4):515-26. PMID: 12189246
150. Cui et al. Shedding of the type II IL-1 decoy receptor requires a multifunctional aminopeptidase, aminopeptidase regulator of TNF receptor type 1 shedding. *J Immunol.* 2003 Dec 15;171(12):6814-9. PMID: 14662887
151. Mehta et al. Genetic variation of antigen processing machinery components and association with cervical carcinoma. *Genes Chromosomes Cancer.* 2007 Jun;46(6):577-86. PMID: 17366619
152. Cheung et al. Targeting therapeutic liabilities engendered by PIK3R1 mutations for cancer treatment. *Pharmacogenomics.* 2016 Feb;17(3):297-307. PMID: 26807692
153. Vallejo-Díaz et al. The Opposing Roles of PIK3R1/p85a and PIK3R2/p85b in Cancer. *Trends Cancer.* 2019 Apr;5(4):233-244. PMID: 30961830
154. Cantley. The phosphoinositide 3-kinase pathway. *Science.* 2002 May 31;296(5573):1655-7. PMID: 12040186
155. Fruman et al. The PI3K Pathway in Human Disease. *Cell.* 2017 Aug 10;170(4):605-635. PMID: 28802037
156. Hwang et al. Cyclin E in normal and neoplastic cell cycles. *Oncogene.* 2005 Apr 18;24(17):2776-86. PMID: 15838514
157. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. *Nat. Rev. Cancer.* 2009 Mar;9(3):153-66. PMID: 19238148
158. Koyama-Nasu et al. The critical role of cyclin D2 in cell cycle progression and tumorigenicity of glioblastoma stem cells. *Oncogene.* 2013 Aug 15;32(33):3840-5. PMID: 22964630
159. Bartek et al. Pathways governing G1/S transition and their response to DNA damage. *FEBS Lett.* 2001 Feb 16;490(3):117-22. PMID: 11223026
160. Schraml et al. Cyclin E overexpression and amplification in human tumours. *J. Pathol.* 2003 Jul;200(3):375-82. PMID: 12845634
161. Bai et al. Proliferation profile of classical Hodgkin's lymphomas. Increased expression of the protein cyclin D2 in Hodgkin's and Reed-Sternberg cells. *Mod. Pathol.* 2004 Nov;17(11):1338-45. PMID: 15354186
162. <https://ir.reparerx.com/news-releases/news-release-details/repere-therapeutics-announces-fast-track-designation-granted-fda>
163. Keyomarsi et al. Cyclin E and survival in patients with breast cancer. *N. Engl. J. Med.* 2002 Nov 14;347(20):1566-75. PMID: 12432043
164. Zhao et al. Prognostic Values of CCNE1 Amplification and Overexpression in Cancer Patients: A Systematic Review and Meta-analysis. *J Cancer.* 2018;9(13):2397-2407. PMID: 30026836
165. Huang et al. Meta-analysis for cyclin E in lung cancer survival. *Clin. Chim. Acta.* 2012 Apr 11;413(7-8):663-8. PMID: 22244930
166. Xia et al. Dominant role of CDKN2B/p15INK4B of 9p21.3 tumor suppressor hub in inhibition of cell-cycle and glycolysis. *Nat Commun.* 2021 Apr 6;12(1):2047. PMID: 33824349
167. Scruggs et al. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. *Am. J. Respir. Cell Mol. Biol.* 2018 Aug;59(2):200-214. PMID: 29420051
168. Rousset. The INK4 family of cell cycle inhibitors in cancer. *Oncogene.* 1999 Sep 20;18(38):5311-7. PMID: 10498883
169. Aytac et al. Rb independent inhibition of cell growth by p15(INK4B). *Biochem. Biophys. Res. Commun.* 1999 Aug 27;262(2):534-8. PMID: 10462509
170. Hill et al. The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet.* 2013;14:257-79. PMID: 23875803
171. Kim et al. The regulation of INK4/ARF in cancer and aging. *Cell.* 2006 Oct 20;127(2):265-75. PMID: 17055429
172. Sekulic et al. Malignant melanoma in the 21st century: the emerging molecular landscape. *Mayo Clin. Proc.* 2008 Jul;83(7):825-46. PMID: 18613999
173. Orlow et al. CDKN2A germline mutations in individuals with cutaneous malignant melanoma. *J. Invest. Dermatol.* 2007 May;127(5):1234-43. PMID: 17218939
174. Bartsch et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann. Surg.* 2002 Dec;236(6):730-7. PMID: 12454511
175. Adib et al. CDKN2A Alterations and Response to Immunotherapy in Solid Tumors. *Clin Cancer Res.* 2021 Jul 15;27(14):4025-4035. PMID: 34074656
176. NCCN Guidelines® - NCCN-Mesothelioma: Peritoneal [Version 2.2026]
177. NCCN Guidelines® - NCCN-Mesothelioma: Pleural [Version 2.2026]
178. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2025]
179. Longwen et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med.* 2019 Jul 29;17(1):245. PMID: 31358010

References (continued)

180. Logan et al. PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity. *Anticancer Res.* 2013 Aug;33(8):2997-3004. PMID: 23898052
181. von Witzleben et al. Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway. *Cancer Res.* 2015 Sep 15;75(18):3823-31. PMID: 26183925
182. Cen et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. *Neuro-oncology.* 2012 Jul;14(7):870-81. PMID: 22711607
183. Vitzthum et al. The role of p16 as a biomarker in nonoropharyngeal head and neck cancer. *Oncotarget.* 2018 Sep 7;9(70):33247-33248. PMID: 30279955
184. Chung et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J. Clin. Oncol.* 2014 Dec 10;32(35):3930-8. PMID: 25267748
185. Bryant et al. Prognostic Role of p16 in Nonoropharyngeal Head and Neck Cancer. *J. Natl. Cancer Inst.* 2018 Dec 1;110(12):1393-1399. PMID: 29878161
186. Stephen et al. Significance of p16 in Site-specific HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma. *Cancer Clin Oncol.* 2013;2(1):51-61. PMID: 23935769
187. Jafri et al. Germline Mutations in the CDKN2B Tumor Suppressor Gene Predispose to Renal Cell Carcinoma. *Cancer Discov.* 2015 Jul;5(7):723-9. PMID: 25873077
188. Tu et al. CDKN2B deletion is essential for pancreatic cancer development instead of unmeaningful co-deletion due to juxtaposition to CDKN2A. *Oncogene.* 2018 Jan 4;37(1):128-138. PMID: 28892048
189. Deshpande et al. Rad50 ATPase activity is regulated by DNA ends and requires coordination of both active sites. *Nucleic Acids Res.* 2017 May 19;45(9):5255-5268. PMID: 28369545
190. Kinoshita et al. RAD50, an SMC family member with multiple roles in DNA break repair: how does ATP affect function?. *Chromosome Res.* 2009;17(2):277-88. PMID: 19308707
191. Rupnik et al. The MRN complex. *Curr. Biol.* 2008 Jun 3;18(11):R455-7. PMID: 18522810
192. Assenmacher et al. MRE11/RAD50/NBS1: complex activities. *Chromosoma.* 2004 Oct;113(4):157-66. PMID: 15309560
193. Hopfner et al. The Rad50 zinc-hook is a structure joining Mre11 complexes in DNA recombination and repair. *Nature.* 2002 Aug 1;418(6897):562-6. PMID: 12152085
194. 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
195. Lord et al. BRCAness revisited. *Nat. Rev. Cancer.* 2016 Feb;16(2):110-20. PMID: 26775620
196. Fan et al. RAD50 germline mutations are associated with poor survival in BRCA1/2-negative breast cancer patients. *Int. J. Cancer.* 2018 Oct 15;143(8):1935-1942. PMID: 29726012
197. Brandt et al. Lack of MRE11-RAD50-NBS1 (MRN) complex detection occurs frequently in low-grade epithelial ovarian cancer. *BMC Cancer.* 2017 Jan 10;17(1):44. PMID: 28073364
198. Wang et al. RAD50 Expression Is Associated with Poor Clinical Outcomes after Radiotherapy for Resected Non-small Cell Lung Cancer. *Clin. Cancer Res.* 2018 Jan 15;24(2):341-350. PMID: 29030353
199. Zhang et al. Copy number deletion of RAD50 as predictive marker of BRCAness and PARP inhibitor response in BRCA wild type ovarian cancer. *Gynecol. Oncol.* 2016 Apr;141(1):57-64. PMID: 27016230
200. Hacker et al. Structure/Function Analysis of Recurrent Mutations in SETD2 Protein Reveals a Critical and Conserved Role for a SET Domain Residue in Maintaining Protein Stability and Histone H3 Lys-36 Trimethylation. *J. Biol. Chem.* 2016 Sep 30;291(40):21283-21295. PMID: 27528607
201. Fahey et al. SETting the Stage for Cancer Development: SETD2 and the Consequences of Lost Methylation. *Cold Spring Harb Perspect Med.* 2017 May 1;7(5). PMID: 28159833
202. Zaghi et al. H3K36 Methylation in Neural Development and Associated Diseases. *Front Genet.* 2020 Jan 9;10:1291. doi: 10.3389/fgene.2019.01291. eCollection 2019. PMID: 31998360
203. Suzuki et al. H3K36 methylation state and associated silencing mechanisms. *Transcription.* 2017 Jan;8(1):26-31. PMID: 27723431
204. Sun et al. H3K36me3, Message From Chromatin to DNA Damage Repair. *Cell Biosci.* 2020 Jan 31;10:9. doi: 10.1186/s13578-020-0374-z. eCollection 2020. PMID: 32021684
205. Li et al. The Histone Mark H3K36me3 Regulates Human DNA Mismatch Repair Through Its Interaction With MutSa. *Cell.* 2013 Apr 25;153(3):590-600. PMID: 23622243
206. Duns et al. Histone methyltransferase gene SETD2 is a novel tumor suppressor gene in clear cell renal cell carcinoma. *Cancer Res.* 2010 Jun 1;70(11):4287-91. PMID: 20501857

References (continued)

207. Dalgliesh et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. *Nature*. 2010 Jan 21;463(7279):360-3. PMID: 20054297
208. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2025]
209. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat. Rev. Genet.* 2006 Aug;7(8):606-19. PMID: 16847462
210. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. *Nat. Rev. Mol. Cell Biol.* 2012 Feb 23;13(3):195-203. PMID: 22358332
211. Chagpar et al. Direct positive regulation of PTEN by the p85 subunit of phosphatidylinositol 3-kinase. *Proc. Natl. Acad. Sci. U.S.A.* 2010 Mar 23;107(12):5471-6. PMID: 20212113
212. Pasca di Magliano et al. Hedgehog signalling in cancer formation and maintenance. *Nat. Rev. Cancer.* 2003 Dec;3(12):903-11. PMID: 14737121
213. Skoda et al. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. *Bosn J Basic Med Sci.* 2018 Feb 20;18(1):8-20. PMID: 29274272
214. Johnson et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science.* 1996 Jun 14;272(5268):1668-71. PMID: 8658145
215. Nag et al. The MDM2-p53 pathway revisited. *J Biomed Res.* 2013 Jul;27(4):254-71. PMID: 23885265
216. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell.* 2014 Mar 17;25(3):304-17. PMID: 24651012
217. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol.* 2010 Jan;2(1):a001008. PMID: 20182602
218. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med.* 2017 Apr 3;7(4). PMID: 28270529
219. Peter S et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012 Sep 27;489(7417):519-25. PMID: 22960745
220. 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
221. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature.* 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
222. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. *Hum. Mutat.* 2002 Jun;19(6):607-14. PMID: 12007217
223. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. *Genes Cancer.* 2011 Apr;2(4):466-74. PMID: 21779514
224. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene.* 2007 Apr 2;26(15):2157-65. PMID: 17401424
225. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. *Hum. Mutat.* 2014 Jun;35(6):766-78. PMID: 24729566
226. <https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html>
227. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. *Front Oncol.* 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
228. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. *Cell. Mol. Life Sci.* 2017 Nov;74(22):4171-4187. PMID: 28643165
229. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021 Aug 2;23(8):1231-1251. PMID: 34185076
230. 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
231. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2026]
232. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2025]
233. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2026]
234. NCCN Guidelines® - NCCN-Acute Lymphoblastic Leukemia [Version 2.2025]
235. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 3.2025]

References (continued)

236. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat. Med.* 2020 Aug 3. PMID: 32747829
237. Namekata et al. MOCA induces membrane spreading by activating Rac1. *J Biol Chem.* 2004 Apr 2;279(14):14331-7. PMID: 14718541
238. Laurin et al. Insights into the biological functions of Dock family guanine nucleotide exchange factors. *Genes Dev.* 2014 Mar 15;28(6):533-47. PMID: 24637113
239. Zhu et al. Inhibition of RAC1-GEF DOCK3 by miR-512-3p contributes to suppression of metastasis in non-small cell lung cancer. *Int J Biochem Cell Biol.* 2015 Apr;61:103-14. PMID: 25687035
240. Caspi et al. A novel functional screen in human cells identifies MOCA as a negative regulator of Wnt signaling. *Mol Biol Cell.* 2008 Nov;19(11):4660-74. PMID: 18716063
241. Cui et al. *Oncotarget.* 2016 Feb 2;7(5):5613-29. PMID: 26716413