

Patient Name: 김현순
Gender: F
Sample ID: N25-127

Primary Tumor Site: Lung
Collection Date: 2025.07.18

Sample Cancer Type: Lung Cancer

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Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	EML4::ALK fusion	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	0.96 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	EML4::ALK fusion echinoderm microtubule associated protein like 4 - ALK receptor tyrosine kinase Locus: chr2:42522590 - chr2:29446394	alectinib 1, 2 / I, II+ brigatinib 1, 2 / I, II+ ceritinib 1, 2 / I, II+ crizotinib 1, 2 / I, II+ ensartinib 1 / I, II+ lorlatinib 1, 2 / I, II+ atezolizumab + bevacizumab + chemotherapy II+	crizotinib 1 / I, II+ alectinib I, II+ brigatinib I, II+ ceritinib I, II+ lorlatinib I, II+	51
IIC	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2

* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO
* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
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>BARD1 deletion</i> BRCA1 associated RING domain 1 Locus: chr2:215593375	None*	None*	1
IIC	<i>LATS2 deletion</i> large tumor suppressor kinase 2 Locus: chr13:21548922	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
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

EML4::ALK fusion  neladalkib¹

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

ARID1B deletion, Microsatellite stable, NOTCH2 p.(R1838*) c.5512C>T, PARP4 deletion, PMS1 deletion, RAD51B deletion, RPA1 deletion, STK11 deletion, XRCC3 deletion, TNFRSF14 deletion, PGD deletion, DNMT3A deletion, ASXL2 deletion, CASP8 deletion, PDCD1 deletion, HLA-A p.(L180*) c.539T>A, PRDM1 deletion, HDAC2 deletion, TNFAIP3 deletion, MAP3K4 deletion, NQO1 p.(P187S) c.559C>T, NCOR1 deletion, ASXL1 deletion, PTPRT deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NOTCH2	p.(R1838*)	c.5512C>T	.	chr1:120462204	2.84%	NM_024408.4	nonsense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	78.35%	NM_001242758.1	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.20%	NM_000903.3	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT CA	.	chr6:31324208	94.55%	NM_005514.8	missense, missense
ARID5B	p.(L143P)	c.428T>C	.	chr10:63700093	51.18%	NM_032199.3	missense

Gene Fusions

Genes	Variant ID	Locus
EML4::ALK	EML4-ALK.E13A20	chr2:42522590 - chr2:29446394
EML4::ALK	EML4-ALK.E13A20.COSF408.2	chr2:42522656 - chr2:29446394

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.68
BARD1	chr2:215593375	1	0.72

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
LATS2	chr13:21548922	0.84	0.64
ARID1B	chr6:157099057	0.87	0.65
PARP4	chr13:25000551	0.68	0.58
PMS1	chr2:190656538	0.98	0.68
RAD51B	chr14:68290164	1	0.71
RPA1	chr17:1733385	0.97	0.68
STK11	chr19:1206847	0.63	0.57
XRCC3	chr14:104165043	0.81	0.63
TNFRSF14	chr1:2488070	0.83	0.63
PGD	chr1:10459132	1.02	0.69
DNMT3A	chr2:25457069	0.95	0.67
ASXL2	chr2:25964858	1	0.68
CASP8	chr2:202122934	1.03	0.69
PDCD1	chr2:242793161	0.78	0.62
PRDM1	chr6:106534408	1	0.69
HDAC2	chr6:114262171	0.79	0.62
TNFAIP3	chr6:138192315	0.94	0.67
MAP3K4	chr6:161412931	0.9	0.66
NCOR1	chr17:15935586	0.95	0.67
ASXL1	chr20:30954155	0.95	0.67
PTPRT	chr20:40710527	0.84	0.64
MYCN	chr2:16082167	0.73	0.6
STAT1	chr2:191839539	0.62	0.57
FOXA1	chr14:38060550	0.62	0.56
AKT1	chr14:105236628	0.71	0.59

Biomarker Descriptions

EML4::ALK fusion

ALK receptor tyrosine kinase, echinoderm microtubule associated protein like 4

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK), which has sequence similarity to the insulin receptor subfamily of kinases¹²³. ALK is frequently altered in cancer, most commonly through chromosomal rearrangements that generate fusion genes containing the intact ALK tyrosine kinase domain combined with various partner genes¹²⁴. ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways^{124,125,126,127}.

Biomarker Descriptions (continued)

Alterations and prevalence: ALK was discovered by positional cloning of translocations involving nucleophosmin 1 (NPM1) on 5q35 with a previously unidentified RTK on 2p23 (ALK), which occur in over 50% of adult and over 80% of pediatric anaplastic large cell lymphoma (ALCL) cases^{123,128,129}. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1^{130,131,132}. Notably, ALK F1174L, F1245C, and R1275Q mutations are found in over 80% of ALK-mutated neuroblastoma¹³³. ALK mutations have also been reported in 5% of pediatric soft tissue sarcomas and less than 1.5% of other solid and hematological malignancies, including peripheral nervous system tumors, gliomas, leukemia, and bone cancer^{6,7}.

Potential relevance: The first-generation small molecule tyrosine kinase inhibitor (TKI), crizotinib¹³⁴, was FDA approved (2011) for the treatment of adults with ALK-positive advanced NSCLC, as well as pediatric and adult populations with ALK-positive ALCL or inflammatory myofibroblastic tumor (IMT). ALK fusions are a diagnostic marker of infant-type hemispheric glioma and ALK-rearranged renal cell carcinoma^{135,136,137}. Kinase domain mutations including L1196M, G1269A, F1174L, G1202R, as well as other variants, have been shown to confer acquired resistance to crizotinib in ALK-positive NSCLC^{138,139,140,141}. Other mechanisms of acquired resistance involve amplification of the ALK fusion gene and activation of alternate or bypass signaling pathways involving EGFR, KIT, MET, and IGF1R¹⁴². In order to overcome acquired resistance, second- and third-generation ALK inhibitors including ceritinib¹⁴³ (2014), alectinib¹⁴⁴ (2015), brigatinib¹⁴⁵ (2017), lorlatinib¹⁴⁶ (2018), and ensartinib¹⁴⁷ (2024) were developed and approved for adults by the FDA. The FDA granted breakthrough therapy designation (2024) to NVL-655¹⁴⁸ for locally advanced or metastatic ALK-positive NSCLC patients who have been previously treated with two or more ALK TKIs.

BRCA2 deletion

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA^{24,25}. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{24,25}. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer^{26,27,28}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{26,29}.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{30,31,32,33,34,35,36,37}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme^{6,7}.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)³⁸. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{39,40}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib⁴¹ (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, olaparib⁴¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib⁴² is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib⁴³ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib⁴³ in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib⁴⁴ (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate⁴⁵ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported⁴⁶. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁴⁷. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁴⁸, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and

Biomarker Descriptions (continued)

genomic instability. In 2024, the FDA granted fast track designation to TNG-348⁴⁹, a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

BARD1 deletion

BRCA1 associated RING domain 1

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene^{1,89}. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage^{1,89,90,91}. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction^{1,90,92,93}. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{93,94}. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility⁹². Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53⁹⁵. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer^{95,96}.

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma^{6,7}. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer^{6,7}.

Potential relevance: The PARP inhibitor, olaparib⁴¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁴⁸, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

LATS2 deletion

large tumor suppressor kinase 2

Background: The LATS2 gene encodes the large tumor suppressor kinase 2¹. 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^{119,120}. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ¹²¹. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes¹²¹. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1¹²².

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^{6,7}. Biallelic deletion of LATS2 is observed in 2% of lung adenocarcinoma and uterine carcinosarcoma^{6,7}.

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

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein¹. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A^{1,207}. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex^{207,208}. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B²⁰⁸. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression^{208,209}. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor²⁰⁷.

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors²⁰⁹. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma^{6,7}. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma^{6,7}.

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases^{23,210}.

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 genome⁹⁷. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{98,99}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2¹⁰⁰. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250¹⁰¹. 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)¹⁰¹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{102,103,104,105,106}. 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 genes⁹⁹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{98,99,103,107}.

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^{98,99,108,109}. 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^{108,109}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹¹⁰ (2014) and nivolumab¹¹¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹¹⁰ 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 indication¹¹⁰. Dostarlimab¹¹² (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^{104,113}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹¹⁴ (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^{104,115,116}. 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 patients¹¹⁶. 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^{117,118}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{117,118}.

NOTCH2 p.(R1838*) c.5512C>T

notch 2

Background: The NOTCH2 gene encodes the notch receptor 2 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, 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 signaling¹⁸¹. 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^{182,183}. 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^{184,185,186,187}.

Alterations and prevalence: Somatic mutations observed in NOTCH2 are primarily missense or truncating and are found in about 11% of uterine cancer, 6% of melanoma and stomach cancer, as well as 3-5% diffuse large B-cell lymphoma (DLBCL), lung, colorectal, bladder, cervical, and head and neck cancers⁶.

Potential relevance: Currently, no therapies are approved for NOTCH2 aberrations.

PARP4 deletion

poly(ADP-ribose) polymerase family member 4

Background: The PARP4 gene encodes the poly(ADP-ribose) polymerase 4 protein¹. PARP4 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP3¹⁶². PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-

Biomarker Descriptions (continued)

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^{162,163}. PARP enzymes are involved in several DNA repair pathways^{162,163}. 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 proteins¹⁶⁴.

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^{6,7}. Biallelic deletions in PARP4 are observed in 2% of diffuse large B-cell lymphoma (DLBCL)^{6,7}.

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^{165,166}. 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. Olaparib⁴¹ (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, olaparib⁴¹ 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. Rucaparib⁴² (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. Talazoparib⁴³ (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib⁴⁴ (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.

PMS1 deletion

PMS1 homolog 1, mismatch repair system component

Background: The PMS1 gene encodes the PMS1 homolog 1 protein, also known as MLH2¹. PMS1 heterodimerizes with MLH1 to form the MutLβ complex, the function of which is not well understood^{77,78}. PMS1 is considered a mismatch repair (MMR) gene due to its functional role in yeast, although its exact MMR role in humans is less clear^{77,78,79}. Unlike other MMR genes, loss of PMS1 does not result in microsatellite instability (MSI), although rare cases of mutation have been observed in patients with Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes^{77,78,80}.

Alterations and prevalence: Somatic mutations in PMS1 are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, lung adenocarcinoma, and colorectal adenocarcinoma, and 2% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and stomach adenocarcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for PMS1 aberrations.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)⁸². RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex⁸³. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP⁸⁴. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss^{85,86}. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents⁸⁷. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk⁸⁸.

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer^{6,7}. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk⁸⁸.

Potential relevance: The PARP inhibitor, olaparib⁴¹ is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁴⁸, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1¹. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)¹⁸⁰. 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)¹⁸⁰. 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 repair¹⁸⁰.

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^{6,7}. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma^{6,7}.

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

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression¹⁵³. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development^{154,155}.

Alterations and prevalence: Somatic mutations in STK11 have been reported in 10% of lung cancer, 4% of cervical cancer, and up to 3% of cholangiocarcinoma and uterine cancer^{6,7,156,157}. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer^{6,7}. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others^{6,7,154,157,158}.

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260¹⁵⁹ in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors¹⁶⁰. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)¹⁶¹.

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs^{1,94}. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)^{94,167}. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability¹⁶⁸.

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma^{6,7}. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin¹⁶⁸.

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14¹. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines²¹¹. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell

Biomarker Descriptions (continued)

differentiation, survival, and death²¹¹. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160^{211,212}. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival²¹¹. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role²¹².

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma^{6,7}. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma²¹³. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma^{214,215}.

PGD deletion

phosphogluconate dehydrogenase

Background: The PGD gene encodes phosphogluconate dehydrogenase, an essential enzyme of the pentose phosphate pathway (PPP) that catalyzes oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and reduction of NADP⁺ to NADPH^{1,199}. PPP mediated generation of pentose phosphates and NADPH is essential for nucleic acid synthesis and fatty acid synthesis, respectively, making it a crucial metabolic pathway for cancer cell survival and proliferation^{200,201}. Although biallelic deletion appears to be more common than amplification across cancer types, post-translational modifications and overexpression of PGD in cancer have also been observed to result in elevated PPP activity, which is associated with cancer cell proliferation^{199,202}.

Alterations and prevalence: Somatic mutations in PGD have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, and bladder urothelial carcinoma^{6,7}. Biallelic loss of PGD has been observed in 4% of adrenocortical carcinoma, 3% of cholangiocarcinoma, and 2% of pheochromocytoma and paraganglioma and diffuse large B-cell lymphoma^{6,7}. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma^{6,7}.

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

DNMT3A deletion

DNA methyltransferase 3 alpha

Background: The DNMT3A gene encodes the DNA methyltransferase 3 alpha which functions as a de novo methyltransferase (DNMT) with equal methylation efficiency for unmethylated and hemimethylated DNA⁸. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression^{9,10}.

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)^{6,11,12,13,14,15,16}. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer^{6,17}. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported^{6,11}. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations^{18,19}. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation^{20,21}. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity²².

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML^{11,14,15,19}. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)²³.

ASXL2 deletion

additional sex combs like 2, transcriptional regulator

Background: The ASXL2 gene encodes the ASXL transcriptional regulator 2 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation^{1,50}. ASXL2 belongs to the ASXL gene family, which also includes ASXL1 and ASXL3⁵⁰. ASXL proteins contain a conserved C-terminal plant homeodomain (PHD), which facilitates interaction with DNA and

Biomarker Descriptions (continued)

histones⁵⁰. ASXL2 influences chromatin remodeling and transcription through interaction with BAP1 as well as other transcriptional activators and repressors⁵⁰.

Alterations and prevalence: Somatic mutations in ASXL2 are observed in 8% of uterine corpus endometrial carcinoma and bladder urothelial carcinoma, 7% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and uterine carcinosarcoma^{6,7}. ASXL2 mutations in acute myeloid leukemia (AML) are observed to co-occur with t(8;21)(q22;q22)/RUNX1::RUNX1T1⁸¹. ASXL2 deletions are observed in 4% diffuse large B-cell lymphoma (DLBCL) and 2% of uterine carcinosarcoma^{6,7}.

Potential relevance: Currently, no therapies are approved for ASXL2 aberrations. ASXL2 mutations have been shown to be associated with better prognosis in pediatric AML with t(8;21)⁸¹.

CASP8 deletion

caspase 8

Background: CASP8 encodes caspase 8, a member of the cysteine-aspartic acid protease (caspase) family consisting of inflammatory caspases and apoptotic caspases. Apoptotic caspases consist of initiator and effector caspases^{1,169,170}. CASP8 functions as an initiator caspase and following external stimulation of death receptors, undergoes processing and activation leading to CASP8 mediated cleavage of downstream targets¹⁷¹. CASP8 propagates the extrinsic apoptotic pathway by direct cleavage of effector caspases such as CASP3 and activates the intrinsic apoptotic pathway by cleaving BID, a pro-apoptotic proximal substrate of CASP8, resulting in an amplification of the death-inducing signal^{171,172}. Certain cancer types have decreased expression or inactivation of CASP8, which results in poor prognosis and metastasis^{173,174}.

Alterations and prevalence: Somatic mutations in CASP8 are observed in 11% head and neck squamous cell carcinoma, 10% uterine corpus endometrial carcinoma, 5% stomach adenocarcinoma, 4% cervical squamous cell carcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, 3% skin cutaneous melanoma, and 2% diffuse large B-cell lymphoma, lung squamous cell carcinoma, uterine carcinosarcoma, and breast invasive carcinoma^{6,7}. Biallelic loss of CASP8 is observed in 2% bladder urothelial carcinoma^{6,7}.

Potential relevance: Currently, no therapies are approved for CASP8 aberrations.

PDCD1 deletion

programmed cell death 1

Background: The PDCD1 gene encodes programmed cell death 1, also known as PD-1 or CD279¹. PDCD1 is a type I transmembrane inhibitory receptor and member of the CD28/CTLA-4 family, which is part of the immunoglobulin superfamily²⁰³. PDCD1 is an immune checkpoint molecule that acts as a gatekeeper of immune responses through a balance of signaling suppression, which is critical in the facilitation of self and non-self cell recognition²⁰⁴. PDCD1 is expressed in a variety of hematopoietic cells, immune cells, tumor cells, and tumor specific T-cells^{203,205}. The two main immunoregulatory ligands of PDCD1 are CD274 (PD-L1) and PDCD1LG2 (PD-L2), which are type I transmembrane proteins expressed in many cells including antigen presenting cells and tumor cells²⁰³. PDCD1 and CD274 act as co-inhibitors and regulate immune tolerance of central and peripheral T-cells and reduce the proliferation of CD8+ T-cells by inhibitor signals^{203,205}.

Alterations and prevalence: Somatic mutations in PDCD1 are observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of uterine carcinosarcoma^{6,7}. Deletions in PDCD1 are observed in 8% of sarcoma, 5% of brain lower grade glioma, 3% of cervical squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, and uveal melanoma^{6,7}.

Potential relevance: Currently, no therapies are approved for PDCD1 aberrations. Immune checkpoint inhibitor therapy uses immunotherapy to block receptor-ligand interactions and enhance immunity activity against tumor cells²⁰⁶. Although not approved for specific PDCD1 aberrations, approved checkpoint inhibitors targeting PDCD1 include the monoclonal antibodies pembrolizumab, nivolumab, and cemiplimab²⁰³.

HLA-A p.(L180*) c.539T>A

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A¹. 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 cells⁷¹. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M⁷². 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,

Biomarker Descriptions (continued)

to the immune system to distinguish self from non-self^{73,74,75}. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A⁷⁶.

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

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

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1¹. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation^{149,150,151}. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs¹⁵². PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression¹⁵¹. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1¹⁵².

Alterations and prevalence: Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma^{6,7}. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)¹⁵². PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma^{6,7}.

Potential relevance: Currently, no therapies are approved for PRDM1 aberrations.

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein¹. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)¹⁸⁸. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8¹⁸⁸. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation^{188,189}. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes¹⁸⁸. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells¹⁸⁸. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development^{188,190}.

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma^{6,7}. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma^{6,7}.

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies¹⁹¹. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy¹⁹². The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL¹⁹³. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens¹⁹⁴.

TNFAIP3 deletion

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3¹. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity²¹⁶. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses^{216,217}. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions²¹⁶. TNFAIP3

Biomarker Descriptions (continued)

deficient cells are observed to promote aberrant NF- κ B signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis^{216,218}.

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma^{6,7}. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma^{6,7,216}.

Potential relevance: Currently, no therapies are approved for TNFAIP3 aberrations.

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4¹. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10¹⁹⁵. Activation of MAPK proteins occurs through a kinase signaling cascade^{195,196,197}. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members^{195,196,197}. 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^{195,196,197}. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4¹⁹⁸.

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma^{6,7}. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)^{6,7}.

Potential relevance: Currently, no therapies are approved for MAP3K4 aberrations.

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)^{1,175,176}. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability^{175,176,177,178}. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models¹⁷⁶. 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^{176,179}.

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^{6,7}. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma^{6,7}. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma^{6,7}.

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

ASXL1 deletion

additional sex combs like 1, transcriptional regulator

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation^{1,50}. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3⁵⁰. ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and histones^{50,51}. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors^{50,52}. In cancer, ASXL1 is the target of somatic mutations which often result in a truncated ASXL1 protein and loss of its PHD^{53,54,55}. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1⁵⁶.

Biomarker Descriptions (continued)

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)^{6,16,52,57,58,59,60,61,62}. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies^{54,59,63}. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence⁶⁴. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing⁶⁵. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation^{57,64,66}.

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic⁶⁷. Mutations in ASXL1 confer poor/adverse risk in AML^{16,68}. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML¹⁷. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM^{69,70}.

PTPRT deletion

protein tyrosine phosphatase, receptor type T

Background: PTPRT encodes protein tyrosine phosphatase receptor type T, part of the protein tyrosine phosphatase (PTP) family which consists of 125 members^{1,2,3}. PTPs are responsible for protein dephosphorylation of tyrosine residues and are involved in several cellular processes including proliferation, differentiation, adhesion, and survival^{4,5}. Aberrant tyrosine phosphorylation resulting from PTP dysfunction has been linked to cancer progression^{4,5}.

Alterations and prevalence: Somatic mutations in PTPRT are observed in 29% of skin cutaneous melanoma, 12% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 10% of colorectal adenocarcinoma and lung adenocarcinoma, 7% of esophageal adenocarcinoma and lung squamous cell carcinoma, 5% of uterine carcinosarcoma and bladder urothelial carcinoma, 4% of head and neck squamous cell carcinoma and cervical squamous cell carcinoma, 3% of glioblastoma multiforme and liver hepatocellular carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, and ovarian serous cystadenocarcinoma^{6,7}. Biallelic loss of PTPRT is observed in about 1% of mesothelioma, prostate adenocarcinoma, and acute myeloid leukemia.^{6,7}

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

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated

 Not recommended

 Resistance

 Breakthrough

 Fast Track

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

EML4::ALK fusion

 neladalkib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ALK fusion

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to a brain-penetrant ALK-selective tyrosine kinase inhibitor (TKI), NVL-655, for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have been previously treated with two or more ALK TKIs.

Reference:
<https://investors.nuvalent.com/2024-05-16-Nuvalent-Receives-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-655>

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, 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, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB1, TGFBR2

Genes Assayed (continued)

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

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

EML4::ALK fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (III)
alectinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (IV)
brigatinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (II)
lorlatinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/> (II)
ceritinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>
ensartinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (II)
atezolizumab + bevacizumab + carboplatin + paclitaxel	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>
alectinib, chemotherapy	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (III)
alectinib, durvalumab	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (III)
neladalkib, alectinib	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/> (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

EML4::ALK fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sacituzumab tirumotecan	×	×	×	×	● (III)
SGN-B6A	×	×	×	×	● (III)
targeted therapy	×	×	×	×	● (III)
alectinib, crizotinib	×	×	×	×	● (II)
alectinib, lorlatinib	×	×	×	×	● (II)
brigatinib, chemotherapy	×	×	×	×	● (II)
chemotherapy, lorlatinib	×	×	×	×	● (II)
ensartinib, radiation therapy, bevacizumab	×	×	×	×	● (II)
IBI323, bevacizumab, chemotherapy	×	×	×	×	● (II)
iruplinalkib	×	×	×	×	● (II)
pembrolizumab, bevacizumab, chemotherapy	×	×	×	×	● (II)
sacituzumab govitecan	×	×	×	×	● (II)
SY-3505	×	×	×	×	● (II)
alectinib, radiation therapy	×	×	×	×	● (I/II)
amivantamab, alectinib, brigatinib, lorlatinib	×	×	×	×	● (I/II)
benmelstobart, catequentinib	×	×	×	×	● (I/II)
DAJH-1050766	×	×	×	×	● (I/II)
furetinib	×	×	×	×	● (I/II)
neladalkib	×	×	×	×	● (I/II)
ramucirumab, lorlatinib	×	×	×	×	● (I/II)
sotiburafusp alfa, HB-0030	×	×	×	×	● (I/II)
APG-2449	×	×	×	×	● (I)
CGT-9475	×	×	×	×	● (I)
gilteritinib	×	×	×	×	● (I)
IBI-318, lenvatinib	×	×	×	×	● (I)
IBI-363, IBI-325, lenvatinib	×	×	×	×	● (I)
LZ-001	×	×	×	×	● (I)
talazoparib, crizotinib	×	×	×	×	● (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

BRCA2 deletion

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

BARD1 deletion

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

LATS2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IAG-933	×	×	×	×	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	17.95%
BRCA2	CNV, CN:1.0
BRCA2	LOH, 13q13.1(32890491-32972932)x1
BARD1	CNV, CN:1.0
BARD1	LOH, 2q35(215593375-215674382)x1
RAD51B	CNV, CN:1.0
RAD51B	LOH, 14q24.1(68290164-69061406)x1

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

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

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. *Nucleic Acids Res.* 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Xie et al. Regulatory Functions of Protein Tyrosine Phosphatase Receptor Type O in Immune Cells. *Front Immunol.* 2021;12:783370. PMID: 34880876
3. Alonso et al. The extended human PTPome: a growing tyrosine phosphatase family. *FEBS J.* 2016 Jun;283(11):2197-201. PMID: 27263510
4. Kumar et al. Activity-based probes for protein tyrosine phosphatases. *Proc Natl Acad Sci U S A.* 2004 May 25;101(21):7943-8. PMID: 15148367
5. Tonks. Protein tyrosine phosphatases: from genes, to function, to disease. *Nat Rev Mol Cell Biol.* 2006 Nov;7(11):833-46. PMID: 17057753
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
8. Okano et al. Cloning and characterization of a family of novel mammalian DNA (cytosine-5) methyltransferases. *Nat Genet.* 1998 Jul;19(3):219-20. PMID: 9662389
9. Fernandez et al. A DNA methylation fingerprint of 1628 human samples. *Genome Res.* 2012 Feb;22(2):407-19. PMID: 21613409
10. Jones et al. The epigenomics of cancer. *Cell.* 2007 Feb 23;128(4):683-92. PMID: 17320506
11. Ley et al. DNMT3A mutations in acute myeloid leukemia. *N. Engl. J. Med.* 2010 Dec 16;363(25):2424-33. PMID: 21067377
12. Marková et al. Prognostic impact of DNMT3A mutations in patients with intermediate cytogenetic risk profile acute myeloid leukemia. *Eur. J. Haematol.* 2012 Feb;88(2):128-35. PMID: 21967546
13. Yang et al. DNMT3A in haematological malignancies. *Nat. Rev. Cancer.* 2015 Mar;15(3):152-65. PMID: 25693834
14. Renneville et al. Prognostic significance of DNA methyltransferase 3A mutations in cytogenetically normal acute myeloid leukemia: a study by the Acute Leukemia French Association. *Leukemia.* 2012 Jun;26(6):1247-54. PMID: 22289988
15. Marcucci et al. Age-related prognostic impact of different types of DNMT3A mutations in adults with primary cytogenetically normal acute myeloid leukemia. *J. Clin. Oncol.* 2012 Mar 1;30(7):742-50. PMID: 22291079
16. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2025]
17. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2025]
18. Kumar et al. DNMT3A (R882) mutation features and prognostic effect in acute myeloid leukemia in Coexistent with NPM1 and FLT3 mutations. *Hematol Oncol Stem Cell Ther.* 2018 Jun;11(2):82-89. PMID: 29079128
19. Thol et al. Incidence and prognostic influence of DNMT3A mutations in acute myeloid leukemia. *J. Clin. Oncol.* 2011 Jul 20;29(21):2889-96. PMID: 21670448
20. Sandoval et al. Mutations in the DNMT3A DNA methyltransferase in acute myeloid leukemia patients cause both loss and gain of function and differential regulation by protein partners. *J. Biol. Chem.* 2019 Mar 29;294(13):4898-4910. PMID: 30705090
21. Holz-Schietinger et al. Mutations in DNA methyltransferase (DNMT3A) observed in acute myeloid leukemia patients disrupt processive methylation. *J. Biol. Chem.* 2012 Sep 7;287(37):30941-51. PMID: 22722925
22. Russler-Germain et al. The R882H DNMT3A mutation associated with AML dominantly inhibits wild-type DNMT3A by blocking its ability to form active tetramers. *Cancer Cell.* 2014 Apr 14;25(4):442-54. PMID: 24656771
23. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 1.2025]
24. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. *Breast Cancer Res.* 2002;4(1):9-13. PMID: 11879553
25. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. *Oncogene.* 2002 Dec 16;21(58):8981-93. PMID: 12483514
26. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA.* 2017 Jun 20;317(23):2402-2416. PMID: 28632866
27. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J. Natl. Cancer Inst.* 2007 Dec 5;99(23):1811-4. PMID: 18042939
28. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br. J. Cancer.* 2007 Jan 15;96(1):11-5. PMID: 17213823
29. Chen et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. *JNCI Cancer Spectr.* 2020 Aug;4(4):pkaa029. PMID: 32676552
30. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. *GeneReviews® [Internet].* PMID: 20301425

References (continued)

31. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin. Proc.* 2010 Dec;85(12):1111-20. PMID: 21123638
32. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc. Natl. Acad. Sci. U.S.A.* 2011 Nov 1;108(44):18032-7. PMID: 22006311
33. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J. Clin. Oncol.* 2012 Jul 20;30(21):2654-63. PMID: 22711857
34. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. *Cancer Epidemiol. Biomarkers Prev.* 2004 Dec;13(12):2078-83. PMID: 15598764
35. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science.* 2003 Oct 24;302(5645):643-6. PMID: 14576434
36. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br. J. Cancer.* 2000 Nov;83(10):1301-8. PMID: 11044354
37. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. *Environ Mol Mutagen.* 2022 Jul;63(6):308-316. PMID: 36054589
38. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. *Br. J. Cancer.* 2018 Nov;119(11):1401-1409. PMID: 30353044
39. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature.* 2005 Apr 14;434(7035):913-7. PMID: 15829966
40. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005 Apr 14;434(7035):917-21. PMID: 15829967
41. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
42. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
43. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217439s000lbl.pdf
44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214876s000lbl.pdf
45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf
46. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. *J. Pathol.* 2013 Feb;229(3):422-9. PMID: 23165508
47. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. *DNA Repair (Amst.).* 2018 Nov;71:172-176. PMID: 30177437
48. <https://www.senhwbio.com/en/news/20220125>
49. <https://ir.tangotx.com/news-releases/news-release-details/tango-therapeutics-reports-third-quarter-2023-financial-results>
50. Katoh. Functional and cancer genomics of ASXL family members. *Br. J. Cancer.* 2013 Jul 23;109(2):299-306. PMID: 23736028
51. Gelsi-Boyer et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. *Br. J. Haematol.* 2009 Jun;145(6):788-800. PMID: 19388938
52. Gelsi-Boyer et al. Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. *J Hematol Oncol.* 2012 Mar 21;5:12. doi: 10.1186/1756-8722-5-12. PMID: 22436456
53. Larsson et al. The changing mutational landscape of acute myeloid leukemia and myelodysplastic syndrome. *Mol. Cancer Res.* 2013 Aug;11(8):815-27. PMID: 23645565
54. Alvarez et al. ASXL1 mutations in myeloid neoplasms: pathogenetic considerations, impact on clinical outcomes and survival. *Curr Med Res Opin.* 2018 May;34(5):757-763. PMID: 28027687
55. Yang et al. Gain of function of ASXL1 truncating protein in the pathogenesis of myeloid malignancies. *Blood.* 2018 Jan 18;131(3):328-341. PMID: 29113963
56. Abdel-Wahab et al. ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. *Cancer Cell.* 2012 Aug 14;22(2):180-93. PMID: 22897849
57. Alberti et al. Discriminating a common somatic ASXL1 mutation (c.1934dup; p.G646Wfs*12) from artifact in myeloid malignancies using NGS. *Leukemia.* 2018 Aug;32(8):1874-1878. PMID: 29959414
58. Kakosaiou et al. ASXL1 mutations in AML are associated with specific clinical and cytogenetic characteristics. *Leuk. Lymphoma.* 2018 Oct;59(10):2439-2446. PMID: 29411666
59. Paschka et al. ASXL1 mutations in younger adult patients with acute myeloid leukemia: a study by the German-Austrian Acute Myeloid Leukemia Study Group. *Haematologica.* 2015 Mar;100(3):324-30. PMID: 25596267

References (continued)

60. Jawhar et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. *Haematologica*. 2017 Jun;102(6):1035-1043. PMID: 28255023
61. Jawhar et al. KIT D816 mutated/CBF-negative acute myeloid leukemia: a poor-risk subtype associated with systemic mastocytosis. *Leukemia*. 2019 May;33(5):1124-1134. PMID: 30635631
62. Damaj et al. ASXL1 but not TET2 mutations adversely impact overall survival of patients suffering systemic mastocytosis with associated clonal hematologic non-mast-cell diseases. *PLoS ONE*. 2014;9(1):e85362. PMID: 24465546
63. Boulton et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. *Leukemia*. 2010 May;24(5):1062-5. doi: 10.1038/leu.2010.20. Epub 2010 Feb 25. PMID: 20182461
64. Yannakou et al. ASXL1 c.1934dup;p.Gly646Trpfs*12-a true somatic alteration requiring a new approach. *Blood Cancer J*. 2017 Dec 15;7(12):656. doi: 10.1038/s41408-017-0025-8. PMID: 29242575
65. Abdel-Wahab et al. The most commonly reported variant in ASXL1 (c.1934dupG;p.Gly646TrpfsX12) is not a somatic alteration. *Leukemia*. 2010 Sep;24(9):1656-7. doi: 10.1038/leu.2010.144. Epub 2010 Jul 1. PMID: 20596031
66. Montes-Moreno et al. Clinical molecular testing for ASXL1 c.1934dupG p.Gly646fs mutation in hematologic neoplasms in the NGS era. *PLoS ONE*. 2018;13(9):e0204218. PMID: 30222780
67. Landrum et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*. 2018 Jan 4;46(D1):D1062-D1067. PMID: 29165669
68. 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
69. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 1.2025]
70. NCCN Guidelines® - NCCN-Systemic Mastocytosis [Version 1.2020]
71. Hulpke et al. The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends Biochem Sci*. PMID: 23849087
72. 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
73. Rossjohn et al. T cell antigen receptor recognition of antigen-presenting molecules. *Annu Rev Immunol*. 2015;33:169-200. PMID: 25493333
74. Parham. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol*. 2005 Mar;5(3):201-14. PMID: 15719024
75. Sidney et al. HLA class I supertypes: a revised and updated classification. *BMC Immunol*. 2008 Jan 22;9:1. PMID: 18211710
76. 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
77. Kunkel et al. DNA mismatch repair. *Annu Rev Biochem*. 2005;74:681-710. PMID: 15952900
78. Li. Mechanisms and functions of DNA mismatch repair. *Cell Res*. 2008 Jan;18(1):85-98. PMID: 18157157
79. Campbell et al. Mlh2 is an accessory factor for DNA mismatch repair in *Saccharomyces cerevisiae*. *PLoS Genet*. 2014 May;10(5):e1004327. PMID: 24811092
80. Peltomäki. Lynch syndrome genes. *Fam Cancer*. 2005;4(3):227-32. PMID: 16136382
81. Yamato et al. ASXL2 mutations are frequently found in pediatric AML patients with t(8;21)/ RUNX1-RUNX1T1 and associated with a better prognosis. *Genes Chromosomes Cancer*. 2017 May;56(5):382-393. PMID: 28063196
82. Sullivan et al. RAD-ical New Insights into RAD51 Regulation. *Genes (Basel)*. 2018 Dec 13;9(12). PMID: 30551670
83. Suwaki et al. RAD51 paralogs: roles in DNA damage signalling, recombinational repair and tumorigenesis. *Semin. Cell Dev. Biol*. 2011 Oct;22(8):898-905. PMID: 21821141
84. Chun et al. Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. *Mol. Cell. Biol*. 2013 Jan;33(2):387-95. PMID: 23149936
85. 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
86. Lord et al. BRCAness revisited. *Nat. Rev. Cancer*. 2016 Feb;16(2):110-20. PMID: 26775620
87. Date et al. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. *Cancer Res*. 2006 Jun 15;66(12):6018-24. PMID: 16778173
88. Pelttari et al. RAD51B in Familial Breast Cancer. *PLoS ONE*. 2016;11(5):e0153788. PMID: 27149063
89. Morris et al. BRCA1 : BARD1 induces the formation of conjugated ubiquitin structures, dependent on K6 of ubiquitin, in cells during DNA replication and repair. *Hum. Mol. Genet*. 2004 Apr 15;13(8):807-17. PMID: 14976165

References (continued)

90. Baer et al. The BRCA1/BARD1 heterodimer, a tumor suppressor complex with ubiquitin E3 ligase activity. *Curr. Opin. Genet. Dev.* 2002 Feb;12(1):86-91. PMID: 11790560
91. Zhao et al. BRCA1-BARD1 promotes RAD51-mediated homologous DNA pairing. *Nature.* 2017 Oct 19;550(7676):360-365. PMID: 28976962
92. Cimmino et al. Dualistic Role of BARD1 in Cancer. *Genes (Basel).* 2017 Dec 8;8(12). PMID: 29292755
93. De et al. BRCAness: a deeper insight into basal-like breast tumors. *Ann. Oncol.* 2013 Nov;24 Suppl 8:viii13-viii21. PMID: 24131964
94. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. *Cold Spring Harb Perspect Biol.* 2015 Apr 1;7(4):a016600. PMID: 25833843
95. Irminger-Finger et al. Identification of BARD1 as mediator between proapoptotic stress and p53-dependent apoptosis. *Mol. Cell.* 2001 Dec;8(6):1255-66. PMID: 11779501
96. Thai et al. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers. *Hum. Mol. Genet.* 1998 Feb;7(2):195-202. PMID: 9425226
97. Lander et al. Initial sequencing and analysis of the human genome. *Nature.* 2001 Feb 15;409(6822):860-921. PMID: 11237011
98. 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
99. Nojadeh et al. Microsatellite instability in colorectal cancer. *EXCLI J.* 2018;17:159-168. PMID: 29743854
100. 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
101. 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
102. 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
103. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis.* 2008 Apr;29(4):673-80. PMID: 17942460
104. NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]
105. Pawlik et al. Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers.* 2004;20(4-5):199-206. PMID: 15528785
106. 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
107. 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
108. 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
109. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol.* 2017;2017. PMID: 29850653
110. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf
111. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125554s129lbl.pdf
112. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761174s009lbl.pdf
113. NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]
114. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125377s133lbl.pdf
115. 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
116. 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
117. Hermel et al. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med.* 2019 Jan 16;9(1). PMID: 30654522
118. Ciardiello et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat. Rev.* 2019 Jun;76:22-32. PMID: 31079031
119. Furth et al. The LATS1 and LATS2 tumor suppressors: beyond the Hippo pathway. *Cell Death Differ.* 2017 Sep;24(9):1488-1501. PMID: 28644436

References (continued)

120. Leroux et al. AGC kinases, mechanisms of regulation #and innovative drug development. *Semin Cancer Biol.* 2018 Feb;48:1-17. PMID: 28591657
121. Meng et al. Mechanisms of Hippo pathway regulation. *Genes Dev.* 2016 Jan 1;30(1):1-17. PMID: 26728553
122. 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
123. Webb et al. Anaplastic lymphoma kinase: role in cancer pathogenesis and small-molecule inhibitor development for therapy. *Expert Rev Anticancer Ther.* 2009 Mar;9(3):331-56. PMID: 19275511
124. Shaw et al. Tyrosine kinase gene rearrangements in epithelial malignancies. *Nat. Rev. Cancer.* 2013 Nov;13(11):772-87. PMID: 24132104
125. Chiarle et al. Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. *Nat. Med.* 2005 Jun;11(6):623-9. PMID: 15895073
126. Bai et al. Nucleophosmin-anaplastic lymphoma kinase associated with anaplastic large-cell lymphoma activates the phosphatidylinositol 3-kinase/Akt antiapoptotic signaling pathway. *Blood.* 2000 Dec 15;96(13):4319-27. PMID: 11110708
127. Hrustanovic et al. RAS signaling in ALK fusion lung cancer. *Small GTPases.* 2016;7(1):32-3. PMID: 26901483
128. Morris et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science.* 1994 Mar 4;263(5151):1281-4. PMID: 8122112
129. Shreenivas et al. ALK fusions in the pan-cancer setting: another tumor-agnostic target?. *NPJ Precis Oncol.* 2023 Sep 29;7(1):101. PMID: 37773318
130. Kwak et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N. Engl. J. Med.* 2010 Oct 28;363(18):1693-703. PMID: 20979469
131. Yu et al. Frequencies of ALK rearrangements in lung adenocarcinoma subtypes: a study of 2299 Chinese cases. *Springerplus.* 2016 Jun 27;5(1):894. doi: 10.1186/s40064-016-2607-5. eCollection 2016. PMID: 27386342
132. Dai et al. Incidence and patterns of ALK FISH abnormalities seen in a large unselected series of lung carcinomas. *Send to Mol Cytogenet.* 2012 Dec 3;5(1):44. doi: 10.1186/1755-8166-5-44. PMID: 23198868
133. Rosswog et al. Genomic ALK alterations in primary and relapsed neuroblastoma. *Br J Cancer.* 2023 Apr;128(8):1559-1571. PMID: 36807339
134. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202570s036lbl.pdf
135. NCCN Guidelines® - NCCN-Pediatric Central Nervous System Cancers [Version 2.2025]
136. Mossé. Anaplastic Lymphoma Kinase as a Cancer Target in Pediatric Malignancies. *Clin Cancer Res.* 2016 Feb 1;22(3):546-52. PMID: 26503946
137. Zhang et al. Genomic alterations and diagnosis of renal cancer. *Virchows Arch.* 2024 Feb;484(2):323-337. PMID: 37999735
138. Choi et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N. Engl. J. Med.* 2010 Oct 28;363(18):1734-9. PMID: 20979473
139. Awad et al. ALK inhibitors in non-small cell lung cancer: crizotinib and beyond. *Clin Adv Hematol Oncol.* 2014 Jul;12(7):429-39. PMID: 25322323
140. Kim et al. Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. *J Thorac Oncol.* 2013 Apr;8(4):415-22. PMID: 23344087
141. Katayama et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci Transl Med.* 2012 Feb 8;4(120):120ra17. doi: 10.1126/scitranslmed.3003316. Epub 2012 Jan 25. PMID: 22277784
142. Katayama. Drug resistance in anaplastic lymphoma kinase-rearranged lung cancer. *Cancer Sci.* 2018 Mar;109(3):572-580. PMID: 29336091
143. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211225s004lbl.pdf
144. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208434s015lbl.pdf
145. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208772s013lbl.pdf
146. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf
147. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218171s000lbl.pdf
148. <https://investors.nuvalent.com/2024-05-16-Nuvalent-Receives-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-655>
149. Martins et al. Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. *Nat Immunol.* 2006 May;7(5):457-65. PMID: 16565721
150. Nutt et al. BLIMP1 guides the fate of effector B and T cells. *Nat Rev Immunol.* 2007 Dec;7(12):923-7. PMID: 17965637

References (continued)

151. Fu et al. New insights into Blimp-1 in T lymphocytes: a divergent regulator of cell destiny and effector function. *J Biomed Sci.* 2017 Jul 21;24(1):49. PMID: 28732506
152. Kallies et al. Terminal differentiation of lymphocytes depends on Blimp-1. *Curr Opin Immunol.* 2007 Apr;19(2):156-62. PMID: 17291741
153. Li et al. Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells (Review). *Oncol. Rep.* 2015 Dec;34(6):2821-6. PMID: 26398719
154. Zhou et al. LKB1 Tumor Suppressor: Therapeutic Opportunities Knock when LKB1 Is Inactivated. *Genes Dis.* 2014 Sep 1;1(1):64-74. PMID: 25679014
155. Hemminki et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* 1998 Jan 8;391(6663):184-7. PMID: 9428765
156. 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
157. 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
158. Sanchez-Cespedes et al. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. *Cancer Res.* 2002 Jul 1;62(13):3659-62. PMID: 12097271
159. <https://ir.tangotx.com/news-releases/news-release-details/tango-therapeutics-announces-first-patient-dosed-tng260-phase-12>
160. Koyama et al. STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. *Cancer Res.* 2016 Mar 1;76(5):999-1008. PMID: 26833127
161. Skoulidis et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discov.* 2018 Jul;8(7):822-835. PMID: 29773717
162. Amé et al. The PARP superfamily. *Bioessays.* 2004 Aug;26(8):882-93. PMID: 15273990
163. 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
164. 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
165. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. *Clin Cancer Res.* 2019 Jul 1;25(13):3759-3771. PMID: 30760478
166. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. *Science.* 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
167. Liu et al. Role of RAD51C and XRCC3 in genetic recombination and DNA repair. *J Biol Chem.* 2007 Jan 19;282(3):1973-9. PMID: 17114795
168. Wilson et al. FANCG promotes formation of a newly identified protein complex containing BRCA2, FANCD2 and XRCC3. *Oncogene.* 2008 Jun 12;27(26):3641-52. PMID: 18212739
169. Julien et al. Caspases and their substrates. *Cell Death Differ.* 2017 Aug;24(8):1380-1389. PMID: 28498362
170. Kantari et al. Caspase-8 and bid: caught in the act between death receptors and mitochondria. *Biochim Biophys Acta.* 2011 Apr;1813(4):558-63. PMID: 21295084
171. Kostova et al. The role of caspase-8 in the tumor microenvironment of ovarian cancer. *Cancer Metastasis Rev.* 2021 Mar;40(1):303-318. PMID: 33026575
172. Fulda et al. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. *Oncogene.* 2006 Aug 7;25(34):4798-811. PMID: 16892092
173. Müller et al. Cancer Cells Employ Nuclear Caspase-8 to Overcome the p53-Dependent G2/M Checkpoint through Cleavage of USP28. *Mol Cell.* 2020 Mar 5;77(5):970-984.e7. PMID: 31982308
174. Jiang et al. The connections between neural crest development and neuroblastoma. *Curr Top Dev Biol.* 2011;94:77-127. PMID: 21295685
175. Geiger et al. Role of the Nuclear Receptor Corepressor 1 (NCOR1) in Atherosclerosis and Associated Immunometabolic Diseases. *Front Immunol.* 2020;11:569358. PMID: 33117357
176. Martínez-Iglesias et al. Tumor suppressive actions of the nuclear receptor corepressor 1. *Pharmacol Res.* 2016 Jun;108:75-79. PMID: 27149915
177. 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

References (continued)

178. Mottis et al. Emerging roles of the corepressors NCoR1 and SMRT in homeostasis. *Genes Dev.* 2013 Apr 15;27(8):819-35. PMID: 23630073
179. 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
180. 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
181. 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
182. Bray. Notch signalling in context. *Nat. Rev. Mol. Cell Biol.* 2016 Nov;17(11):722-735. PMID: 27507209
183. Kopan et al. The canonical Notch signaling pathway: unfolding the activation mechanism. *Cell.* 2009 Apr 17;137(2):216-33. PMID: 19379690
184. 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
185. Goriki et al. Unravelling disparate roles of NOTCH in bladder cancer. *Nat Rev Urol.* 2018 Jun;15(6):345-357. PMID: 29643502
186. 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
187. 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
188. Falkenberg et al. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. *Nat Rev Drug Discov.* 2014 Sep;13(9):673-91. PMID: 25131830
189. Li et al. HDAC2 promotes the migration and invasion of non-small cell lung cancer cells via upregulation of fibronectin. *Biomed Pharmacother.* 2016 Dec;84:284-290. PMID: 27665474
190. Li et al. HDACs and HDAC Inhibitors in Cancer Development and Therapy. *Cold Spring Harb Perspect Med.* 2016 Oct 3;6(10). PMID: 27599530
191. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021991s009lbl.pdf
192. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022393s017lbl.pdf
193. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206256Orig1s006lbl.pdf
194. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf
195. 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
196. 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
197. 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
198. Yang et al. Mitogen-activated protein kinase kinase 4 deficiency in intrahepatic cholangiocarcinoma leads to invasive growth and epithelial-mesenchymal transition. *Hepatology.* 2015 Dec;62(6):1804-16. PMID: 26340507
199. Liu et al. Tyrosine phosphorylation activates 6-phosphogluconate dehydrogenase and promotes tumor growth and radiation resistance. *Nat Commun.* 2019 Mar 1;10(1):991. PMID: 30824700
200. Patra et al. The pentose phosphate pathway and cancer. *Trends Biochem Sci.* 2014 Aug;39(8):347-54. PMID: 25037503
201. Kowalik et al. Emerging Role of the Pentose Phosphate Pathway in Hepatocellular Carcinoma. *Front Oncol.* 2017;7:87. PMID: 28553614
202. Rao et al. O-GlcNAcylation of G6PD promotes the pentose phosphate pathway and tumor growth. *Nat Commun.* 2015 Sep 24;6:8468. PMID: 26399441
203. Ai et al. Research Status and Outlook of PD-1/PD-L1 Inhibitors for Cancer Therapy. *Drug Des Devel Ther.* 2020;14:3625-3649. PMID: 32982171
204. He et al. Immune checkpoint signaling and cancer immunotherapy. *Cell Res.* 2020 Aug;30(8):660-669. PMID: 32467592
205. Han et al. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res.* 2020;10(3):727-742. PMID: 32266087
206. Marin-Acevedo et al. Next generation of immune checkpoint therapy in cancer: new developments and challenges. *J Hematol Oncol.* 2018 Mar 15;11(1):39. PMID: 29544515
207. Wu et al. ARID1A mutations in cancer: another epigenetic tumor suppressor?. *Cancer Discov.* 2013 Jan;3(1):35-43. PMID: 23208470

References (continued)

208. Wilson et al. SWI/SNF nucleosome remodellers and cancer. *Nat. Rev. Cancer*. 2011 Jun 9;11(7):481-92. PMID: 21654818
209. Alver et al. The SWI/SNF Chromatin Remodelling Complex Is Required for Maintenance of Lineage Specific Enhancers. *Nat Commun*. 8;14648. PMID: 28262751
210. McKinney et al. The Genetic Basis of Hepatosplenic T-cell Lymphoma. *Cancer Discov*. 2017 Apr;7(4):369-379. PMID: 28122867
211. So et al. The TNF-TNFR Family of Co-signal Molecules. *Adv Exp Med Biol*. 2019;1189:53-84. PMID: 31758531
212. Costello et al. Stimulation of non-Hodgkin's lymphoma via HVEM: an alternate and safe way to increase Fas-induced apoptosis and improve tumor immunogenicity. *Leukemia*. 2003 Dec;17(12):2500-7. PMID: 14562115
213. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 2.2025]
214. Launay et al. High rate of TNFRSF14 gene alterations related to 1p36 region in de novo follicular lymphoma and impact on prognosis. *Leukemia*. 2012 Mar;26(3):559-62. PMID: 21941365
215. Cheung et al. Acquired TNFRSF14 mutations in follicular lymphoma are associated with worse prognosis. *Cancer Res*. 2010 Nov 15;70(22):9166-74. PMID: 20884631
216. Malynn et al. A20: A multifunctional tool for regulating immunity and preventing disease. *Cell Immunol*. 2019 Jun;340:103914. PMID: 31030956
217. Giordano et al. The tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20) imposes a brake on antitumor activity of CD8 T cells. *Proc Natl Acad Sci U S A*. 2014 Jul 29;111(30):11115-20. PMID: 25024217
218. Küppers. The biology of Hodgkin's lymphoma. *Nat Rev Cancer*. 2009 Jan;9(1):15-27. PMID: 19078975