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Patient Name: 아이아름
Gender: F
Sample ID: N25-30

Primary Tumor Site: lung
Collection Date: 2025.05.15

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights
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Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	***EML4::ALK fusion***	MET	None detected
BRAF	None detected	NRG1	None detected
EGFR	None detected	NTRK1	***NTRK1 p.(H604Y) c.1810C>T***
ERBB2	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	ROS1	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***1.89 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: chr2:42522656 - 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	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	7

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	*BARD1 deletion* BRCA1 associated RING domain 1 Locus: chr2:215593375	None*	None*	2
IIC	*NTRK1 p.(H604Y) c.1810C>T* neurotrophic receptor tyrosine kinase 1 Allele Frequency: 31.25% Locus: chr1:156848918 Transcript: NM_002529.3	None*	None*	2
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	*PMS1 deletion* PMS1 homolog 1, mismatch repair system component Locus: chr2:190656538	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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	**neladalkib** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

ARID1B deletion, DPYD p.(M166V) c.496A>G, IDH1 p.(G131D) c.392G>A, Microsatellite stable, DNMT3A deletion, ASXL2 deletion, ACVR2A deletion, HLA-B deletion, PRDM1 deletion, HDAC2 deletion, PPP6C deletion, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
DPYD	p.(M166V)	c.496A>G	.	chr1:98165091	47.96%	NM_000110.4	missense
NTRK1	p.(H604Y)	c.1810C>T	.	chr1:156848918	31.25%	NM_002529.3	missense
IDH1	p.(G131D)	c.392G>A	.	chr2:209113115	27.58%	NM_005896.4	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	52.40%	NM_000903.3	missense
ERCC2	p.(G261D)	c.782G>A	.	chr19:45867526	50.03%	NM_000400.4	missense
DDX3X	p.(M221T)	c.662T>C	.	chrX:41202587	44.80%	NM_001356.5	missense

Variant Details (continued)

Gene Fusions

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

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
DNMT3A	chr2:25457069	0.89	0.64
ASXL2	chr2:25964858	0.97	0.67
ACVR2A	chr2:148602708	0.95	0.66
PMS1	chr2:190656538	0.95	0.66
BARD1	chr2:215593375	1	0.68
HLA-B	chr6:31322252	1.02	0.68
PRDM1	chr6:106534408	1.06	0.7
HDAC2	chr6:114262171	0.8	0.61
ARID1B	chr6:157099057	1.06	0.7
MTAP	chr9:21802646	0.85	0.63
CDKN2A	chr9:21968178	0.02	0.35
CDKN2B	chr9:22005728	0.15	0.4
PPP6C	chr9:127911878	1.06	0.69
MYCN	chr2:16082167	0.69	0.58
NFE2L2	chr2:178095457	0.88	0.64
STAT1	chr2:191839539	0.95	0.66
SF3B1	chr2:198256951	1.03	0.69
FGFR3	chr4:1801456	0.55	0.53
KDR	chr4:55955541	0.85	0.62
FYN	chr6:111982890	0.98	0.67
ESR1	chr6:152163831	0.92	0.65

Biomarker Descriptions

DPYD p.(M166V) c.496A>G

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DPYD.

IDH1 p.(G131D) c.392G>A

isocitrate dehydrogenase (NADP(+)) 1, cytosolic

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG)[6]. The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform.

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)[7]. Recurrent IDH1 variants include predominately R132H/C plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[8]. Although wild-type enzymatic activity is ablated, recurrent IDH1 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair[6,9]. Recurrent IDH1 mutations are present in 5-10% of patients with AML and 5% of patients with MDS[10,11,12]. Recurrent IDH1 mutations are present in nearly 80% of lower grade diffuse gliomas[4,5].

Potential relevance: The IDH1 and IDH2 inhibitor vorasidenib[13] is FDA-approved (2024) for the treatment of Grade 2 astrocytoma and oligodendroglioma with IDH1 R132C/G/H/L/S mutations. Additionally, olutasidenib[14] (2022) and ivosidenib[15] (2018) are FDA-approved for treating IDH1 R132C/G/H/L/S variants in AML. Ivosidenib is also approved for treating cholangiocarcinoma patients with the same IDH1 variants[16]. Ivosidenib was granted breakthrough therapy designation (2020) for the treatment of IDH1 mutated relapsed or refractory myelodysplastic syndrome (MDS)[17]. IDH1 mutations are associated with inferior leukemia-free survival in primary myelofibrosis (PMF) and inferior overall survival in polycythemia vera (PV) but have been shown to confer improved prognosis in lower grade gliomas[18,19,20]. Mutations in IDH1 are diagnostic of astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q-codeleted subtypes of central nervous system (CNS) tumors[21,22].

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 DNA[23]. 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[24,25].

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)[4,26,27,28,29,30,31]. 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[4,32]. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported[4,26]. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations[33,34]. 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[35,36]. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity[37].

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML[26,29,30,34]. 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)[38].

Biomarker Descriptions (continued)

ACVR2A deletion

activin A receptor type 2A

Background: The ACVR2A gene encodes the activin A type 2A receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family[1,39]. ACVR2A is a type II receptor that forms heterotetrametric complex with at least two type I receptors (ACVR1 and ACVR1B) and two type II receptors (including BMPR2 and ACVR2B)[39,40]. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrametric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream signaling[39,40]. Downregulation of ACVR2A has been associated with increased cell migration, tumor progression, and metastases in colon cancer[41].

Alterations and prevalence: Somatic mutations of ACVR2A are observed in 11% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 7% of colorectal adenocarcinoma, 3% of liver hepatocellular carcinoma, skin cutaneous melanoma, and cholangiocarcinoma, 2% of cervical squamous cell carcinoma, and 1% of kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, and glioblastoma multiforme, and esophageal adenocarcinoma[4,5]. Biallelic deletion of ACVR2A is observed in 4% of prostate adenocarcinoma, 2% of liver hepatocellular carcinoma, and 1% of stomach adenocarcinoma, thymoma, testicular germ cell tumors, esophageal adenocarcinoma, and colorectal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ACVR2A aberrations.

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[42]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[42]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[42,43]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[42]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[42]. 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[42,44].

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[4,5]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[4,5].

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 therapies[45]. 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 therapy[46]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[47]. 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 regimens[48].

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[49,50]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[50].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[50,51]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma,

Biomarker Descriptions (continued)

adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes the cyclin-dependent kinase inhibitor 2A protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[52,53,54]. CDKN2A codes for two alternate transcript variants namely p16 and p14ARF, both of which exhibit differential tumor suppressor function[55]. Specifically, the CDKN2A/p16 transcript functions as an inhibitor of cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript variant stabilizes the tumor suppressor protein p53 to prevent its degradation[1,55,56]. CDK2NA aberrations commonly co-occur with CDKN2B. Loss of CDKN2A/p16 demonstrates downstream inactivation of Rb and p53 pathways leading to uncontrolled cell proliferation[57]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[58,59].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations. Copy number loss of CDKN2A is observed in 63% of esophageal cancer, 54% of glioblastoma, 45% of pleural mesothelioma, 31% of bladder urothelial carcinoma, and 29% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma[4,5]. Additionally, CDKN2A mutations have been observed in 19% of pancreatic adenocarcinoma and 6% of bladder urothelial carcinoma cases[4,5].

Potential relevance: CDKN2A loss can be useful in the diagnosis of mesothelioma and mutations are used as an ancillary diagnostic marker of malignant peripheral nerve sheath tumors[60,61,62]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[63,64,65]. Alternatively, CDK2NA expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[66]. CDKN2A (p16) expression is also associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[67,68,69,70,71].

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes the cyclin-dependent kinase inhibitor 2B protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[52,53,54]. CDK2NB is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,72,73].

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 56% of esophageal squamous cell carcinoma, 54% of glioblastoma, 42% of pleural mesothelioma, 31% of bladder urothelial carcinoma, 28% of head and neck squamous cell carcinoma, and 27% of pancreatic adenocarcinoma[5].

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations.

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[74]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[75]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[76,77,78]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[79].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal

Biomarker Descriptions (continued)

adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[4,5]. Biallelic loss of HLA-B is observed in 5% of DLBCL[4,5].

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

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[1]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[1,80]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[80,81].The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[81]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[81,82]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[80].

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 tumors[82]. 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[4,5]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[4,5].

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[38,83].

PMS1 deletion

PMS1 homolog 1, mismatch repair system component

Background: The PMS1 gene encodes the PMS1 homolog 1 protein, also known as MLH2[1]. PMS1 heterodimerizes with MLH1 to form the MutLβ complex, the function of which is not well understood[84,85]. 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[84,85,86]. 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[84,85,87].

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[4,5].

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

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[1,88]. ASXL2 belongs to the ASXL gene family, which also includes ASXL1 and ASXL3[88]. ASXL proteins contain a conserved C-terminal plant homeodomain (PHD), which facilitates interaction with DNA and histones[88]. ASXL2 influences chromatin remodeling and transcription through interaction with BAP1 as well as other transcriptional activators and repressors[88].

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[4,5]. ASXL2 mutations in acute myeloid leukemia (AML) are observed to co-occur with t(8;21)(q22;q22)/RUNX1::RUNX1T1[89]. ASXL2 deletions are observed in 4% diffuse large B-cell lymphoma (DLBCL) and 2% of uterine carcinosarcoma[4,5].

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)[89].

Biomarker Descriptions (continued)

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[1,90]. 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[1,90,91,92]. 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[1,91,93,94]. 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[94,95]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[93]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[96]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[96,97].

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[4,5]. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[98] 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, pidnarulex[99], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[100]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[101,102]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[103]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[104]. 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)[104]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[105,106,107,108,109]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[102]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[101,102,106,110].

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[101,102,111,112]. 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[111,112].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[113] (2014) and nivolumab[114] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[113] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[113]. Dostarlimab[115] (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[107,116]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[117] (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[107,118,119]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[119]. 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[120,121]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[120,121].

Biomarker Descriptions (continued)

NTRK1 p.(H604Y) c.1810C>T

neurotrophic receptor tyrosine kinase 1

Background: The NTRK genes encode a family of neurotrophic receptor tyrosine kinases that function as receptors for nerve growth factors. NTRKs are activated by different neurotrophins and are important for the development of the nervous system[122]. The NTRK1,2,3 proteins are also known as tropomyosin related kinases (TrkA,B,C) because NTRK1 was originally discovered as part of a chimeric fusion gene with tropomyosin-3 isolated from a human colon carcinoma cell line[123]. NTRKs are the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact tyrosine kinase domain combined with numerous fusion partner genes[124,125]. NTRK fusion kinases are constitutively active and lead to increased RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, or PLCγ/PKC pathway signaling and can promote cell growth and proliferation[124,126].

Alterations and prevalence: NTRK fusions are infrequently observed in diverse cancer types including glioma, glioblastoma, lung adenocarcinoma, colorectal carcinoma, thyroid cancer, and sarcoma[4,124,127,128,129]. In certain cancer subtypes, including infantile fibrosarcoma, papillary thyroid carcinoma, and secretory carcinoma of the breast or salivary gland, NTRK fusions are more prevalent[124,130,131,132].

Potential relevance: The first-generation selective tropomyosin receptor kinase (TRK) inhibitor, larotrectinib[133], is approved (2018) for the treatment of patients with any solid tumors harboring NTRK gene fusions and is the first approved small molecule inhibitor with tissue agnostic indication. Entrectinib[134] is another first-generation TRK inhibitor approved (2019) for NTRK fusion-positive solid tumors as well as ROS1-positive non-small cell lung cancer (NSCLC). However, acquired resistance to first-generation NTRK inhibition is often mediated by the acquisition of solvent-front and gatekeeper mutations in the kinase domain[135]. Consequently, the second generation TRK inhibitor, repotrectinib[136], is approved by the FDA (2024) for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion.

EML4::ALK fusion

ALK receptor tyrosine kinase, echinoderm microtubule associated protein like 4

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK) with sequence similarity to the insulin receptor subfamily of kinases[137]. ALK is the target of recurrent alterations in cancer, the most common being chromosomal rearrangements that generate fusion genes containing the intact ALK tyrosine kinase domain combined with multiple partner genes[138]. ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways[138,139,140,141].

Alterations and prevalence: ALK was discovered by positional cloning of translocations involving nucleophosmin (NPM) on 5q35 with a previously unidentified RTK on 2p23 (ALK), which occur in over 50% of anaplastic large cell lymphoma cases (ALCL)[137,142]. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1[143,144,145].

Potential relevance: The first generation small molecule tyrosine kinase inhibitor (TKI), crizotinib[146], was FDA approved (2011) for the treatment of ALK positive advanced NSCLC as well as ALK positive ALCL or inflammatory myofibroblastic tumor (IMT). 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[147,148,149,150]. 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 IGF1R[151]. In order to overcome acquired resistance, second and third-generation ALK inhibitors including ceritinib[152] (2014), alectinib[153] (2015), brigatinib[154] (2017), lorlatinib[155] (2018), and ensartinib[156] (2024) were developed and approved by the FDA. Two phase III trials evaluating crizotinib and alectinib as first line therapy in NSCLC, including patients with asymptomatic central nervous system (CNS) disease, were conducted and both studies showed consistent higher objective response rates (ORR) with alectinib relative to crizotinib[157,158]. For this reason, alectinib is a preferred first-line treatment of ALK positive NSCLC[159]. The FDA granted breakthrough therapy designation (2024) to NVL-655 for locally advanced or metastatic ALK-positive NSCLC patients who have been previously treated with two or more ALK TKIs[160].

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1[1]. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation[161,162,163]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[164]. 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 repression[163]. 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 PRDM1[164].

Biomarker Descriptions (continued)

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[4,5]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[164]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[4,5].

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

PPP6C deletion

protein phosphatase 6 catalytic subunit

Background: PPP6C encodes protein phosphatase 6 catalytic subunit and is a member of the serine/threonine protein phosphatase family[1,165]. As the catalytic subunit of the heterotrimeric phosphoprotein phosphatase 6 (PP6) holoenzyme, PPP6C is involved in diverse processes such as cell cycle regulation, DNA damage response, autophagy, miRNA processing, inflammatory signaling, and lymphocyte development[165,166]. Loss of PPP6C results in hyperphosphorylation of Aurora A kinase, which results in defects in mitotic spindle assembly and subsequent genomic instability[166]. Overexpression of PPP6C has been observed to result in decreased colony formation of human endometrial carcinoma cells in vitro, supporting a possible tumor suppressor role for PPP6C[167].

Alterations and prevalence: Somatic mutations in PPP6C are observed in 7% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of colorectal adenocarcinoma[4,5]. Biallelic loss of PPP6C is observed in 1% of thyroid carcinoma, pancreatic adenocarcinoma, and skin cutaneous melanoma[4,5]. Amplification of PPP6C is observed in 2% kidney chromophobe[4,5].

Potential relevance: Currently, no therapies are approved for PPP6C aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-03-19. 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, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed (continued)

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

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

Genes Assayed for the Detection of Fusions

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

Genes Assayed with Full Exon Coverage

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

Relevant Therapy Summary

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

EML4::ALK fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	◑	◑	●	●	● (III)
alectinib	●	◑	●	●	● (IV)
ceritinib	●	◑	●	●	● (IV)
lorlatinib	●	◑	●	●	● (II)
brigatinib	●	◑	●	●	● (I/II)
ensartinib	●	●	✖	✖	● (II)
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
alectinib, chemotherapy	✖	✖	✖	✖	● (III)
alectinib, durvalumab	✖	✖	✖	✖	● (III)
neladalkib, alectinib	✖	✖	✖	✖	● (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)
TGRX-326, crizotinib	✖	✖	✖	✖	● (III)
alectinib, crizotinib	✖	✖	✖	✖	● (II)
alectinib, lorlatinib	✖	✖	✖	✖	● (II)
brigatinib, chemotherapy	✖	✖	✖	✖	● (II)
brigatinib, chemotherapy, radiation therapy	✖	✖	✖	✖	● (II)
chemotherapy, lorlatinib	✖	✖	✖	✖	● (II)
ensartinib, radiation therapy, bevacizumab	✖	✖	✖	✖	● (II)
IBI323, bevacizumab, chemotherapy	✖	✖	✖	✖	● (II)
iruplinalkib	✖	✖	✖	✖	● (II)
pembrolizumab, bevacizumab, chemotherapy	✖	✖	✖	✖	● (II)
sacituzumab govitecan	✖	✖	✖	✖	● (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)
SY-3505	✖	✖	✖	✖	● (I/II)
APG-2449	✖	✖	✖	✖	● (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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
MRTX1719	✖	✖	✖	✖	● (I/II)
TNG-462	✖	✖	✖	✖	● (I/II)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)

BARD1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
talazoparib, palbociclib, axitinib, crizotinib	✖	✖	✖	✖	● (I)

NTRK1 p.(H604Y) c.1810C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IBI-363, IBI-325, lenvatinib	✖	✖	✖	✖	● (I)
LZ-001	✖	✖	✖	✖	● (I)

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

PMS1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib, palbociclib, axitinib, crizotinib	✖	✖	✖	✖	● (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	***21.96%***
BARD1	***CNV, CN:1.0***
BARD1	***LOH, 2q35(215593375-215674382)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 Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.0.2 data version 2025.04(004)). 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 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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