삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Patient Name: 이재욱
Gender: M
Sample ID: N25-318

Primary Tumor Site: Lung
Collection Date: 2025.11.14.

Sample Cancer Type: Lung Cancer

Report Highlights

5 Relevant Biomarkers
0 Therapies Available
12 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	***ALK amplification***	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	***8.52 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*FGFR1 amplification* fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	7
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	4
IIC	*ALK amplification* ALK receptor tyrosine kinase Locus: chr2:29416263	None*	None*	1
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
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.

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Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*TP53 p.(R248Q) c.743G>A* tumor protein p53 Allele Frequency: 57.10% Locus: chr17:7577538 Transcript: NM_000546.6	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

*KMT2D p.(P1097Qfs*22) c.3290delC, Microsatellite stable, UGT1A1 p.(G71R) c.211G>A, IKBKB amplification, NQO1 p.(P187S) c.559C>T, YES1 amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TP53	p.(R248Q)	c.743G>A	COSM10662	chr17:7577538	57.10%	NM_000546.6	missense
KMT2D	p.(P1097Qfs*22)	c.3290delC	.	chr12:49444080	32.99%	NM_003482.4	frameshift Deletion
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	42.50%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	37.76%	NM_000903.3	missense
CDH10	p.(S70C)	c.209C>G	.	chr5:24593391	35.49%	NM_006727.5	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	98.46%	NM_005514.8	missense, missense
CSMD3	p.(S3535N)	c.10604G>A	.	chr8:113249442	35.41%	NM_198123.2	missense
FAM135B	p.(T66A)	c.196A>G	.	chr8:139278047	32.78%	NM_015912.4	missense
KMT2D	p.(T1359S)	c.4075A>T	.	chr12:49442498	50.95%	NM_003482.4	missense
FANCM	p.(R1719C)	c.5155C>T	.	chr14:45658380	3.30%	NM_020937.4	missense
AXIN1	p.(G49S)	c.145G>A	.	chr16:396881	42.20%	NM_003502.4	missense
PPL	p.(T1152A)	c.3454A>G	.	chr16:4935202	39.22%	NM_002705.5	missense
JAK3	p.(I213F)	c.637A>T	.	chr19:17953349	51.54%	NM_000215.4	missense
SRC	p.(V284M)	c.850G>A	.	chr20:36026248	19.30%	NM_198291.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
FGFR1	chr8:38271452	6.82	2.2
CDKN2A	chr9:21968178	0	0.47
ALK	chr2:29416263	5.14	1.78

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Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CDKN2B	chr9:22005728	0	0.47
IKBKB	chr8:42129602	6.56	2.14
YES1	chr18:724481	5.74	1.94
CUL4A	chr13:113863977	4.82	1.71

Biomarker Descriptions

FGFR1 amplification

fibroblast growth factor receptor 1

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4[7]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[7]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[15,16,17].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[18]. Amplification of FGFR1 is observed in 17% of lung squamous cell carcinoma, 11% of breast invasive carcinoma, 8% of bladder urothelial carcinoma, 7% of uterine carcinosarcoma and head and neck squamous cell carcinoma, 6% of esophageal adenocarcinoma, 5% of sarcoma, 4% of colorectal adenocarcinoma and pancreatic adenocarcinoma, 3% of prostate adenocarcinoma, ovarian serous cystadenocarcinoma, and lung adenocarcinoma, and 2% of uterine corpus endometrial carcinoma[5,6,19,20,21]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[22]. Somatic mutations in FGFR1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma[5,6]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but are less common in solid tumors[23,24,25]. Alterations in FGFR1 are rare in pediatric cancers[5,6]. Amplification of FGFR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases). Somatic mutations in FGFR1 are observed in 6% of non-Hodgkin Lymphoma, 3% of soft tissue sarcoma, 2% of glioma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[5,6].

Potential relevance: The FGFR kinase inhibitor, pemigatinib[26] (2022) is approved for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. Additionally, the FDA granted fast-track designation to Debio 1347[27] (2018) for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members[28]. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[29,30,31,32,33,34,35]. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification[36]. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months[36]. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, the median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks[37]. Rearrangements in FGFR1 are associated with poor risk pediatric and adult acute lymphoblastic leukemia[38,39,40].

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[7]. 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)[110]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[111,112,113]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[114]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[7,114,115]. CDKN2A aberrations commonly co-occur with CDKN2B[110]. Loss of CDKN2A/p16 results in downstream

Biomarker Descriptions (continued)

inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[116]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[117,118].

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[119]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[5,6]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[5,6]. Alterations in CDKN2A are also observed in pediatric cancers[6]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[6]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[6].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[120,121,122]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[123]. 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[124,125,126]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[127]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[128,129,130,131].

ALK amplification

ALK receptor tyrosine kinase

Background: The ALK gene encodes the ALK receptor tyrosine kinase (RTK), which has sequence similarity to the insulin receptor subfamily of kinases[84]. 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 genes[85]. ALK fusion kinases are constitutively activated and drive oncogenic transformation via activation of downstream STAT3, PI3K/AKT/MTOR, and RAS/RAF/MEK/ERK pathways[85,86,87,88].

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[84,89,90]. In contrast, about 5% of non-small cell lung cancer (NSCLC) cases generate recurrent ALK fusions with EML4, KIF5B, and HIP1[91,92,93]. Notably, ALK F1174L, F1245C, and R1275Q mutations are found in over 80% of ALK-mutated neuroblastoma[94]. 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[5,6].

Potential relevance: The first-generation small molecule tyrosine kinase inhibitor (TKI), crizotinib[95], 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[96,97,98]. 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[99,100,101,102]. 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[103]. In order to overcome acquired resistance, second- and third-generation ALK inhibitors including ceritinib[104] (2014), alectinib[105] (2015), brigatinib[106] (2017), lorlatinib[107] (2018), and ensartinib[108] (2024) were developed and approved for adults by the FDA. The FDA granted breakthrough therapy designation (2024) to NVL-655[109] for locally advanced or metastatic ALK-positive NSCLC patients who have been previously treated with two or more ALK TKIs.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[7,110]. 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)[110]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6,

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Biomarker Descriptions (continued)

thereby preventing the phosphorylation of Rb[111,112,113]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[110]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[7,133,134].

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B -cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[5,6]. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma[5,6]. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers[5,6]. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)[5,6].

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma[123].

TP53 p.(R248Q) c.743G>A

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[7]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[41]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[42]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[43,44].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[5,6,19,45,46,47]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[48,49,50,51]. Alterations in TP53 are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[5,6]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[52] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[53,54]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[55]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[38,56,57,58,59]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[60]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[61].

KMT2D p.(P1097Qfs*22) c.3290delC

lysine methyltransferase 2D

Background: The KMT2D gene encodes the lysine methyltransferase 2D protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[7]. KMT2D belongs to the SET domain protein methyltransferase superfamily[132]. KMT2D is known to be involved in the regulation of cell differentiation, metabolism, and tumor suppression due to its methyltransferase activity[132]. Mutations or deletions in the enzymatic SET domain of KMT2D are believed to result in loss of function and may contribute to defective enhancer regulation and altered gene expression[132].

Alterations and prevalence: Somatic mutations in KMT2D are predominantly missense or truncating and are observed in 29% of diffuse large B-cell lymphoma (DLBCL), 28% of bladder urothelial carcinoma, 27% of uterine corpus endometrial carcinoma, 22% of lung

Biomarker Descriptions (continued)

squamous cell carcinoma, 21% of skin cutaneous melanoma, 17% of stomach adenocarcinoma, 15% of head and neck squamous cell carcinoma, and 14% of cervical squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KMT2D aberrations.

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[62]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[63,64]. 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[65]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[66]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[66]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[67,68,69,70,71]. 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[64]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[63,64,68,72].

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[63,64,73,74]. 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[73,74].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[75] (2014) and nivolumab[76] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[75] 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[75]. Dostarlimab[77] (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[69,78]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[79] (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[69,80,81]. 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[81]. 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[82,83]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[82,83].

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[7,135]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[135,136]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[137]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[137,138,139,140]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[141].

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

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

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Biomarker Descriptions (continued)

IKBKB amplification

inhibitor of nuclear factor kappa B kinase subunit beta

Background: The IKBKB gene encodes the nuclear factor kappa B kinase subunit beta, also known as IKK-B. IKBKB is a serine/threonine kinase, which acts as an enzyme protein subunit of the IKK complex[1]. IKBKB and IKBKA dimerize to form the regulatory subunit of the IKK complex. Along with modulator IKKγ/NEMO, the IKK complex acts as a master regulator of the family of NF-κB transcription factors.[1]. NF-κB signaling is critical in the inflammatory response and is also known to be implicated in other important physiological processes including cell proliferation[2]. In resting cells, NF-κB dimers are sequestered in the cytoplasm by IκB proteins[2]. Upon signal initiation, IκB proteins are phosphorylated by the IKK complex, leading to IκB protein degradation and liberation of NF-κB dimers[2]. Subsequently, released NF-κB dimers undergo nuclear translocation which leads to the expression of various proinflammatory and cell survival genes[3,4].

Alterations and prevalence: Somatic mutations in IKBKB are observed in 6% of uterine carcinoma, 5% of melanoma and diffuse large B-cell lymphoma (DLBCL)[5,6]. Amplifications are observed in 14% of uterine carcinosarcoma, 7% of breast invasive carcinoma and esophageal cancer[5,6]. IKBKB activating mutations are most commonly found at lysine 175 and are observed in 8% of splenic marginal B-cell lymphomas[1].

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

YES1 amplification

YES proto-oncogene 1, Src family tyrosine kinase

Background: YES1 encodes the YES proto-oncogene 1 and is part of the SRC family kinases (SFKs) which includes SRC, LCK, LYN, BLK, HCK, FYN, FGR, and YRK[7,8,9]. SFKs are membrane-associated, non-receptor tyrosine kinases that are involved in several cellular functions such as growth, survival, and differentiation[8,9,10]. YES1 alterations have been identified in several cancer types and are associated with tumor progression[8,11,12,13,14].

Alterations and prevalence: Somatic mutations in YES1 are observed in 5% of uterine corpus endometrial carcinoma and 2% diffuse large B-cell lymphoma, esophageal adenocarcinoma, skin cutaneous melanoma, and uterine carcinosarcoma[5,6]. Amplification of YES1 is observed in 5% of esophageal adenocarcinoma, 4% of bladder urothelial carcinoma, uterine carcinosarcoma, 3% of head and neck squamous cell carcinoma, lung squamous cell carcinoma, 2% of sarcoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous cell carcinoma, skin cutaneous melanoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Biallelic loss of YES1 is observed in 2% diffuse large B-cell lymphoma and testicular germ cell tumors[5,6].

Potential relevance: Currently, no therapies are approved for YES1 aberrations. YES1 amplification and overexpression is associated with resistance to EGFR, HER2, and ALK inhibitors[11,12,14].

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

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Genes Assayed (continued)

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, 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

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Relevant Therapy Summary

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

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pemigatinib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sintilimab, pemigatinib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
BBI-355, futibatinib	✖	✖	✖	✖	● (I/II)

CDKN2A deletion

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

ALK amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
crizotinib	✖	✖	✖	✖	● (I)

CDKN2B deletion

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

TP53 p.(R248Q) c.743G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (I)

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

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HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***40.02%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x3***
ATM	***LOH, 11q22.3(108098341-108236285)x2***
CHEK1	***LOH, 11q24.2(125496639-125525271)x2***
RAD51B	***LOH, 14q24.1(68290164-69061406)x2***
RAD54L	***LOH, 1p34.1(46714017-46743978)x2***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(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 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. 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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