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Patient Name: 주정숙
Gender: F
Sample ID: N25-121

Primary Tumor Site: lung
Collection Date: 2025.07.14

Sample Cancer Type: Lung Cancer

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Report Highlights

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Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	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	***16.21 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*ESR1 p.(D426Y) c.1276G>T* estrogen receptor 1 Allele Frequency: 53.75% Locus: chr6:152382166 Transcript: NM_001122740.2	None*	**elacestrant** [1, 2 / I, II+]	0
IIC	*SMARCA4 p.(E990*) c.2968G>T* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 Allele Frequency: 52.98% Locus: chr19:11134302 Transcript: NM_001128849.3	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

KEAP1 p.(Y396) c.1187_1188insAAAA, MUTYH p.(G286E) c.857G>A, Microsatellite stable, TP53 p.(A159P) c.475G>C, XRCC3 deletion, ERRFI1 p.(Y224Cfs*3) c.671_672delAT, ERAP2 deletion, TPMT amplification, NOTCH4 p.(G349Afs*49) c.1044delC, PIM1 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
ESR1	p.(D426Y)	c.1276G>T	.	chr6:152382166	53.75%	NM_001122740.2	missense
SMARCA4	p.(E990*)	c.2968G>T	.	chr19:11134302	52.98%	NM_001128849.3	nonsense
KEAP1	p.(Y396*)	c.1187_1188insAAAA	.	chr19:10602390	51.84%	NM_203500.2	nonsense
MUTYH	p.(G286E)	c.857G>A	.	chr1:45797914	16.71%	NM_001128425.2	missense
TP53	p.(A159P)	c.475G>C	COSM43836	chr17:7578455	55.04%	NM_000546.6	missense
ERRFI1	p.(Y224Cfs*3)	c.671_672delAT	.	chr1:8073986	60.96%	NM_018948.4	frameshift Deletion
NOTCH4	p.(G349Afs*49)	c.1044delC	.	chr6:32188296	32.33%	NM_004557.4	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	48.12%	NM_000903.3	missense
XIRP2	p.(S3472P)	c.10414T>C	.	chr2:168108316	47.97%	NM_152381.6	missense
MLH1	p.(D601H)	c.1801G>C	.	chr3:37089079	56.92%	NM_000249.4	missense
PRDM9	p.(L171H)	c.512T>A	.	chr5:23522416	36.09%	NM_020227.4	missense
PDE1C	p.(L236F)	c.706C>T	.	chr7:31912988	20.06%	NM_001191058.4	missense
MTERF1	p.(L303V)	c.907C>G	.	chr7:91503201	36.53%	NM_006980.5	missense
CSMD3	p.(S2696N)	c.8087G>A	.	chr8:113317129	36.06%	NM_198123.2	missense
CCDC15	p.(Q707K)	c.2119C>A	.	chr11:124862563	76.48%	NM_025004.3	missense
FLT3	p.(A948Qfs*51)	c.2842delG	.	chr13:28588605	56.16%	NM_004119.3	frameshift Deletion
F10	p.(A281D)	c.842C>A	.	chr13:113801787	53.06%	NM_000504.4	missense
PALB2	p.(F557L)	c.1669T>C	.	chr16:23646198	50.10%	NM_024675.4	missense
DSC3	p.(W97L)	c.290G>T	.	chr18:28611003	36.22%	NM_001941.5	missense
ZNF682	p.(R473Sfs*11)	c.1415_1416delAG	.	chr19:20116894	77.95%	NM_033196.3	frameshift Deletion
PPP2R1A	p.(R249H)	c.746G>A	.	chr19:52716302	55.76%	NM_014225.6	missense
ITSN1	p.(S36P)	c.106T>C	.	chr21:35093560	6.38%	NM_003024.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
XRCC3	chr14:104165043	0.75	0.65
ERAP2	chr5:96219500	0	0.4

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
TPMT	chr6:18130879	6	2.12
PIM1	chr6:37138341	11.27	3.6
YES1	chr18:724481	5.75	2.05
FANCE	chr6:35420188	5.61	2.01
CDKN1A	chr6:36645655	5.79	2.06
ERCC4	chr16:14013959	5.86	2.08

Biomarker Descriptions

ESR1 p.(D426Y) c.1276G>T

estrogen receptor 1

Background: The ESR1 gene encodes estrogen receptor 1 (ERα), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses. A related gene, ESR2, encodes the cognate ERβ protein. ERα is a ligand-activated transcription factor regulated by the hormone estrogen[72,73]. Estrogen binding to ERα results in receptor dimerization, nuclear translocation, and target gene transcription. In addition, estrogen binding to the ERα results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival[74].

Alterations and prevalence: Approximately 70% of breast cancers express ERα and ERβ positivity. Mutations in the ERα ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance[75,76,77,78]. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease[79,80,81,82,83].

Potential relevance: The FDA has approved elacestrant[84] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer[85]. The FDA has also granted fast track designations to the following therapies: AC699[86] (2024) and lasofoxifene[87] (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizaestrant[88] for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel[89] (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[90] (1977), fulvestrant[91] (2002), letrozole[92] (1995), and exemestane[93] (2005) are FDA approved for ER-positive metastatic breast cancers[94,95]. Although ERα and ERβ positivity predicts response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance[96,97,98].

SMARCA4 p.(E990*) c.2968G>T

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4

Background: The SMARCA4 gene encodes the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4 protein[1]. SMARCA4, also known as BRG1, is a core member of ATP-dependent, multisubunit SWI/SNF chromatin-remodeling complex, along with SMARCB1/SNF5, SMARCC1/BAF155, SMARCC2/BAF170, and SMARCA2/BRM[27]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[27,28]. SMARCA4 and SMARCA2 are highly homologous and are mutually exclusive ATPase catalytic subunits for SWI/SNF chromatin remodeling complexes[27,28]. Germline loss of function mutations in SMARCA4 are associated with atypical teratoid/rhabdoid tumors (AT/RT), and a rare form of ovarian cancer called small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which highlights the tumor suppressor function of SMARCA4.[29,30].

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[28]. Recurrent somatic mutations in SMARCA4 are observed in 10% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, and 7% of esophageal adenocarcinoma[9,10].

Potential relevance: Currently, no therapies are approved for SMARCA4 aberrations. SMARCA4 mutations and deletions are considered a diagnostic marker for the SMARCA4-deficient uterine sarcoma (SDUS) subtype[31].

Biomarker Descriptions (continued)

KEAP1 p.(Y396*) c.1187_1188insAAAA

kelch like ECH associated protein 1

Background: The KEAP1 gene encodes the kelch like ECH associated protein 1, a tumor suppressor and a member of the KEAP1-CUL3-RBX1 E3 ubiquitin ligase complex[1,32]. KEAP1 helps facilitate the negative regulation of the proto-oncogene NFE2L2 (NRF2) through ubiquitination, which leads to proteasomal degradation of NFE2L2[33]. Aberrations in KEAP1 can result in loss of function leading to accumulation of NFE2L2, thereby altering the transcription genes involved in antioxidant response, drug metabolism, DNA repair, autophagy, cell survival, and proliferation[33,34,35].

Alterations and prevalence: Somatic mutations in KEAP1 are observed in 18% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 6% of cholangiocarcinoma, 5% of liver hepatocellular carcinoma, and 4% of head and neck squamous cell carcinoma[9,10].

Potential relevance: Currently, no therapies are approved for KEAP1 aberrations.

MUTYH p.(G286E) c.857G>A

mutY DNA glycosylase

Background: The MUTYH gene encodes the mutY DNA glycosylase protein[1]. DNA glycosylases are structurally specific enzymes that function in base excision repair (BER) by removing damaged or incorrect bases in DNA[21]. MUTYH functions by removing adenine residues that have been misincorporated opposite of 8-oxoG (7,8-dihydro-8-oxoguanine) and FapyG (2,6-diamino-4-hydroxy-5-formamidopyrimidine)[21]. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer[22,23].

Alterations and prevalence: Somatic mutations in MUTYH are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 2% of lung squamous cell carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma[9,10]. Biallelic deletions in MUTYH are observed in 2% of pheochromocytoma and paraganglioma[9,10].

Potential relevance: Currently, no therapies are approved for MUTYH 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[99]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[100,101]. 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[102]. 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[103]. 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)[103]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[104,105,106,107,108]. 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[101]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[100,101,105,109].

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[100,101,110,111]. 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[110,111].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[112] (2014) and nivolumab[113] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[112] 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[112]. Dostarlimab[114] (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[106,115]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[116] (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[106,117,118]. 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[118]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those

Biomarker Descriptions (continued)

with MSI-H tumors[119,120]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[119,120].

TP53 p.(A159P) c.475G>C

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[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[46]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[47]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[48,49].

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%)[9,10,50,51,52,53]. 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[9,10]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[54,55,56,57]. Alterations in TP53 are also observed in pediatric cancers[9,10]. 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)[9,10]. 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)[9,10].

Potential relevance: The small molecule p53 reactivator, PC14586[58] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[59], (2019) and breakthrough designation[60] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[61,62]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[63]. 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)[64,65,66,67,68,69]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[70]. 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[71].

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[1,11]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[11,12]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[13].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[9,10]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[9,10].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[13].

ERRFI1 p.(Y224Cfs*3) c.671_672delAT

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,36]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[36,37]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[36,38]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[36,39,40,41,42]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[36,39,40,43,44].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[9,10]. Biallelic loss of ERRFI1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme[9,10].

Potential relevance: Currently, no therapies are approved for ERRFI1 aberrations.

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[24,25]. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules[24,26]. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic[24].

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma[9,10]. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma[9,10].

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

TPMT amplification

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,121,122]. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine[121,122,123]. Inherited TPMT polymorphisms, including TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, and TPMT*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure[121,123].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[9,10]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[9,10]. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[9,10].

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

NOTCH4 p.(G349Afs*49) c.1044delC

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[14]. 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[15,16]. 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[17,18,19,20].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[9].

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

Biomarker Descriptions (continued)

PIM1 amplification

Pim-1 proto-oncogene, serine/threonine kinase

Background: The PIM1 gene encodes the PIM-1 proto-oncogene, serine/threonine kinase protein[1]. PIM1, also known as PIM, is an oncogene that belongs to the PIM family of serine threonine kinases, which includes PIM2 and PIM3[45]. PIM1 is capable of phosphorylating CDC25A and CDC25C, which promotes G1 and S phase cell cycle progression, and G2/M phase progression, respectively[45]. PIM1 also targets proteins involved in cell survival, proliferation and apoptosis, including activation of MYC and BAD[45].

Alterations and prevalence: Somatic mutations in PIM1 are observed in 20% of diffuse large B-cell lymphoma (DLBCL)[9,10]. PIM1 amplification is observed in 5% of ovarian serous cystadenocarcinoma, 3% of skin cutaneous melanoma, cholangiocarcinoma, esophageal adenocarcinoma, 2% of DLBCL and liver hepatocellular carcinoma[9,10].

Potential relevance: Currently, no therapies are approved for PIM1 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[1,2,3]. SFKs are membrane-associated, non-receptor tyrosine kinases that are involved in several cellular functions such as growth, survival, and differentiation[2,3,4]. YES1 alterations have been identified in several cancer types and are associated with tumor progression[2,5,6,7,8].

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[9,10]. 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[9,10]. Biallelic loss of YES1 is observed in 2% diffuse large B-cell lymphoma and testicular germ cell tumors[9,10].

Potential relevance: Currently, no therapies are approved for YES1 aberrations. YES1 amplification and overexpression is associated with resistance to EGFR, HER2, and ALK inhibitors[5,6,8].

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,

Genes Assayed (continued)

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

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

Relevant Therapy Summary

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

ESR1 p.(D426Y) c.1276G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
elacestrant	○	○	○	✖	✖

* 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

SMARCA4 p.(E990*) c.2968G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
PRT-SCA2, chemotherapy	✖	✖	✖	✖	● (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	***54.13%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x2***
ATM	***LOH, 11q22.3(108098341-108236285)x2***
CHEK1	***LOH, 11q24.2(125496639-125525271)x2***
CHEK2	***LOH, 22q12.1(29083868-29130729)x2***
PALB2	***SNV, F557L, AF:0.5***
RAD54L	***LOH, 1p34.1(46714017-46743978)x2***

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

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

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