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Report Date: 11 Jul 2025 1 of 15

Patient Name: 박진수 Gender: N25-88 Sample ID:

Primary Tumor Site: 2025.06.27 **Collection Date:**

Sample Cancer Type: Lung Cancer

Table of Contents Variant Details Biomarker Descriptions Alert Details Relevant Therapy Summary	Page 2 3 7 8
Relevant Therapy Summary	8

Report Highlights 3 Relevant Biomarkers 4 Therapies Available 37 Clinical Trials

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	CD74::ROS1 fusion	
MET	None detected				
Genomic Alt	eration	Finding			
Tumor Mu	ıtational Burden	5.68 Mut/Mb measured			

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	CD74::ROS1 fusion CD74 molecule - ROS proto-oncogene 1, receptor tyrosine kinase Locus: chr5:149782684 - chr6:117650609	crizotinib 1,2/I,II+ entrectinib 1,2/I,II+ repotrectinib 1,2/I,II+ lorlatinib II+	crizotinib ⁺ entrectinib ⁺	34
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	CTNNB1 p.(S37C) c.110C>G catenin beta 1 Allele Frequency: 16.65% Locus: chr3:41266113 Transcript: NM_001904.4	None*	None*	1

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

* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Line of therapy: I: First-line therapy, II+: Other line of therapy
Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Report Date: 11 Jul 2025 2 of 15

Relevant Biomarkers (continued)

🛕 Alerts informed by public data sources: 🧿 Contraindicated, 🄻 Resistance, 🗳 Breakthrough, 🗚 Fast Track

CD74::ROS1 fusion

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

DNMT3A p.(Y526*) c.1578C>G, FAT1 p.(T2369Rfs*2) c.7105delA, Microsatellite stable, TP53 p.(P191Sfs*17) c.571_572delCC, NQO1 p.(P187S) c.559C>T, Tumor Mutational Burden

Variant Details

RAD51C

KMT2B

p.(L69V)

p.(W101L)

Copy Number Variations

c.205C>G

c.302G>T

DNA S	Sequence Variar	nts					
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
CTNNB1	p.(S37C)	c.110C>G	COSM5679	chr3:41266113	16.65%	NM_001904.4	missense
DNMT3A	p.(Y526*)	c.1578C>G		chr2:25467498	3.00%	NM_022552.5	nonsense
FAT1	p.(T2369Rfs*2)	c.7105delA		chr4:187540634	19.95%	NM_005245.4	frameshift Deletion
TP53	p.(P191Sfs*17)	c.571_572delCC		chr17:7578276	20.02%	NM_000546.6	frameshift Deletion
NQ01	p.(P187S)	c.559C>T		chr16:69745145	99.35%	NM_000903.3	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT CA		chr6:31324208	100.00%	NM_005514.8	missense, missense
HDAC9	p.(D986H)	c.2956G>C		chr7:18993787	22.09%	NM_178425.3	missense
PRUNE2	p.(E1696*)	c.5086G>T		chr9:79322104	14.45%	NM_015225.3	nonsense
PITRM1	p.([P767=;R768H])	c.2301_2303delGCGins	S.	chr10:3189378	48.55%	NM_001242307.1	synonymous, missense
ATM	p.(A1812V)	c.5435C>T		chr11:108173695	51.57%	NM_000051.4	missense

Gene Fusions		
Genes	Variant ID	Locus
CD74::ROS1	CD74-ROS1.C7R32.Non-Targeted	chr5:149782684 - chr6:117650609
CD74::ROS1	CD74-ROS1.C6R32.COSF1202.1	chr5:149784243 - chr6:117650609
CD74::ROS1	CD74-ROS1.C6R33	chr5:149784243 - chr6:117647577
CD74::ROS1	CD74-ROS1.C6R34.COSF1200.1	chr5:149784243 - chr6:117645578
CD74::ROS1	CD74-ROS1.C6R35.1	chr5:149784243 - chr6:117642557

chr17:56772351

chr19:36209222

7.47% NM 058216.3

8.95% NM_014727.3

missense

missense

Copy Number Variations					
Gene	Locus	Copy Number	CNV Ratio		
CDKN2A	chr9:21968178	0.62	0.58		

Biomarker Descriptions

CD74::ROS1 fusion

CD74 molecule, ROS proto-oncogene 1, receptor tyrosine kinase

<u>Background</u>: The ROS1 gene encodes the ROS proto-oncogene receptor tyrosine kinase 1, which exhibits structural similarity to anaplastic lymphoma kinase (ALK)^{1,2}. Like ALK, ROS1 is the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact ROS1 tyrosine kinase domain combined with numerous fusion partner genes³. ROS1 fusion kinases are constitutively activated and drive oncogenic transformation⁴.

Alterations and prevalence: Somatic mutations in ROS1 are observed in 24% of skin cutaneous melanoma, 13% of uterine corpus endometrial carcinoma, 8% of lung squamous cell carcinoma, 7% of colorectal adenocarcinoma, 6% of stomach adenocarcinoma, 5% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and diffuse large B-cell lymphoma, 4% of lung adenocarcinoma and uterine carcinosarcoma, 3% of adrenocortical carcinoma, esophageal adenocarcinoma, cholangiocarcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, and glioblastoma multiforme, and 2% of mesothelioma, brain lower grade glioma, breast invasive carcinoma, and acute myeloid leukemia^{5,6}. ROS1 fusions are observed in cholangiocarcinoma, gastric cancer, and ovarian cancer and have been reported in approximately 1-2% of non-small cell lung cancer (NSCLC) and glioblastoma^{1,7,8,9,10,11}. ROS1 amplification is observed in 3% of sarcoma^{5,6}. Alterations in ROS1 are rare in pediatric cancers^{5,6}. Somatic mutations are observed in 2% of bone cancer and embryonal tumors, and 1% or less in B-lymphoblastic leukemia/lymphoma (3 in 252 cases), glioma (3 in 297 cases), leukemia (1 in 311 cases), peripheral nervous system tumors (3 in 1158 cases), and Wilms tumor (1 in 710 cases)^{5,6}. Amplification of ROS1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)^{5,6}.

Potential relevance: The tyrosine kinase inhibitor (TKI), entrectinib¹² (2019), is approved for the treatment of ROS1 fusion-positive metastatic NSCLC. Crizotinib¹³ (2011), originally approved for the treatment of ALK-positive NSCLC, is also approved (2016) for the treatment of ROS1-positive NSCLC¹⁴. Acquired resistance to crizotinib in ROS1-positive NSCLC is associated with kinase domain mutations S1986F/Y, G2032R, D2033N, and L2155S¹⁵.¹6.¹7. Repotrectinib¹³ (2023) is a kinase inhibitor approved for the treatment of locally advanced or metastatic ROS1-positive NSCLC. In 2024, zidesamtinib¹³ received breakthrough designation for the treatment of patients with ROS1-positive NSCLC who have been previously treated with two or more ROS1 TKIs. The ROS1 inhibitor, taletrectinib²⁰ (2022), was also granted breakthrough designation for the treatment of adult patients with advanced or metastatic ROS1-positive NSCLC who are ROS1 tyrosine kinase inhibitor (TKI) treatment-naïve or previously treated with crizotinib. Ceritinib²¹ (2017) is a second-generation ALK inhibitor approved for ALK-positive NSCLC that has also shown efficacy in ROS1-positive NSCLC²². In a phase II study, ceritinib demonstrated systemic and intra-cranial activity with an objective response rate (ORR) of 62% in patients with advanced ROS1 positive NSCLC²². Lorlatinib²³, a CNS-penetrant third-generation ALK and ROS1 inhibitor, is FDA approved (2018) for ALK-positive metastatic NSCLC. Emerging pre-clinical evidence suggests that Iorlatinib may target almost all known ALK and ROS1 resistance mutations²⁴.⁵ In a phase I/II study of Iorlatinib in advanced ROS1-positive NSCLC, objective responses were observed in both TKI-naïve and those previously treated with crizotinib, regardless of CNS metastasis²⁶. Lorlatinib is recommended for subsequent therapy in ROS1 fusion-positive NSCLC patients who have progressed after treatment with crizotinib, entrectinib, or ceritinib²².

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression⁴⁶. 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)¹⁰⁹. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb^{110,111,112}. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions¹¹³. 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^{46,113,114}. CDKN2A aberrations commonly co-occur with CDKN2B¹⁰⁹. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation¹¹⁵. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer^{116,117}.

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 ¹¹⁸. 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,

Biomarker Descriptions (continued)

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 cancers⁶. 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 tumors⁶. 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^{43,119,120}. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma¹²¹. 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^{122,123,124}. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme¹²⁵. 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^{126,127,128,129}.

CTNNB1 p.(S37C) c.110C>G

catenin beta 1

Background: The CTNNB1 gene encodes catenin beta-1 (β-catenin), an integral component of cadherin-based adherens junctions, which are involved in maintaining adhesion and regulating the growth of epithelial cell layers²⁸. CTNNB1 binds to the APC protein in the cytoplasm and interacts with TCF and LEF transcription factors in the nucleus to regulate WNT signaling²⁹. Steady-state levels of CTNNB1 are regulated by ubiquitin-dependent proteolysis^{30,31,32}. CTNNB1 exon 3 mutations can lead to persistent activation of the WNT/β-catenin pathway and alter downstream nuclear transcription³³.

Alterations and prevalence: Recurrent somatic mutations leading to CTNNB1 activation are common in cancer. The most prevalent alterations include missense mutations in exon 3 at codons S33, S37, T41, and S45 that block phosphorylation by GSK-3β and inhibit CTNNB1 degradation^{33,34,35,36}. These activating mutations are observed in diverse solid tumors and have a prevalence of 20-30% in hepatocellular carcinoma, 20% in uterine carcinoma, and 15% in adrenocortical carcinoma^{5,6,37,38,39,40,41}. Alterations in CTNNB1 are also observed in pediatric cancers^{5,6}. Somatic mutations are observed in 36% of hepatobiliary cancer (4 in 11 cases), 6% of embryonal tumor (21 in 332 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of Wilms tumor (11 in 710 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases) and bone cancer (1 in 327 cases)^{5,6}.

<u>Potential relevance:</u> Currently, no therapies have been approved for CTNNB1 aberrations. CTNNB1 alterations have been proposed to promote cancer progression and limit the response to EGFR tyrosine kinase inhibitors in EGFR mutant lung cancer⁴². Mutation of CTNNB1 is considered an ancillary diagnostic biomarker for desmoid fibromatosis and WNT-activated medulloblastoma^{43,44,45}.

DNMT3A p.(Y526*) c.1578C>G

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 DNA⁷². 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^{73,74}.

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)^{5,64,75,76,77,78,79}. 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^{5,66}. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported^{5,75}. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations^{80,81}. 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^{82,83}. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity⁸⁴.

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML^{75,78,79,81}. 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)⁸⁵.

Biomarker Descriptions (continued)

FAT1 p.(T2369Rfs*2) c.7105delA

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats^{46,86}. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions⁸⁶. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion⁸⁶. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition⁸⁶. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1⁸⁶.

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot^{5,6}. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma^{5,6}. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma^{5,6}.

Potential relevance: Currently, no therapies are approved for FAT1 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 genome⁸⁷. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue^{88,89}. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2⁹⁰. 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 D17S250⁹¹. 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)⁹¹. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS^{92,93,94,95,96}. 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 genes⁸⁹. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer^{88,89,93,97}.

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^{88,89,98,99}. 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^{98,99}.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab¹⁰⁰ (2014) and nivolumab¹⁰¹ (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab¹⁰⁰ 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 indication¹⁰⁰. Dostarlimab¹⁰² (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^{94,103}. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab¹⁰⁴ (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^{94,105,106}. 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 patients¹⁰⁶. 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^{107,108}. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers^{107,108}.

TP53 p.(P191Sfs*17) c.571_572delCC

tumor protein p53

<u>Background:</u> 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 repair⁴⁶. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis⁴⁷. Alterations in TP53 are required

Biomarker Descriptions (continued)

for oncogenesis as they result in loss of protein function and gain of transforming potential⁴⁸. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{49,50}.

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%)^{5,6,51,52,53,54}. 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^{55,56,57,58}. 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, PC14586⁵⁹ (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, eprenetapopt⁶⁰, (2019) and breakthrough designation⁶¹ (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^{62,63}. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma⁴⁵. 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 transplant⁷⁰. 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 system⁷¹.

7 of 15 Report Date: 11 Jul 2025

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended



Resistance



Breakthrough



FDA information is current as of 2025-04-16. For the most up-to-date information, search www.fda.gov.

CD74::ROS1 fusion

taletrectinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Supporting Statement:

The FDA has granted Breakthrough Therapy designation (BTD) to the ROS-1 inhibitor, taletrectinib, for the treatment of adult patients with advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) who have not been previously treated with ROS1 tyrosine kinase inhibitors or crizotinib.

Reference:

https://www.anhearttherapeutics.com/news/press-releases/080322/

zidesamtinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ROS1 fusion

Supporting Statement:

The FDA has granted Breakthrough Therapy designation to the brain-penetrant ROS1-selective tyrosine kinase inhibitor (TKI), zidesamtinib (NVL-520), for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have been previously treated with two or more ROS1 TKIs.

Reference:

https://investors.nuvalent.com/2024-02-27-Nuvalent-Receives-U-S-FDA-Breakthrough-Therapy-Designation-for-NVL-520

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XP01, 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,

8 of 15

Report Date: 11 Jul 2025

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, 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	O In other cancer type	In this cancer type and other cancer types		X No evidend	ce	
CD74::ROS1 fus	sion					
Relevant Therapy		FDA	NCCN	EMA	ESMO	Clinical Trials*
entrectinib		•	•			(II/III)
crizotinib		•	•			(II)
repotrectinib		•	•	•	•	(I/II)
lorlatinib		×	•	×	×	×

^{*} 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

O In other cancer type

• In this cancer type and other cancer types

× No evidence

CD74::ROS1 fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
entrectinib, crizotinib	×	×	×	×	(III)
repotrectinib, crizotinib	×	×	×	×	(III)
sacituzumab tirumotecan	×	×	×	×	(III)
taletrectinib, crizotinib	×	×	×	×	(III)
targeted therapy	×	×	×	×	(III)
cabozantinib	×	×	×	×	(II)
ceritinib	×	×	×	×	(II)
sacituzumab govitecan	×	×	×	×	(II)
taletrectinib	×	×	×	×	(II)
amivantamab, lorlatinib, entrectinib	×	×	×	×	(1/11)
benmelstobart, catequentinib	×	×	×	×	(1/11)
furetinib	×	×	×	×	(/)
ICP-723	×	×	×	×	(1/11)
XZP-5955	×	×	×	×	(1/11)
zidesamtinib	×	×	×	×	(1/11)
APG-2449	×	×	×	×	(I)
HG 030	×	×	×	×	(I)
JYP-0322	×	×	×	×	(I)
LZ-001	×	×	×	×	(I)
talazoparib, crizotinib	×	×	×	×	(I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	(II)
palbociclib, abemaciclib	×	×	×	×	(II)
AMG 193	×	×	×	×	(1/11)

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

Report Date: 11 Jul 2025 10 of 15

Relevant Therapy Summary (continued)

■ In this cancer type
O In other cancer type
O In this cancer type and other cancer types
X No evidence

CINNBI p.(537C) c.110C>G					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tegatrabetan	×	×	×	×	(1/11)

^{*} 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	13.54%
ATM	SNV, A1812V, AF:0.52
RAD51C	SNV, L69V, AF:0.07

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 2025.05(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-04-16. NCCN information was sourced from www.nccn.org and is current as of 2025-04-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-04-16. ESMO information was sourced from www.esmo.org and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. 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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13 of 15

Report Date: 11 Jul 2025

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