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Patient Name: 오승택
Gender: M
Sample ID: N25-323

Primary Tumor Site: lung
Collection Date: 20251117

Sample Cancer Type: Lung Cancer

Table of Contents	Page

Report Highlights
2 Relevant Biomarkers
7 Therapies Available
22 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	***KIF5B::RET fusion***
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***6.65 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*KIF5B::RET fusion* kinesin family member 5B - ret proto-oncogene Locus: chr10:32306980 - chr10:43612032	**pralsetinib** [1 / I] **selpercatinib** [1, 2 / I] cabozantinib [II+]	**pralsetinib** [1 / I, II+] **selpercatinib** [1, 2 / I, II+]	17
IIC	*PIK3CA p.(E545K) c.1633G>A* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 28.71% Locus: chr3:178936091 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1 / I] **alpelisib + hormone therapy** [1, 2 / II+] **capivasertib + hormone therapy** [1, 2 / II+] aspirin [II+]	5

*** 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.

Alerts informed by public data sources: ⊘ Contraindicated, Resistance, Breakthrough, Fast Track

KIF5B::RET fusion	**A-400** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

*GNAS amplification, MDM2 amplification, Microsatellite stable, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 p.(E3430Rfs*11) c.10287_10288insC, PTPRT deletion, ZNF217 amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(E545K)	c.1633G>A	COSM763	chr3:178936091	28.71%	NM_006218.4	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	43.80%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	50.05%	NM_000903.3	missense
ZFHX3	p.(E3430Rfs*11)	c.10287_10288insC	.	chr16:72821887	64.33%	NM_006885.4	frameshift Insertion
EPHA2	p.(G339C)	c.1015G>T	.	chr1:16464645	52.23%	NM_004431.5	missense
CDC73	p.(E24D)	c.72A>C	.	chr1:193091402	10.46%	NM_024529.5	missense
CDC73	p.(E29G)	c.86A>G	.	chr1:193091416	13.33%	NM_024529.5	missense
SETD2	p.(L1771V)	c.5311C>G	.	chr3:47127771	11.73%	NM_014159.7	missense
CELF2	p.(?)	c.977-6_977-5insGTTT	.	chr10:11356096	95.45%	NM_006561.3	unknown
GNA13	p.(K42N)	c.126G>C	.	chr17:63052586	31.10%	NM_006572.6	missense
CUL4B	p.(S53Y)	c.158C>A	.	chrX:119694390	34.86%	NM_003588.3	missense

Gene Fusions

Genes	Variant ID	Locus
KIF5B::RET	KIF5B-RET.K23R12.COSF1234.1	chr10:32306980 - chr10:43612032

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
GNAS	chr20:57415551	7.95	2.78
MDM2	chr12:69202958	16.05	5.22
HLA-A	chr6:29910229	0.2	0.46
PTPRT	chr20:40710527	0.97	0.69
ZNF217	chr20:52188253	12.57	4.17

Biomarker Descriptions

KIF5B::RET fusion

kinesin family member 5B, ret proto-oncogene

Background: The RET gene encodes the RET receptor tyrosine kinase, which is activated by a ligand family of glial cell line-derived neurotrophic factors (GDNF)[84]. RET is the target of recurrent chromosomal rearrangements that generate fusion proteins containing

Biomarker Descriptions (continued)

the intact RET tyrosine kinase domain combined with several fusion partner genes[84]. RET fusion kinases are constitutively activated and drive oncogenic transformation, which can lead to activation of the PI3K/AKT, RAS/RAF/MEK/ERK, and PLCγ/PKC pathways, resulting in cell survival and proliferation[85].

Alterations and prevalence: RET fusions occur in approximately 55% of papillary thyroid carcinomas (PTC), with even higher frequencies observed in PTC patients with radiation exposure[86,87,88]. RET rearrangement is also present in 6% of thyroid carcinoma and 1-2% of non-small cell lung cancer (NSCLC)[8,9,89]. Point mutations in RET are relatively common in sporadic medullary thyroid cancer (MTC), with 6% of patients found to contain germline mutations[90]. Somatic mutations (specifically at codon 918), which leads to increased kinase activity, have been observed in at least 25% of MTC cases[90]. Somatic mutations have also been observed in 8% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of stomach adenocarcinoma and lung squamous cell carcinoma, 3% of pheochromocytoma and paraganglioma, lung adenocarcinoma, cholangiocarcinoma, and head and neck squamous cell carcinoma, and 2% of adrenocortical carcinoma, esophageal adenocarcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[8,9]. Amplification of RET is observed in 3% of cholangiocarcinoma[8,9]. Alterations in RET are rare in pediatric cancers[8,9]. Somatic mutations are observed in 3% of soft tissue sarcoma, and less than 1% of glioma (2 in 297 cases), bone cancer (2 in 327 cases), leukemia (2 in 354 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[8,9]. RET amplification is observed in less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[8,9].

Potential relevance: Selpercatinib[91] is approved (2020) for RET fusion-positive NSCLC, thyroid cancer in adults and children, and metastatic solid tumors in adults and children that have progressed following systemic treatment. Selpercatinib[91] is also approved for RET-mutation positive medullary thyroid cancer (MTC). Additionally, the RET inhibitor, pralsetinib[92], is approved (2020) for RET fusion-positive NSCLC in adults and RET fusion-positive thyroid cancer in children and adults. In 2024, the FDA granted fast track designation to the selective RET inhibitor, EP0031/A400[93], as a potential treatment option for RET-fusion positive NSCLC. Point mutations involving codons 804 and 806 have been shown to confer resistance to selective kinase inhibitors including vandetanib[94,95]. The small-molecule tyrosine kinase inhibitor, cabozantinib, is a treatment option for advanced or metastatic NSCLC with RET rearrangements[96]. Cabozantinib has also demonstrated clinical benefit in RET-mutated medullary thyroid cancer patients[97]. RET mutations at codon 918 are associated with high risk and adverse prognosis in patients diagnosed with MTC[98].

PIK3CA p.(E545K) c.1633G>A

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[56]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[57,58]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[57]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[59,60]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[59,60,61,62]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[63,64,65].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[8,9]. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[66,67]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[68,69,70]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[8,9].

Potential relevance: The PI3K inhibitor, alpelisib[71], is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[72]. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations[72]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[73]. The FDA also approved the kinase inhibitor, capivasertib (2023)[74] in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib[75], is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus

Biomarker Descriptions (continued)

and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[76,77]. In colorectal cancers, PIK3CA mutations predict significantly improved survival and reduced disease recurrence with adjuvant aspirin therapy, compared to no benefit in wild-type PIK3CA tumors[41,50,78,79].

GNAS amplification

GNAS complex locus

Background: GNAS encodes the stimulatory alpha subunit of the guanine nucleotide-binding protein (G-protein). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNAS links receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses.

Alterations and prevalence: Recurrent somatic mutations at amino acid positions R201 and Q227 lead to constitutive activation of GNAS and are observed in pancreatic cancer (3%) as well as lung adenocarcinoma, colorectal, and gastric cancers (approximately 1%)[8,9,80,81]. In colorectal cancer, GNAS mutations were enriched in right-sided tumors[82]. In lung adenocarcinoma, GNAS mutations were enriched in female patients with invasive mucinous adenocarcinoma[81]. Specifically, GNAS mutations in these patients were exclusively observed at R201C/H, along with concurrent mutations in KRAS or BRAF.[81].

Potential relevance: Currently, no therapies are approved for GNAS aberrations. A case study of a patient with appendiceal adenocarcinoma harboring a GNAS R201H mutation reported a progression-free survival (PFS) of 4 months when treated with the MEK inhibitor trametinib[83].

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING domain[14]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[14]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[15]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[15]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[15].

Alterations and prevalence: MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma[8,9]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[16]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[17,18].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[19].

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[34]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[35,36]. 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[37]. 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[38]. 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)[38]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[39,40,41,42,43]. 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[36]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[35,36,40,44].

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[35,36,45,46]. 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[45,46].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[47] (2014) and nivolumab[48] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[47] is also approved

Biomarker Descriptions (continued)

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[47]. Dostarlimab[49] (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[41,50]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[51] (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[41,52,53]. 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[53]. 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[54,55]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[54,55].

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[1,99]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[99,100]. 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[101]. 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[101,102,103,104]. 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[105].

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[8,9].

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

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[2]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[3]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[4,5,6]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[7].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[8,9]. Biallelic loss of HLA-A is observed in 4% of DLBCL[8,9].

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

ZFHX3 p.(E3430Rfs*11) c.10287_10288insC

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,24,25]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[25,26]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[27,28,29,30,31]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[27,30,32,33].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[8,9]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[8,9].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

PTPRT deletion

protein tyrosine phosphatase, receptor type T

Background: PTPRT encodes protein tyrosine phosphatase receptor type T, part of the protein tyrosine phosphatase (PTP) family which consists of 125 members[1,10,11]. PTPs are responsible for protein dephosphorylation of tyrosine residues and are involved in several cellular processes including proliferation, differentiation, adhesion, and survival[12,13]. Aberrant tyrosine phosphorylation resulting from PTP dysfunction has been linked to cancer progression[12,13].

Alterations and prevalence: Somatic mutations in PTPRT are observed in 29% of skin cutaneous melanoma, 12% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 10% of colorectal adenocarcinoma and lung adenocarcinoma, 7% of esophageal adenocarcinoma and lung squamous cell carcinoma, 5% of uterine carcinosarcoma and bladder urothelial carcinoma, 4% of head and neck squamous cell carcinoma and cervical squamous cell carcinoma, 3% of glioblastoma multiforme and liver hepatocellular carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, and ovarian serous cystadenocarcinoma[8,9]. Biallelic loss of PTPRT is observed in about 1% of mesothelioma, prostate adenocarcinoma, and acute myeloid leukemia.[8,9].

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

ZNF217 amplification

zinc finger protein 217

Background: ZNF217 encodes zinc finger protein 217, a member of the Krüppel-like family of transcription factors[1,20]. While ZNF217 positively regulates gene expression, it also interacts with corepressors and histone-modifying proteins demonstrating its complexity as a transcriptional regulator[20,21,22]. ZNF217 coordinates several cellular processes involved in tumorigenesis, such as proliferation, survival, invasion, and metastasis[22]. In breast cancer, functional crosstalk between the estrogen receptor and ZNF217 has been a suggested mechanism for endocrine therapy resistance and high expression of ZNF217 may confer poor prognosis[23].

Alterations and prevalence: Somatic mutations in ZNF217 are observed in 7% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, lung adenocarcinoma, and head and neck squamous cell carcinoma[8,9]. Amplification of ZNF217 is found in 9% of uterine carcinosarcoma, 8% of stomach adenocarcinoma, 7% of colorectal adenocarcinoma and breast invasive carcinoma, 5% of esophageal adenocarcinoma and lung adenocarcinoma, 4% of ovarian serous cystadenocarcinoma, 3% of uterine corpus endometrial carcinoma, and 2% of sarcoma, pancreatic adenocarcinoma, and liver hepatocellular carcinoma[8,9].

Potential relevance: Currently, no therapies are approved for ZNF217 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

KIF5B::RET fusion

A-400

Cancer type: Non-Small Cell Lung Cancer

Variant class: RET fusion

Supporting Statement:
The FDA has granted Fast Track designation to the selective RET inhibitor, EP0031/A400, for the potential treatment of RET-fusion positive Non-Small Cell Lung Cancer (NSCLC).

Reference:

https://ellipses.life/ellipses-next-generation-selective-ret-inhibitor-ep0031-a400-granted-fast-track-designation-by-fda/

Genes Assayed

Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

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

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

KIF5B::RET fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selpercatinib	◑	◑	◑	◑	✖
pralsetinib	◑	◑	✖	◑	● (II)
cabozantinib	✖	●	✖	✖	✖
entrectinib	✖	✖	✖	✖	● (II/III)
HA121-28	✖	✖	✖	✖	● (II)
JS-207, chemotherapy	✖	✖	✖	✖	● (II)
LMV-12, osimertinib	✖	✖	✖	✖	● (II)
A-400	✖	✖	✖	✖	● (I/II)
amivantamab, selpercatinib, pralsetinib	✖	✖	✖	✖	● (I/II)
BYS-10	✖	✖	✖	✖	● (I/II)
HEC-169096	✖	✖	✖	✖	● (I/II)
TAS-0953	✖	✖	✖	✖	● (I/II)
APS-03118	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

KIF5B::RET fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IBI-363, IBI-325, lenvatinib	✖	✖	✖	✖	● (I)
ND-003	✖	✖	✖	✖	● (I)
SYS-6023	✖	✖	✖	✖	● (I)
TGRX-1942	✖	✖	✖	✖	● (I)
TY-1091	✖	✖	✖	✖	● (I)

PIK3CA p.(E545K) c.1633G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✖
capivasertib + fulvestrant	○	○	○	✖	✖
inavolisib + palbociclib + fulvestrant	○	○	✖	✖	✖
aspirin	✖	○	✖	✖	✖
ETX-636	✖	✖	✖	✖	● (I/II)
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
RLY-2608	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (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	***10.94%***
Not Detected	***Not Applicable***

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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