



Sample Information

Patient Name: 紀淵泉**Gender:** Male**ID No.:** M101077686**History No.:** 42322098**Age:** 70**Ordering Doctor:** DOC6259E 湯宇碩**Ordering REQ.:** 0ASXMXF**Signing in Date:** 2020/06/23**Path No.:** S109-99623**MP No.:** F20037**Assay:** Oncomine Focus Assay**Sample Type:** FFPE**Block No.:** S108-24076H**Percentage of tumor cells:** 30%**Note:**

Sample Cancer Type: Non-Small Cell Lung Cancer

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Report Highlights

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Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		



Relevant Biomarkers

■ Indicated ■ Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
PIK3CA p.(E542K) c.1624G>A phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Tier: IIC Allele Frequency: 4.76%	None	■ alpelisib + fulvestrant ¹	11
FGFR1 amplification fibroblast growth factor receptor 1 Tier: IIC	None	None	11

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
PIK3CA	p.(E542K)	c.1624G>A	COSM760	chr3:178936082	4.76%	NM_006218.3	missense	1994
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	50.95%	NM_002227.3	synonymous	1998
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	46.80%	NM_004304.4	missense	2000
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.85%	NM_004304.4	missense	1998
ALK	p.(=)	c.3600G>C	.	chr2:29443617	52.52%	NM_004304.4	synonymous	1967
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.90%	NM_004304.4	synonymous	1991
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.80%	NM_000142.4	synonymous	1997
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.75%	NM_006206.5	synonymous	1999
KIT	p.(=)	c.1638A>G	.	chr4:55593481	45.92%	NM_000222.2	synonymous	1999
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.25%	NM_213647.2	missense	1999
BRAF	p.(=)	c.2235A>G	.	chr7:140434463	56.23%	NM_004333.4	synonymous	1999
RET	p.(=)	c.2307G>T	.	chr10:43613843	99.95%	NM_020975.4	synonymous	1999

Copy Number Variations

Gene	Locus	Copy Number
FGFR1	chr8:38271445	12.93



Biomarker Descriptions

FGFR1 (fibroblast growth factor receptor 1)

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival^{1,2,3}.

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions⁴. Amplification of FGFR1 is observed in 15-20% of squamous lung cancer, 10-15% of breast cancer, 8% of bladder cancer, and 2-5% of uterine cancer cases^{5,6,7,8,9,9}. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types¹⁰. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but less common in solid tumors^{11,12,13}.

Potential relevance: The FDA has granted fast track designation to Debio 1347¹⁴ (2018) for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations^{15,16,17,18,19,20,21}. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months²². Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks²³.

PIK3CA (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) enzyme²⁴. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples the p110α subunit (PI3K) to activated tyrosine protein kinases. 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^{25,26}. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism^{25,26,27,28}. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in activation of the PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability^{29,30,31}.

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 cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation^{32,33,34}. 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, alpelisib³⁵, 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, 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 tumors³⁶. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations³⁶. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations³⁷. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers^{38,39}.



Relevant Therapy Summary

● In this cancer type ○ In other cancer type ● In this cancer type and other cancer types
 ⛔ Contraindicated ⚠ Both for use and contraindicated ✕ No evidence

PIK3CA p.(E542K) c.1624G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	✕	✕	✕
capiasertib	✕	✕	✕	✕	● (II)
paxalisib	✕	✕	✕	✕	● (II)
samotolisib	✕	✕	✕	✕	● (II)
sirolimus	✕	✕	✕	✕	● (II)
temsirolimus	✕	✕	✕	✕	● (II)
atezolizumab + ipatasertib	✕	✕	✕	✕	● (I/II)
ARQ-751, fulvestrant, chemotherapy	✕	✕	✕	✕	● (I)
copanlisib, olaparib, durvalumab	✕	✕	✕	✕	● (I)
GDC-0077	✕	✕	✕	✕	● (I)
gedatolisib + palbociclib	✕	✕	✕	✕	● (I)

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
erdafitinib	✕	✕	✕	✕	● (II)
futibatinib	✕	✕	✕	✕	● (II)
nintedanib	✕	✕	✕	✕	● (II)
ponatinib	✕	✕	✕	✕	● (II)
sunitinib	✕	✕	✕	✕	● (II)
pemigatinib, pembrolizumab, trastuzumab, chemotherapy, INCMGA00012	✕	✕	✕	✕	● (I/II)
CPL-304-110	✕	✕	✕	✕	● (I)
Debio 1347	✕	✕	✕	✕	● (I)
pemigatinib	✕	✕	✕	✕	● (I)

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



Relevant Therapy Details

Current FDA Information

☒ In this cancer type
 ☐ In other cancer type
 ☐ In this cancer type and other cancer types
 ☒ Contraindicated
 ☒ Not recommended
 ☒ Resistance

FDA information is current as of 2020-02-28. For the most up-to-date information, search www.fda.gov.

PIK3CA p.(E542K) c.1624G>A

☐ alpelisib + fulvestrant

Cancer type: Breast Cancer

Label as of: 2019-05-24

Variant class: PIK3CA E542K mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Indications and usage:

PIQRAY® is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf



Current NCCN Information

☒ In this cancer type
 ☐ In other cancer type
 ☐ In this cancer type and other cancer types
 ☒ Contraindicated
 ☐ Not recommended
 ☐ Resistance

NCCN information is current as of 2019-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

PIK3CA p.(E542K) c.1624G>A

☐ alpelisib + fulvestrant

Cancer type: Breast Cancer

Variant class: PIK3CA mutation

Other criteria: ERBB2 negative, ER positive, PR positive

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Recurrent or Stage IV Invasive Breast Cancer; Postmenopausal or Premenopausal receiving ovarian ablation or suppression (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 1.2020]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:



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