Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
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Sample Information

Patient Name: 洪苡溱
Gender: Female
ID No.: A224879886
History No.: 46338005
Age: 43

Ordering Doctor: DOC5636D 吳紋綺
Ordering REQ.: 0BWTMGW
Signing in Date: 2022/06/23

Path No.: S111-99612
MP No.: F22064
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S111-76392B
Percentage of tumor cells: 90%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Melanoma

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Relevant Melanoma Variants

Gene	Finding
BRAF	None detected
KIT	***KIT p.(L576P) c.1727T>C, KIT amplification***
NRAS	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*KIT p.(L576P) c.1727T>C* KIT proto-oncogene, receptor tyrosine kinase Allele Frequency: 43.38%	imatinib	imatinib	0
IIC	*BAG4-FGFR1 fusion* BAG cochaperone 4 - fibroblast growth factor receptor 1	None	None	1

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], 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.

Prevalent cancer biomarkers without relevant evidence based on included data sources
KIT amplification

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KIT	p.(L576P)	c.1727T>C	COSM1290	chr4:55593661	43.38%	NM_000222.3	missense	1948

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
BAG4-FGFR1	BAG4-FGFR1.B1F2	chr8:38034657 - chr8:38315052	753

Copy Number Variations

Gene	Locus	Copy Number
KIT	chr4:55529117	7.41

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 fusions[4]. 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]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[10]. 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 (2018) to Debio 1347[14] for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and

Biomarker Descriptions (continued)

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 months[22]. 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 weeks[23].

KIT (KIT proto-oncogene, receptor tyrosine kinase)

Background: The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR[24,25]. KIT is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells[26]. The KIT gene is flanked by the PDGFRA and KDR genes on chromosome 4q12. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways promoting cell proliferation and survival[27].

Alterations and prevalence: Recurrent somatic KIT alterations are observed in both solid and hematological cancers and include activating mutations such as single nucleotide variants, small duplications, and complex in-frame insertions or deletions (indels). Mutations in KIT exons 8, 9, 11, and 17 disrupt auto-inhibitory mechanisms and lead to constitutive activity[28]. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma[29]. Somatic mutations in exon 11 occur in 60-70% of all gastrointestinal stromal tumor (GIST), whereas alterations in exons 8 and 17 are more common in myeloid cancers[9,28,29]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis[30,31].

Potential relevance: Imatinib[32] (2001) is approved for KIT positive malignant GIST and adult patients with aggressive systemic mastocytosis (SM) harboring D816V mutations. Imatinib is also recommended for KIT activating mutations in melanoma and exon 9 and 11 mutations in GIST[33,34,35]. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib[36]. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse[37]. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease[38,39].

Relevant Therapy Summary

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

KIT p.(L576P) c.1727T>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
imatinib	✖	◑	✖	✖	✖

BAG4-FGFR1 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
erdafitinib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Details

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2022-03-31. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KIT p.(L576P) c.1727T>C

● imatinib

Cancer type: Cutaneous Melanoma **Variant class:** KIT L576P mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2022]

○ imatinib

Cancer type: Gastrointestinal Stromal Tumor **Variant class:** KIT exon 11 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Resectable (Neoadjuvant therapy); Preferred intervention
- Resected (Adjuvant therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Gastrointestinal Stromal Tumor [Version 1.2022]

Clinical Trials in Taiwan region:

Clinical Trials Summary

BAG4-FGFR1 fusion

NCT ID	Title	Phase
NCT04083976	A Phase II Study of Erdafitinib in Subjects With Advanced Solid Tumors and FGFR Gene Alterations.	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2022-04-13. For the most up-to-date information, search www.fda.gov.

BAG4-FGFR1 fusion

Debio 1347

Cancer type: Solid Tumor

Variant class: FGFR1 aberration

Supporting Statement:
The FDA has granted Fast Track Designation to the FGFR 1-3 inhibitor, debio 1347, for FGFR1/2/3 alterations in unresectable or metastatic solid tumors.

Reference:

https://www.debiopharm.com/drug-development/press-releases/fda-grants-fast-track-designation-to-debiopharm-internationals-debio-1347-for-the-treatment-of-patients-with-unresectable-or-metastatic-tumors-with-a-specific-fgfr-gene-alteration/

Signatures

Testing Personnel:

2022.07.04
09:12:23 +08'00'

Laboratory Supervisor:

2022.07.04
09:12:35 +08'00'

Pathologist:

2022.07.04
09:12:46 +08'00'

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