Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
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Sample Information

Patient Name: 林順安
Gender: Male
ID No.: V120354580
History No.: 41901375
Age: 58

Ordering Doctor: DOC3109L 邱昭華
Ordering REQ.: D61NMPK
Signing in Date: 2021/02/24

Path No.: S110-98260
MP No.: F21015
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-75011A
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Other Solid Tumor

Report Highlights

1 Relevant Biomarkers
0 Therapies Available
16 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*KIT p.(K558N) c.1674G>T* KIT proto-oncogene receptor tyrosine kinase Allele Frequency: 45.01%	None	None	16

Public data sources included in relevant therapies: FDA1, 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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KIT	p.(K558N)	c.1674G>T	.	chr4:55593608	45.01%	NM_000222.2	missense	1962
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	50.23%	NM_004304.4	missense	1999
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.90%	NM_004304.4	missense	1997

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
ALK	p.(=)	c.3375C>A	.	chr2:29445458	50.58%	NM_004304.4	synonymous	1997
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.70%	NM_000142.4	synonymous	1989
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.90%	NM_006206.5	synonymous	1999
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	98.75%	NM_213647.2	missense	1998
RET	p.(=)	c.2307G>T	.	chr10:43613843	62.70%	NM_020975.4	synonymous	1992
KRAS	p.(?)	c.111+2T>C	.	chr12:25398206	43.11%	NM_033360.3	unknown	1995

Biomarker Descriptions

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[1,2]. KIT is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells[3]. 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[4].

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[5]. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma[6]. 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[5,6,7]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis[8,9].

Potential relevance: Imatinib[10] (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[11,12,13]. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib[14]. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse[15]. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease[16,17].

Relevant Therapy Summary

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

KIT p.(K558N) c.1674G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
imatinib	✖	✖	✖	✖	◑ (III)
ponatinib	✖	✖	✖	✖	◑ (II)
dasatinib, sunitinib	✖	✖	✖	✖	● (II)
nilotinib, pazopanib	✖	✖	✖	✖	● (II)

* 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

KIT p.(K558N) c.1674G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sunitinib	✖	✖	✖	✖	● (II)
sunitinib, regorafenib	✖	✖	✖	✖	● (II)
ripretinib	✖	✖	✖	✖	● (I)
avelumab, axitinib	✖	✖	✖	✖	○ (II)
pexidartinib	✖	✖	✖	✖	○ (II)
regorafenib	✖	✖	✖	✖	○ (II)
anlotinib hydrochloride	✖	✖	✖	✖	○ (I/II)
pembrolizumab, imatinib	✖	✖	✖	✖	○ (I/II)
spartalizumab, imatinib	✖	✖	✖	✖	○ (I/II)

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

Clinical Trials Summary

KIT p.(K558N) c.1674G>T

NCT ID	Title	Phase
NCT02461849	A Phase II, Open-label, Study in Patients With Refractory, Metastatic Cancer Harboring KIT Mutation or Amplification to Investigate the Clinical Efficacy and Safety of Imatinib Therapy.	II
NCT02465060	Molecular Analysis for Therapy Choice (MATCH).	II
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT02571036	A Multicenter Phase I, Open-Label Study of DCC-2618 to Assess Safety,Tolerability, and Pharmacokinetics in Patients With Advanced Malignancies	I
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT02272998	Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1)	II
NCT02413736	Three versus Five Years of Adjuvant Imatinib as Treatment of Patients with Operable GIST with a High Risk for Recurrence: A Randomised Phase III Study	III
NCT02712112	Randomized Phase 2 Study of Intermittent vs Continuous Dosing Schedule of Imatinib in Patients With Tyrosine Kinase Inhibitor Refractory Gastrointestinal Stromal Tumors (GISTs)	II
NCT02071940	A Phase II Trial of PLX3397 in the Treatment of KIT Mutated Advanced Acral and Mucosal Melanoma	II

Clinical Trials Summary (continued)

KIT p.(K558N) c.1674G>T (continued)

NCT ID	Title	Phase
NCT03171389	Phase II Trial of Ponatinib in Patients With Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) Following Failure or Intolerance of Prior Therapy With Imatinib (POETIG trial – POnatinib after rEsisTance to Imatinib in GIST)	II
NCT02501551	A Phase II Study to Evaluate the Efficacy of Regorafenib in C-kit Mutated Metastatic Malignant Melanoma Failed First-Line Dacarbazine, Temozolomide or Immune Therapy	II
NCT04004975	Phase II Clinical Trials on Anlotinib for the Treatment of Recurrent Glioblastoma	I/II
NCT04546074	Imatinib Mesylate in Combination With Pembrolizumab in Patients With Advanced KIT-mutant Melanoma Following Progression on Standard Therapy: a Phase I/II Trial	I/II
NCT03609424	A Phase Ib/II Study Of PDR001 Plus Imatinib For Metastatic Or Unresectable GIST With Prior Failure Of Imatinib, Sunitinib And Regorafenib	I/II
NCT04258956	A Phase II, Single Arm Study of Avelumab In Combination With Axitinib in Patients With Unresectable/ Metastatic Gastrointestinal Stromal Tumor After Failure of Standard Therapy - AXAGIST	II

Signatures

Testing Personnel:

2021.02.25
13:39:20 +08'00'

Laboratory Supervisor:

2021.02.25
13:39:39 +08'00'

Pathologist:

2021.02.25
13:39:53 +08'00'

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