Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 羅雪香
Gender: Female
ID No.: G201055697
History No.: 46942976
Age: 66

Ordering Doctor: DOC8518J 黃昱凱
Ordering REQ.: 0BGCVRY
Signing in Date: 2021/05/20

Path No.: S110-98843
MP No.: F21042
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-66363E
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Gastrointestinal Stromal Tumor

Report Highlights

1 Relevant Biomarkers
1 Therapies Available
11 Clinical Trials

Relevant Gastrointestinal Stromal Tumor Variants

Gene	Finding
KIT	***KIT exon 11 deletion***
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected
PDGFRA	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*KIT exon 11 deletion* KIT proto-oncogene, receptor tyrosine kinase Allele Frequency: 34.63%	imatinib	imatinib	11

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.(D579del)	c.1735_1737delGAT	COSM1294	chr4:55593666	34.63%	NM_000222.2	nonframeshift Deletion	1975
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	76.29%	NM_002227.3	synonymous	1881
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	49.17%	NM_004304.4	missense	1997
ALK	p.(=)	c.3375C>A	.	chr2:29445458	46.07%	NM_004304.4	synonymous	1995
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.05%	NM_213647.2	missense	2000
MET	p.(N375S)	c.1124A>G	.	chr7:116340262	50.58%	NM_001127500.2	missense	1997

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 exon 11 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
imatinib	✖	◑	✖	●	● (III)
avelumab, axitinib	✖	✖	✖	✖	● (II)
cabozantinib	✖	✖	✖	✖	● (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 exon 11 deletion (continued)

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

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 2021-04-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KIT exon 11 deletion

● imatinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Progression, Resectable (Neoadjuvant therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Gastrointestinal Stromal Tumor [Version 1.2021]

○ imatinib

Cancer type: Melanoma **Variant class:** KIT exon 11 activating mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

Current ESMO Information

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

ESMO information is current as of 2021-04-01. For the most up-to-date information, search www.esmo.org.

KIT exon 11 deletion

● **imatinib**

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

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Advanced, Metastatic (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Gastrointestinal Stromal Tumours [Ann Oncol (2018) 29 (Suppl 4): iv68–iv78. (Corrigendum: 05 September 2018)]

Clinical Trials Summary

KIT exon 11 deletion

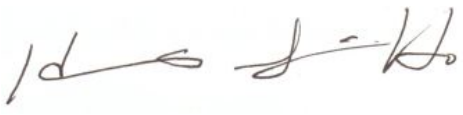
NCT ID	Title	Phase
NCT02413736	Three versus Five Years of Adjuvant Imatinib as Treatment of Patients with Operable GIST with a High Risk for Recurrence: A Randomised Phase III Study	III
NCT02712112	Randomized Phase 2 Study of Intermittent vs Continuous Dosing Schedule of Imatinib in Patients With Tyrosine Kinase Inhibitor Refractory Gastrointestinal Stromal Tumors (GISTs)	II
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
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
NCT04116541	MegaMOST - A Multicenter, Open-label, Biology Driven, Phase II Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations /Characteristics in Advanced / Metastatic Tumors.	II
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
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
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

Signatures

Testing Personnel:

2021.05.20
12:08:02 +08'00'

Laboratory Supervisor:



2021.05.20
12:08:14 +08'00'

Pathologist:

2021.05.20
12:08:23 +08'00'

References

1. Ségaliny et al. Receptor tyrosine kinases: Characterisation, mechanism of action and therapeutic interests for bone cancers. J Bone Oncol. 2015 Mar;4(1):1-12. PMID: 26579483
2. Berenstein. Class III Receptor Tyrosine Kinases in Acute Leukemia - Biological Functions and Modern Laboratory Analysis. Biomark Insights. 2015;10(Suppl 3):1-14. PMID: 26309392
3. Ashman. The biology of stem cell factor and its receptor C-kit. Int. J. Biochem. Cell Biol. 1999 Oct;31(10):1037-51. PMID: 10582338
4. Cardoso et al. The SCF/c-KIT system in the male: Survival strategies in fertility and cancer. Mol. Reprod. Dev. 2014 Dec;81(12):1064-79. PMID: 25359157
5. Abbaspour et al. Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. Drug Des Devel Ther. 2016;10:2443-59. PMID: 27536065
6. Liang et al. The C-kit receptor-mediated signal transduction and tumor-related diseases. Int. J. Biol. Sci. 2013;9(5):435-43. PMID: 23678293
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Garcia-Montero et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. Blood. 2006 Oct 1;108(7):2366-72. PMID: 16741248
9. Chatterjee et al. Mastocytosis: a mutated KIT receptor induced myeloproliferative disorder. Oncotarget. 2015 Jul 30;6(21):18250-64. PMID: 26158763
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021588s056s057lbl.pdf
11. NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]
12. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2021]
13. Casali et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2018 Oct 1;29(Supplement_4):iv68-iv78. PMID: 29846513
14. KIT Oncogenic Mutations: Biologic Insights, Therapeutic Advances, and Future Directions. Cancer Res. 2016 Nov 1;76(21):6140-6142. PMID: 27803101
15. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2021]
16. Lim et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009 Jun 4;113(23):5727-36. PMID: 19363219
17. Verstovsek. Advanced systemic mastocytosis: the impact of KIT mutations in diagnosis, treatment, and progression. Eur. J. Haematol. 2013 Feb;90(2):89-98. PMID: 23181448