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: 楊惠敏
Gender: Female
ID No.: U200683483
History No.: 47041612
Age: 69

Ordering Doctor: DOC8528A 劉思妤
Ordering REQ.: 0BHVHRJ
Signing in Date: 2021/07/14

Path No.: S110-99090
MP No.: F21056
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-19195A
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page

Report Highlights

2 Relevant Biomarkers
1 Therapies Available
9 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

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	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*KIT p.(M541L) c.1621A>C* KIT proto-oncogene, receptor tyrosine kinase Allele Frequency: 39.39%	None	imatinib	6
IIC	*MYC amplification* MYC proto-oncogene, bHLH transcription factor	None	None	3

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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KIT	p.(M541L)	c.1621A>C	.	chr4:55593464	39.39%	NM_000222.3	missense	1998
JAK1	p.(P733=)	c.2199A>G	.	chr1:65310489	46.40%	NM_002227.4	synonymous	1998
IDH1	p.(G105=)	c.315C>T	.	chr2:209113192	55.85%	NM_005896.3	synonymous	2000
PDGFRA	p.(G313=)	c.939T>G	.	chr4:55133726	39.18%	NM_006206.6	synonymous	1996
PDGFRA	p.(V824=)	c.2472C>T	.	chr4:55152040	39.40%	NM_006206.6	synonymous	2000
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.50%	NM_213647.3	missense	2000

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	80.35

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

Biomarker Descriptions (continued)

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].

MYC (MYC proto-oncogene, bHLH transcription factor)

Background: The MYC gene encodes the MYC proto-oncogene (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[18,19,20,21]. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions[22]. MYC functions as a heterodimer in complex with the transcription factor MAX[19,23].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[24,25]. MYC gene amplification is particularly common in diverse solid tumors. MYC amplification is observed in 30% of serous ovarian cancer, 20% of uterine serous carcinoma, 15% of esophageal and breast cancers, and is common (1-10%) in numerous other cancer types[7,26,27]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt's lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, which results in increased MYC expression[28,29].

Potential relevance: Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression[18,30,31,32].

Relevant Therapy Summary

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

KIT p.(M541L) c.1621A>C

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

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BMS-986158	✖	✖	✖	✖	● (I)
KB-0742	✖	✖	✖	✖	● (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 NCCN Information

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

NCCN information is current as of 2021-05-03. 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.(M541L) c.1621A>C

○ imatinib

Cancer type: Cutaneous Melanoma

Variant class: KIT activating 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 2.2021]

Clinical Trials Summary

KIT p.(M541L) c.1621A>C

NCT ID	Title	Phase
NCT04771520	Phase II Study of Avapritinib in Patients With CKIT or PDGFRA Mutation-Positive Malignant Solid Tumors	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
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

MYC amplification

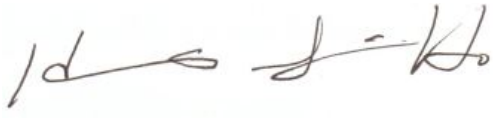
NCT ID	Title	Phase
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT03936465	Phase I Study of the Bromodomain (BRD) and Extra-Terminal Domain (BET) Inhibitor BMS-986158 in Pediatric Cancer	I
NCT04718675	Phase I, First-in-human, Open-label Dose Escalation and Cohort Expansion Study of KB-0742 in Patients With Relapsed or Refractory Solid Tumors or Non-Hodgkin Lymphoma	I

Signatures

Testing Personnel:

2021.07.15 16:32:33 +08'00'

Laboratory Supervisor:



2021.07.15 16:34:09 +08'00'

Pathologist:

2021.07.15 16:34:52 +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 2.2021]
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
18. Chen et al. Targeting oncogenic Myc as a strategy for cancer treatment. Signal Transduct Target Ther. 2018 Feb 23;3:5. doi: 10.1038/s41392-018-0008-7. eCollection 2018. PMID: 29527331
19. Dang. MYC on the path to cancer. Cell. 2012 Mar 30;149(1):22-35. PMID: 22464321
20. Dominguez-Sola et al. Non-transcriptional control of DNA replication by c-Myc. Nature. 2007 Jul 26;448(7152):445-51. PMID: 17597761
21. Wahlström et al. Impact of MYC in regulation of tumor cell metabolism. Biochim. Biophys. Acta. 2015 May;1849(5):563-9. PMID: 25038584
22. Dang et al. The c-Myc target gene network. Semin. Cancer Biol. 2006 Aug;16(4):253-64. PMID: 16904903
23. Blackwood et al. Myc and Max function as a nucleoprotein complex. Curr. Opin. Genet. Dev. 1992 Apr;2(2):227-35. PMID: 1638116
24. Chakraborty et al. A common functional consequence of tumor-derived mutations within c-MYC. Oncogene. 2015 Apr 30;34(18):2406-9. PMID: 24998853
25. Xu-Monette et al. Clinical and Biologic Significance of MYC Genetic Mutations in De Novo Diffuse Large B-cell Lymphoma. Clin. Cancer Res. 2016 Jul 15;22(14):3593-605. PMID: 26927665
26. Kalkat et al. MYC Deregulation in Primary Human Cancers. Genes (Basel). 2017 May 25;8(6). PMID: 28587062
27. Beroukhim et al. The landscape of somatic copy-number alteration across human cancers. Nature. 2010 Feb 18;463(7283):899-905. doi: 10.1038/nature08822. PMID: 20164920
28. Taub et al. Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. Proc Natl Acad Sci U S A. 1982 Dec;79(24):7837-41. PMID: 6818551

References (continued)

29. Ott et al. Understanding MYC-driven aggressive B-cell lymphomas: pathogenesis and classification. Hematology Am Soc Hematol Educ Program. 2013;2013:575-83. PMID: 24319234
30. Posternak et al. Strategically targeting MYC in cancer. F1000Res. 2016;5. PMID: 27081479
31. Carabet et al. Therapeutic Inhibition of Myc in Cancer. Structural Bases and Computer-Aided Drug Discovery Approaches. Int J Mol Sci. 2018 Dec 29;20(1). PMID: 30597997
32. Shahbazi et al. The Bromodomain Inhibitor JQ1 and the Histone Deacetylase Inhibitor Panobinostat Synergistically Reduce N-Myc Expression and Induce Anticancer Effects. Clin. Cancer Res. 2016 May 15;22(10):2534-44. PMID: 26733615