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: 邱鈺倫
Gender: Female
ID No.: K220923417
History No.: 41242006
Age: 49

Ordering Doctor: DOC8769F 黃紹禮
Ordering REQ.: 0BRFUEN
Signing in Date: 2022/01/21

Path No.: S111-98214
MP No.: MY22003
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/01/18

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

Table of Contents

Report Highlights

1 Relevant Biomarkers
1 Therapies Available
0 Clinical Trials

Relevant Acute Myeloid Leukemia Variants

Gene	Finding	Gene	Finding
ABL1	None detected	MECOM	None detected
ASXL1	None detected	MLLT3	None detected
CEBPA	None detected	MYH11	None detected
CREBBP	None detected	NPM1	None detected
FLT3	None detected	NUP214	None detected
IDH1	None detected	RARA	None detected
IDH2	None detected	RUNX1	None detected
KMT2A	None detected	TP53	None detected

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
SF3B1 p.(K666N) c.1998G>C splicing factor 3b subunit 1 Allele Frequency: 4.55% **Prognostic significance:** None **Diagnostic significance:** None	None	luspatercept	0

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
TET2 p.(Q1546) c.4636C>T, JAK2 p.(V617F) c.1849G>T*

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
SF3B1	p.(K666N)	c.1998G>C	COSM132937	chr2:198267359	4.55%	NM_012433.4	missense	2000
TET2	p.(Q1546*)	c.4636C>T	.	chr4:106196303	49.60%	NM_001127208.2	nonsense	1996
JAK2	p.(V617F)	c.1849G>T	COSM12600	chr9:5073770	86.62%	NM_004972.4	missense	1950
EZH2	p.(E745K)	c.2233G>A	.	chr7:148504761	46.47%	NM_004456.5	missense	1999

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
FHIT-TIRAP	FHIT-TIRAP.F8T4.Non-Targeted	chr3:59908072 - chr11:126168153	441

Biomarker Descriptions

JAK2 (Janus kinase 2)

Background: The JAK2 gene encodes a non-receptor, membrane associated protein tyrosine kinase (PTK). JAK2 is a member of the Janus kinase (JAK) family that includes JAK1, JAK2, JAK3, and TYK2. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[1]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[1,2,3]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit presentation of tumor antigens and contribute to immune evasion[4,5].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) has been associated with loss of heterozygosity on chromosome 9p and subsequently to the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[6,7]. The JAK2 V617F mutation has been observed rarely in acute myeloid leukemia (AML)[8,9]. Mutations in the pseudokinase domain of JAK2 including R683G have been detected in 8% of ALL[10,11]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR genes[12,13,14,15]. JAK2 fusions are infrequently observed in solid tumors[16]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[16].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. The JAK2 V617F mutation is considered diagnostic of the various MPNs including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)[17,18,19]. In addition to JAK2 V617F, JAK2 exon 12 mutations are also a major diagnostic criteria of PV[18]. Ruxolitinib[20] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012)

Biomarker Descriptions (continued)

and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[21]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[12,13,14,15].

SF3B1 (splicing factor 3b subunit 1)

Background: The SF3B1 gene encodes the splicing factor 3b subunit 1 protein, a core component of the U2 small nuclear ribonucleoprotein (snRNP) complex of the spliceosome responsible for RNA splicing. SF3B1 is involved in recognition of the branch point sequence during selection of the 3' splice site. Recurrent somatic mutations in SF3B1 and other components of the splicing machinery including SRSF2, U2AF1, and ZRSR2, are common in myelodysplasia. These components experience mutations in a mutually exclusive manner suggesting a common impact on RNA splicing and the pathogenesis of myelodysplasia[22]. SF3B1 mutations are believed to contribute to aberrant post-translational inactivation of the regulatory complex PPP2R5A of protein phosphatase 2A (PP2A), leading to the activation and stabilization of MYC activation and impairing apoptosis[23].

Alterations and prevalence: SF3B1 mutations occur in the majority (70-80%) of myelodysplastic syndromes (MDS) with ring sideroblasts (RS) and at lower frequency in other myeloid neoplasms including MDS without RS (7%), chronic myelomonocytic leukemia (5-6%), therapy-related acute myeloid leukemia (AML) or AML with MDS features (5%), and de novo AML (3%)[22,24,25]. Recurrent somatic SF3B1 mutations are also common in certain solid cancers including uveal melanoma (20-30%) and breast cancer (2%) and at lower frequencies in diverse cancer types[16,26,27,28,29,30,31,32]. Cancer-associated recurrent missense mutations in SF3B1 occur within the HEAT repeat domains 5-9 at codon positions R625, K666, K700, G742, and D781[33]. The functional significance of recurrent SF3B1 mutations is to alter branch point selection thus inducing cryptic 3' splice site selection[33,34,35]

Potential relevance: Currently, no therapies are approved for SF3B1 aberrations. SF3B1 mutations are associated with aggressive disease and shorter survival in patients diagnosed with chronic lymphocytic leukemia (CLL)[36]. Investigational inhibitors of the spliceosome are in early clinical development[37,38].

TET2 (tet methylcytosine dioxygenase 2)

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[39]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[40,41]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[42]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[39,40,41]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[43]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[40,44]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[18,45]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[18,46]

Relevant Therapy Summary

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

SF3B1 p.(K666N) c.1998G>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
luspatercept	✖	✖	✖	○	✖

Relevant Therapy Details

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 2021-11-01. For the most up-to-date information, search www.esmo.org.

SF3B1 p.(K666N) c.1998G>C

○ luspatercept

Cancer type: Myelodysplastic Syndrome **Variant class:** SF3B1 mutation

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

Population segment (Line of therapy):
- Refractory (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Myelodysplastic Syndromes [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.11.002]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

References

1. Babon et al. The molecular regulation of Janus kinase (JAK) activation. Biochem. J. 2014 Aug 15;462(1):1-13. PMID: 25057888
2. Müller et al. The protein tyrosine kinase JAK1 complements defects in interferon-alpha/beta and -gamma signal transduction. Nature. 1993 Nov 11;366(6451):129-35. PMID: 8232552
3. Ren et al. JAK1 truncating mutations in gynecologic cancer define new role of cancer-associated protein tyrosine kinase aberrations. Sci Rep. 2013 Oct 24;3:3042. PMID: 24154688
4. Zaretsky et al. Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. N. Engl. J. Med. 2016 Sep 1;375(9):819-29. PMID: 27433843
5. Garcia-Diaz et al. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. Cell Rep. 2017 May 9;19(6):1189-1201. PMID: 28494868
6. Baxter et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005 Mar 19-25;365(9464):1054-61. PMID: 15781101
7. Kralovics et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N. Engl. J. Med. 2005 Apr 28;352(17):1779-90. PMID: 15858187
8. Hidalgo-López et al. Morphologic and Molecular Characteristics of De Novo AML With JAK2 V617F Mutation. J Natl Compr Canc Netw. 2017 Jun;15(6):790-796. PMID: 28596259
9. Aynardi et al. JAK2 V617F-positive acute myeloid leukaemia (AML): a comparison between de novo AML and secondary AML transformed from an underlying myeloproliferative neoplasm. A study from the Bone Marrow Pathology Group. Br. J. Haematol. 2018 Jul;182(1):78-85. PMID: 29767839
10. Mullighan et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc. Natl. Acad. Sci. U.S.A. 2009 Jun 9;106(23):9414-8. PMID: 19470474
11. Scott. Lymphoid malignancies: Another face to the Janus kinases. Blood Rev. 2013 Mar;27(2):63-70. PMID: 23340138
12. Chase et al. Ruxolitinib as potential targeted therapy for patients with JAK2 rearrangements. Haematologica. 2013 Mar;98(3):404-8. PMID: 22875628
13. Rumi et al. Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J. Clin. Oncol. 2013 Jun 10;31(17):e269-71. PMID: 23630205
14. Schwaab et al. Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. Ann. Hematol. 2015 Feb;94(2):233-8. PMID: 25260694
15. Rumi et al. Efficacy of ruxolitinib in myeloid neoplasms with PCM1-JAK2 fusion gene. Ann. Hematol. 2015 Nov;94(11):1927-8. PMID: 26202607
16. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
17. Chen et al. Janus kinase deregulation in leukemia and lymphoma. Immunity. 2012 Apr 20;36(4):529-41. PMID: 22520846
18. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2021]
19. Swerdlow et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. WHO Classification of Tumours, Revised 4th Edition, Volume 2. WHO-2017
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202192s025lbl.pdf
21. Shin et al. Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations. Cancer Discov. 2017 Feb;7(2):188-201. PMID: 27903500
22. Yoshida et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature. 2011 Sep 11;478(7367):64-9. PMID: 21909114
23. Liu et al. Mutations in the RNA Splicing Factor SF3B1 Promote Tumorigenesis through MYC Stabilization. Cancer Discov. 2020 Mar 18. PMID: 32188705
24. Patnaik et al. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management. Am. J. Hematol. 2017 Mar;92(3):297-310. PMID: 28188970
25. Patnaik et al. Spliceosome mutations involving SRSF2, SF3B1, and U2AF35 in chronic myelomonocytic leukemia: prevalence, clinical correlates, and prognostic relevance. Am. J. Hematol. 2013 Mar;88(3):201-6. PMID: 23335386
26. 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
27. Ellis et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. Nature. 2012 Jun 10;486(7403):353-60. PMID: 22722193

References (continued)

28. Maguire et al. SF3B1 mutations constitute a novel therapeutic target in breast cancer. J. Pathol. 2015 Mar;235(4):571-80. PMID: 25424858
29. Harbour et al. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. Nat. Genet. 2013 Feb;45(2):133-5. PMID: 23313955
30. Martin et al. Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3. Nat. Genet. 2013 Aug;45(8):933-6. PMID: 23793026
31. Furney et al. SF3B1 mutations are associated with alternative splicing in uveal melanoma. Cancer Discov. 2013 Oct;3(10):1122-1129. PMID: 23861464
32. Dono et al. Mutation frequencies of GNAQ, GNA11, BAP1, SF3B1, EIF1AX and TERT in uveal melanoma: detection of an activating mutation in the TERT gene promoter in a single case of uveal melanoma. Br. J. Cancer. 2014 Feb 18;110(4):1058-65. PMID: 24423917
33. DeBoever et al. Transcriptome sequencing reveals potential mechanism of cryptic 3' splice site selection in SF3B1-mutated cancers. PLoS Comput. Biol. 2015 Mar;11(3):e1004105. PMID: 25768983
34. Darman et al. Cancer-Associated SF3B1 Hotspot Mutations Induce Cryptic 3' Splice Site Selection through Use of a Different Branch Point. Cell Rep. 2015 Nov 3;13(5):1033-45. PMID: 26565915
35. Alsafadi et al. Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage. Nat Commun. 2016 Feb 4;7:10615. doi: 10.1038/ncomms10615. PMID: 26842708
36. Wan et al. SF3B1 mutations in chronic lymphocytic leukemia. Blood. 2013 Jun 6;121(23):4627-34. PMID: 23568491
37. Seiler et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. Nat. Med. 2018 May;24(4):497-504. PMID: 29457796
38. Lee et al. Therapeutic targeting of splicing in cancer. Nat. Med. 2016 Sep 7;22(9):976-86. PMID: 27603132
39. Pan et al. The TET2 interactors and their links to hematological malignancies. IUBMB Life. 2015 Jun;67(6):438-45. PMID: 26099018
40. Ko et al. Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature. 2010 Dec 9;468(7325):839-43. PMID: 21057493
41. Solary et al. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014 Mar;28(3):485-96. PMID: 24220273
42. An et al. TET family dioxygenases and DNA demethylation in stem cells and cancers. Exp. Mol. Med. 2017 Apr 28;49(4):e323. PMID: 28450733
43. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2022]
44. Kosmider et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood. 2009 Oct 8;114(15):3285-91. PMID: 19666869
45. Arber et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. PMID: 27069254
46. Lundberg et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood. 2014 Apr 3;123(14):2220-8. PMID: 24478400