Taipei Veterans General Hospital

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Sample Information

Patient Name: 林正泰
Gender: Male
ID No.: A102543956
History No.: 10768464
Age: 77

Ordering Doctor: DOC1697J 蔡淳光
Ordering REQ.: H46NJAH
Signing in Date: 2023/06/07

Path No.: M112-00132
MP No.: MY23032
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/06/05

Reporting Doctor: DOC5444B 楊靜芬 (Phone: 8#5444)

Note:

Sample Cancer Type: Myeloproliferative Neoplasms

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Relevant Myeloproliferative Neoplasms Variants

Gene	Finding	Gene	Finding
ASXL1	None detected	MPL	None detected
CALR	None detected	SF3B1	None detected
EZH2	None detected	SH2B3	None detected
IDH1	None detected	SRSF2	None detected
IDH2	None detected	TET2	***TET2 p.(A951Lfs*2) c.2851delG***
JAK2	***JAK2 p.(V617F) c.1849G>T***	TP53	None detected
KMT2A	None detected	U2AF1	None detected
MECOM	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*JAK2 p.(V617F) c.1849G>T* Janus kinase 2 Allele Frequency: 77.76% **Diagnostic significance:** Polycythemia Vera, Essential Thrombocythemia, Primary Myelofibrosis	None	None	0

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

Prevalent cancer biomarkers without relevant evidence based on included data sources
*TET2 p.(A951Lfs*2) c.2851delG*

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
TET2	p.(A951Lfs*2)	c.2851delG	.	chr4:106157949	45.71%	NM_001127208.2	frameshift Deletion	1993
JAK2	p.(V617F)	c.1849G>T	COSM12600	chr9:5073770	77.76%	NM_004972.4	missense	1983
CEBPA	p.(H195_P196dup)	c.589_590insACCCGC	.	chr19:33792731	37.93%	NM_004364.4	nonframeshift Insertion	1168

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) 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].

Biomarker Descriptions (continued)

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[22]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[23,24]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[25]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[22,23,24]

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)[26]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[23,27]. 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[18,28]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[18,29]

Diagnostic Details

Current NCCN Information

NCCN information is current as of 2023-03-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

JAK2 p.(V617F) c.1849G>T

Diagnostic significance: Polycythemia Vera

Variant class: JAK2 V617F mutation

NCCN Recommendation category: 2A

Diagnostic notes:
- 2017 WHO Diagnostic Criteria for Polycythemia Vera

Reference: NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 3.2022]

Current ESMO Information

ESMO information is current as of 2023-03-01. For the most up-to-date information, search www.esmo.org.

JAK2 p.(V617F) c.1849G>T

Diagnostic significance: Essential Thrombocythemia

Variant class: JAK2 V617F mutation

Other criteria: BCR-ABL1 fusion negative

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

Diagnostic notes:
- Essential Thrombocythemia; The WHO 2008 diagnostic criteria
- Post Essential Thrombocythemia Myelofibrosis; International Working Group for Myeloproliferative Neoplasm Research and Treatment (IWG-MRT)

Reference: ESMO Clinical Practice Guidelines - ESMO-Philadelphia Chromosome-Negative Chronic Myeloproliferative Neoplasms [Ann Oncol (2015) 26 (suppl 5): v85-v99.]

Diagnostic significance: Primary Myelofibrosis

Variant class: JAK2 V617F mutation

Other criteria: BCR-ABL1 fusion negative

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

Diagnostic notes:
- The WHO 2008 diagnostic criteria

Reference: ESMO Clinical Practice Guidelines - ESMO-Philadelphia Chromosome-Negative Chronic Myeloproliferative Neoplasms [Ann Oncol (2015) 26 (suppl 5): v85-v99.]

Diagnostic significance: Polycythemia Vera

Variant class: JAK2 V617F mutation

Other criteria: BCR-ABL1 fusion negative

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

Diagnostic notes:
- Polycythemia Vera; The WHO 2008 diagnostic criteria
- Post Polycythemia Vera Myelofibrosis; International Working Group for Myeloproliferative Neoplasm Research and Treatment (IWG-MRT)

Reference: ESMO Clinical Practice Guidelines - ESMO-Philadelphia Chromosome-Negative Chronic Myeloproliferative Neoplasms [Ann Oncol (2015) 26 (suppl 5): v85-v99.]

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