Taipei Veterans General Hospital

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Sample Information

Patient Name: 蔡况治
Gender: Female
ID No.: W200235640
History No.: 36397292
Age: 66

Ordering Doctor: DOC1697J 蔡淳光
Ordering REQ.: 0CQBLEC
Signing in Date: 2023/08/24

Path No.: M112-00231
MP No.: MY23063
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/08/22

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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Relevant Biomarkers

No clinically significant biomarkers found in this sample.

Prevalent cancer biomarkers without relevant evidence based on included data sources
JAK2 p.(V617F) c.1849G>T, SH2B3 p.(Q353) c.1057C>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
JAK2	p.(V617F)	c.1849G>T	COSM12600	chr9:5073770	25.34%	NM_004972.4	missense	1985
SH2B3	p.(Q353*)	c.1057C>T	.	chr12:111885169	5.75%	NM_005475.3	nonsense	2000
TP53	p.(I232T)	c.695T>C	.	chr17:7577586	5.35%	NM_000546.5	missense	1999
U2AF1	p.(P40=)	c.120G>A	.	chr21:44524437	49.15%	NM_006758.2	synonymous	2000

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. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of PV[17,18]. Ruxolitinib[19] (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. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[20]. 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].

SH2B3 (SH2B adaptor protein 3)

Background: The SH2B3 gene encodes SH2B adapter protein 3, a member of the Src homology 2-B (SH2B) adapter family of proteins which are involved in the regulation of receptor tyrosine kinase (RTK) and cytokine mediated signaling[22]. SH2B3 contains an SH2 domain, responsible for binding phosphorylated tyrosine residues on activated RTKs as well as several other proteins[22]. Specifically, SH2B3 is known to inhibit RTK and cytokine mediated activation of the RAS/RAF/MEK/ERK and JAK/STAT pathways and contributes to the negative regulation of cellular processes such as hematopoiesis and inflammation[22,23]. SH2B3 is the target of somatic mutations in hematological malignancies as well as solid tumors[16,24]. Loss of function mutations in SH2B3 are reported to contribute to leukemic transformation, supporting its role as tumor suppressor gene in cancer[22,24]. Additionally, germline mutations in SH2B3 confer a predisposition to acute lymphoblastic leukemia (ALL) and are associated with myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPN)[25,26].

Alterations and prevalence: Mutations in SH2B3 have been reported in approximately 6% of MDS/MPN, 4% of B-cell lymphoblastic leukemia/lymphoma, 2.5% of MPN, and 1.5% of MDS and ALL[25,27]. Additionally, SH2B3 mutations are reported in solid tumors including approximately 2% of uterine cancer and 1% of lung, colorectal, esophageal, bladder, and head and neck cancers[16].

Potential relevance: SH2B3 mutations are associated with inferior survival in essential thrombocythemia (ET), independent of the age or karyotype[17]

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