Taipei Veterans General Hospital

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Sample Information

Patient Name: 張承平
Gender: Male
ID No.: A101030898
History No.: 28079869
Age: 75

Ordering Doctor: DOC1654E 林庭安
Ordering REQ.: 0BWPZTD
Signing in Date: 2022/06/23

Path No.: S111-99623
MP No.: MY22015
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/06/16

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Myelodysplastic Syndrome Variants

Gene	Finding	Gene	Finding
ASXL1	None detected	NPM1	None detected
BCOR	None detected	NRAS	None detected
CBL	None detected	NUP214	None detected
CREBBP	None detected	RUNX1	None detected
ETV6	None detected	SF3B1	None detected
EZH2	None detected	SRSF2	***SRSF2 p.(P95R) c.284C>G***
FLT3	None detected	STAG2	***STAG2 p.(Y195*) c.585T>A***
GATA2	None detected	TP53	None detected
IDH2	None detected	U2AF1	None detected
KIT	None detected	WT1	None detected
KMT2A	None detected	ZRSR2	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	*SRSF2 p.(P95R) c.284C>G* serine and arginine rich splicing factor 2 Allele Frequency: 39.09% **Prognostic significance:** NCCN: Poor	None	None	0
IA	*STAG2 p.(Y195*) c.585T>A* stromal antigen 2 Allele Frequency: 77.16% **Prognostic significance:** NCCN: Poor	None	None	0

Public data sources included in relevant therapies: FDA1, 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.(Q674Ifs*12) c.2020_2039delCAGTCACTGTGTGGCACTAG*

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.(Q674Ifs*12)	c.2020_2039delCAGTCACTGTGTGGCACTAG	.	chr4:106157117	43.74%	NM_001127208.2	frameshift Deletion	1982
SRSF2	p.(P95R)	c.284C>G	COSM211661	chr17:74732959	39.09%	NM_003016.4	missense	1929
STAG2	p.(Y195*)	c.585T>A	.	chrX:123179136	77.16%	NM_001042749.2	nonsense	1992
DNMT3A	p.(P743H)	c.2228C>A	.	chr2:25463265	3.30%	NM_022552.4	missense	1999

Biomarker Descriptions

SRSF2 (serine and arginine rich splicing factor 2)

Background: The SRFS2 gene encodes the serine/arginine (SR)-rich splicing factor 2, a member of the SR-rich family of pre-mRNA splicing factors which make up part of the spliceosome. SRFS2 contains an RNA recognition motif (RRM) that recognizes and binds exonic splicing enhancers (ESE) in a sequence-specific manner[1]. SR proteins are essential regulators of alternative RNA splicing due to their ability to bind RNA and interact with other splicing factors. These proteins can influence the exclusion of cassette exons, a form of alternative splicing also known as exon skipping, which allows for the production of different protein isoforms[1,2]. SRSF2 is the target of somatic missense mutations and in-frame deletions in hematological malignancies, particularly myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and myeloproliferative neoplasms (MPN)[3,4,5]. Such mutations in SRSF2 result in a differential gain of function which influences cassette exon exclusion, thereby supporting an oncogenic role in cancer[6].

Alterations and prevalence: Mutations in SRSF2 are observed in approximately 10% of MDS cases and 30-40% of CMML[4,7,8]. Missense mutations at P95 are most recurrent, which leads to an amino acid change from proline to histidine (H), leucine (L), or arginine (R)[8]. Specifically, the P95H substitution alters SRSF2 affinity for ESEs and drives preferential recognition of cassette exons containing C- versus G-rich ESEs[5,6]. Although less prevalent, recurrent in-frame deletions (P95H_R102del) are observed in primary myelofibrosis (PMF)[9]. This mutation results in the deletion of 8 amino acids which has been shown to exhibit greater variation of splicing events relative to the P95 missense mutation alone[10].

Potential relevance: In CMML, SRSF2 mutations are often enriched and can be used to support diagnosis[11,12]. SRSF2 mutations confer poor prognosis in MDS and systemic mastocytosis (SM) and are associated with decreased overall survival (OS)[12,13,14]. In MPN, SRSF2

Biomarker Descriptions (continued)

mutations are considered high-risk mutations and are independently associated with inferior OS as well as leukemia-free survival[15,16]. Additionally, SRSF2 mutations are predictive of leukemic transformation in patients with PMF[15].

STAG2 (stromal antigen 2)

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[17,18]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[19,20]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[19,21].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[12]. Somatic mutations in STAG2 are observed in various solid tumors including 14% of bladder cancer, 10% of uterine cancer, 3% of stomach cancer, and 4% of lung adenocarcinoma[22]. In addition, mutations in STAG2 are observed in 5-10% of myelodysplastic syndrome(MDS), 3% of acute myeloid leukemia, and 2% of diffuse large B-cell lymphoma[12,22].

Potential relevance: Nonsense, frameshift, and splice site STAG2 mutations are associated with poor prognosis in MDS[12]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[23].

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[24]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[25,26]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[27]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[24,25,26]

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)[12]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[25,28]. 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[11,15]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[15,29]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2022-03-31. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

SRSF2 p.(P95R) c.284C>G

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** SRSF2 P95 mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® associate the biomarker with poor prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2022]

STAG2 p.(Y195*) c.585T>A

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** STAG2 truncating mutation

NCCN Recommendation category: 2A

Summary:

- NCCN Guidelines® associate the biomarker with poor prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2022]

Signatures

Testing Personnel:  2022.06.24 14:11:32 +08'00'

Laboratory Supervisor:  2022.06.24 14:11:51 +08'00'

Pathologist:  2022.06.24 14:12:03 +08'00'

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