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: 張麗卿
Gender: Male
ID No.: Y100209067
History No.: 44507779
Age: 86

Ordering Doctor: DOC6499J 鍾承翰
Ordering REQ.: 0CUHTJG
Signing in Date: 2023/12/06

Path No.: M112-00312
MP No.: MY23083
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/12/05

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*CEBPA p.(G114Rfs*54) c.340_344delGGCCC, CEBPA p.(G116Rfs*54) c.345_346insC* CCAAT enhancer binding protein alpha Allele Frequency: 46.86%, 47.29% (2 variants)	None	allogeneic stem cells cytarabine cytarabine + daunorubicin cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy	0

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

TET2 p.(D1129) c.3384_3385insT*

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.(D1129*)	c.3384_3385insT	.	chr4:106158482	47.43%	NM_001127208.2	nonsense	1988
CEBPA	p.(G116Rfs*54)	c.345_346insC	.	chr19:33792975	47.29%	NM_004364.4	frameshift Insertion	1641
CEBPA	p.(G114Rfs*54)	c.340_344delGGCCC	.	chr19:33792976	46.86%	NM_004364.4	frameshift Deletion	1641

Biomarker Descriptions

CEBPA (CCAAT enhancer binding protein alpha)

Background: The CEBPA gene encodes the enhancer binding protein alpha, a member of the basic region leucine zipper family of transcription factors that recognizes the CCAAT promoter[1]. CEBPA gives rise to two protein isoforms— p42 and p30, where p30 is the shorter isoform lacking the N-terminal 117 amino acids that is present in p42. Both isoforms contain the basic leucine zipper (bZip) domain involved in hetero/homo-dimerization with other CEBP family members and are required for DNA binding[1]. CEBPA is a tumor suppressor gene that plays a critical role in the development of granulocytes[1]. Specifically, CEBPA can influence the expression of granulocyte colony-stimulating factor (G-CSF) and interleukin 6 (IL-6), which are required for neutrophil maturation[2,3]. CEBPA also directly interacts and inhibits cell cycle kinases, including CDK2 and CDK4, thereby hindering cell proliferation[4]. CEBPA is the target of monoallelic or biallelic mutations leading to a loss of function, which can promote the development of cancers such as acute myeloid leukemia (AML)[5]. Germline mutations in CEBPA are also frequent among AML patients and are associated with predisposition to the disease[6,7].

Alterations and prevalence: Mutations in CEBPA are reported in 6-18% of all AML cases[8,9,10,11]. In AML, CEBPA mutations are observed to occur as either monoallelic (single mutant) or bi-allelic (double mutant)[11,12,13]. Biallelic CEBPA mutations are heterozygous and occur as a specific combination of an N-terminal frameshift on one allele and a C-terminal in frame mutation on the other, referred to as an N/C mutant[13,14]. Frameshift mutations result in the N-terminal truncation of approximately 120 amino acids while preserving the remaining 300 amino acids that are initiated further downstream[14]. C-terminal in-frame mutations disrupt the bZip domain which interferes with DNA binding and hetero/homo-dimerization with other CEBP family members. Specifically, N/C mutants possess one N-terminal truncated allele coding for the p30 isoform while the other allele codes for either p30 or p42 isoforms harboring C-terminal mutations[13].

Potential relevance: Single mutations located in the basic leucine zipper (bZIP) region of the gene (smbZIP-CEBPA) as well as biallelic CEBPA mutations are recognized as a diagnostic entity for AML with CEBPA mutation by the World Health Organization (WHO)[15]. The in-frame mutations affecting the basic leucine zipper (bZIP) region in biallelic CEBPA as well as in smbZIP are associated with a favorable prognosis in AML[16,17].

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[18]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[19,20]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[21]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[18,19,20]

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)[22]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[19,23]. 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[24]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[24,25]

Relevant Therapy Summary

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

CEBPA p.(G114Rfs*54) c.340_344delGGCCC, CEBPA p.(G116Rfs*54) c.345_346insC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✖	○	✖	✖	✖
cytarabine	✖	○	✖	✖	✖
cytarabine + daunorubicin	✖	○	✖	✖	✖
cytarabine + idarubicin	✖	○	✖	✖	✖
cytarabine + mitoxantrone	✖	○	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	○	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim	✖	○	✖	✖	✖

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 2023-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

CEBPA p.(G114Rfs*54) c.340_344delGGCCC, CEBPA p.(G116Rfs*54) c.345_346insC

○ Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

○ cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

CEBPA p.(G114Rfs*54) c.340_344delGGCCC, CEBPA p.(G116Rfs*54) c.345_346insC (continued)

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

CEBPA p.(G114Rfs*54) c.340_344delGGCCC, CEBPA p.(G116Rfs*54) c.345_346insC (continued)

○ cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

○ gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

Other criteria: CD33 positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

○ gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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