Taipei Veterans General Hospital

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Sample Information

Patient Name: 蔡國雄
Gender: Male
ID No.: P121745534
History No.: 43629385
Age: 60

Ordering Doctor: DOC8919E 周逸峰
Ordering REQ.: 0BWRAAC
Signing in Date: 2022/06/23

Path No.: S111-99624
MP No.: MY22016
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/06/17

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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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	***RUNX1-RUNX1T1 fusion***
KMT2A	None detected	TP53	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*RUNX1-RUNX1T1 fusion* RUNX family transcription factor 1 - RUNX1 partner transcriptional co-repressor 1	cytarabine + daunorubicin cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy	None	0
	Prognostic significance: ELN 2017: Favorable **Diagnostic significance:** Acute Myeloid Leukemia			

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.(L1447Rfs*33) c.4339_4340insGTTACCC*

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.(L1447Rfs*33)	c.4339_4340insGTTACCC	.	chr4:106193877	44.75%	NM_001127208.2	frameshift Insertion	1991
CSF3R	p.(E815*)	c.2442_2443insT	.	chr1:36932107	46.76%	NM_156039.3	nonsense	1989
SH2B3	p.(D569Y)	c.1705G>T	.	chr12:111886083	48.95%	NM_005475.3	missense	2000
CEBPA	p.(H195_P196dup)	c.589_590insACCCGC	.	chr19:33792731	22.32%	NM_004364.4	nonframeshift Insertion	

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
RUNX1-RUNX1T1	RUNX1-RUNX1T1.R3R3	chr21:36231771 - chr8:93029591	25898

Biomarker Descriptions

RUNX1 (RUNX family transcription factor 1)

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[1]. All RUNX proteins share several conserved regions with similar functionality including a highly conserved N-terminal 'runt' domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[2]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[3,4]. RUNX1 is frequently mutated in various hematological malignancies[4]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[5,6]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[4].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[7]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6-RUNX1 fusion and is observed in 20-25% of

Biomarker Descriptions (continued)

childhood ALL[8,9,10]. This translocation is also observed in adult ALL at a lower frequency (2%)[9,10]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1-RUNX1T1 fusion and is observed in 5-10% of AML[11]. The RUNX1-RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNXT1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[4,11]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[4]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[4,12,13,14].

Potential relevance: The t(8;21)(q22;q22.1)/RUNX1-RUNX1T1 translocation is recognized as a distinct AML disease category by the World Health Organization (WHO)[15]. Additionally, AML with RUNX1 mutations is a provisional entity in the WHO[15]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1-RUNX1T1 in AML and t(12;21)(q34;q11)/ETV6-RUNX1 in ALL, are associated with favorable risk[12,16]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[12,13,17]

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)[13]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[19,22]. 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[15,23]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[23,24]

Relevant Therapy Summary

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

RUNX1-RUNX1T1 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	●	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
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 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.

RUNX1-RUNX1T1 fusion

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

● cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

● cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

RUNX1-RUNX1T1 fusion (continued)

cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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 2022-03-31. For the most up-to-date information, search www.esmo.org.

RUNX1-RUNX1T1 fusion

● gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

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

Population segment (Line of therapy):
- Core Bindig Factor (Induction therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Acute Myeloblastic Leukaemia in Adult Patients [Ann Oncol (2020); 31(6): 697-712.]

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.

RUNX1-RUNX1T1 fusion

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

NCCN Recommendation category: 2A

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

Current ESMO Information

ESMO information is current as of 2022-03-31. For the most up-to-date information, search www.esmo.org.

RUNX1-RUNX1T1 fusion

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

Reference: ESMO Clinical Practice Guidelines - ESMO-Acute Myeloblastic Leukaemia in Adult Patients [Ann Oncol (2020); 31(6): 697-712.]

Diagnostic 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.

RUNX1-RUNX1T1 fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: t(8;21)

NCCN Recommendation category: 2A

Diagnostic notes:
- WHO 2016 classification defined as ≥20% blasts in blood or bone marrow, or in appropriate clinical setting with <20% blasts and recurrent cytogenetic abnormalities.

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

Diagnostic significance: Acute Myeloid Leukemia

Variant class: t(8;21)

NCCN Recommendation category: 2A

Diagnostic notes:
- Karyotypes t(8;21), inv16, and t(15;17) are considered to be Acute Myeloid Leukemia even if the marrow blast count is less than 20%

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

Current ESMO Information

ESMO information is current as of 2022-03-31. For the most up-to-date information, search www.esmo.org.

RUNX1-RUNX1T1 fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

Diagnostic notes:
- AML with recurrent genetic abnormalities; WHO classification of AML

Reference: ESMO Clinical Practice Guidelines - ESMO-Acute Myeloblastic Leukaemia in Adult Patients [Ann Oncol (2020); 31(6): 697-712.]

Signatures

Testing Personnel:  2022.06.24 14:25:05 +08'00'

Laboratory Supervisor:  2022.06.24 14:25:18 +08'00'

Pathologist:  2022.06.24 14:25:30 +08'00'

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