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Sample Information

Patient Name: 張予欣
Gender: Female
ID No.: J223599592
History No.: 44280286
Age: 7

Ordering Doctor: DOC3939K 侯明欣
Ordering REQ.: 0CUSBUV
Signing in Date: 2023/12/14

Path No.: M112-00327
MP No.: MY23085
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/12/14

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*RUNX1::MECOM fusion* RUNX family transcription factor 1 - MDS1 and EVI1 complex locus	allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine liposomal cytarabine-daunorubicin CPX-351	None	0

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		venetoclax + chemotherapy		
	Diagnostic significance: Acute Myeloid Leukemia			

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
CBL p.(C416R) c.1246T>C

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
CBL	p.(C416R)	c.1246T>C	COSM1724993	chr11:119149238	51.53%	NM_005188.4	missense	1999
RB1	p.(T58I)	c.173C>T	.	chr13:48881451	52.50%	NM_000321.2	missense	1998
CEBPA	p.(H195_P196dup)	c.589_590insACCCGC	.	chr19:33792731	37.04%	NM_004364.4	nonframeshift Insertion	945
BCOR	p.(A1527=)	c.4581C>T	.	chrX:39916422	49.40%	NM_001123385.2	synonymous	2000

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
RUNX1-MECOM	RUNX1-MECOM.R4M2	chr21:36206707 - chr3:169099312	7751
RUNX1-MECOM	RUNX1-MECOM.R3M2	chr21:36231771 - chr3:169099312	2061

Biomarker Descriptions

CBL (Cbl proto-oncogene)

Background: The CBL gene encodes the casitas B-lineage lymphoma (CBL) ubiquitin ligase, a member of the ubiquitin ligase (E3) protein family that also includes CBL-b and CBL-c[1]. CBL proteins are characterized by their highly conserved N-terminal tyrosine kinase binding (TKB) domain and RING finger (RF) catalytic domain which are directly involved in the regulation of receptor tyrosine kinase (RTK) signaling[1,2]. Upon recognition of an activated RTK via its TKB domain, CBL mediates the transfer of ubiquitin from the ubiquitin-conjugating enzyme (E2) via its RF domain, consequently targeting the RTK for proteasome degradation. CBL can also function as an adaptor protein via recruitment of signaling molecules to active RTKs[2]. CBL is the target of genetic aberrations, including missense mutations and translocations, which can lead to oncogenic transformation in hematological malignancies as well as solid tumors[2,3,4,5]. Mutations in CBL often result in a loss of E3 ligase activity, thereby preventing proteasome-mediated RTK degradation, which supports the role of CBL as a tumor suppressor gene[3]. However, CBL mutants often maintain their adapter function, contributing to their transforming potential and suggesting a simultaneous oncogenic role for CBL in cancer[2]. Hereditary mutations in CBL lead to constitutive activation of RAS and MAPK pathways resulting in genetic disorders known as RASopathies which can lead to increased cancer risk[6].

Alterations and prevalence: Genetic alterations in CBL were first recognized in acute myeloid leukemia (AML) as a result of an interstitial deletion leading to MLL-CBL fusion[7,8]. However, fusions involving CBL are relatively rare. Aberrations in CBL most often involve missense mutations which commonly cluster in the linker region or RF domain corresponding to exons 8 and 9[2,3]. Such mutations lead to disruption of E3 ligase activity and have been reported in systemic mastocytosis (SM), 1-3% of de novo AML, 10% of secondary AML, 8% of atypical AML, and 10-15% of juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML)[2,9,10,11,12,13,14]. Mutations in CBL have also been reported in 1-6% of melanomas, lung, stomach, colorectal, esophageal, and uterine cancers[5,11].

Biomarker Descriptions (continued)

Potential relevance: Mutations in CBL confer adverse prognosis in SM and have been shown to be independently predictive of inferior survival[10,15].

MECOM (MDS1 and EVI1 complex locus)

Background: The MECOM gene encodes the MDS1 and EVI1 complex locus (MECOM), a zinc-finger transcriptional factor that regulates hematopoietic cell differentiation[16]. The MECOM locus encodes multiple alternative splice variants that result in MDS1-EVI1, MDS1, and EVI1 protein isoforms[17]. The EVI1 isoform is the most abundant and oncogenic form of MECOM that is expressed in various cancers including acute myeloid leukemia (AML)[17,18]. MECOM is a frequent target of chromosomal translocation which can lead to MECOM overexpression and leukemogenesis[19].

Alterations and prevalence: Somatic mutations MECOM are observed in up to 22% of malignant melanoma; 75% of these mutations are missense and the remaining 25% are truncating mutations[11,20,21]. MECOM amplifications are observed in up to 35% of lung squamous cell carcinoma, 30% of ovarian serous cystadenocarcinoma, and 20% of esophageal adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[11,21]. MECOM rearrangements occur with various partner genes including ETV6, RUNX1, and H2AFY[22]. The t(3;21)(q26;q22) translocation that results in the MECOM-RUNX1 fusion is most commonly observed in chronic myeloid leukemia (CML) in blast crisis. The t(3;3)(q21.3;q26.2)/ inv(3)(q21.3;q26.3) translocation, also referred to as inv(3)/t(3;3), results in a GATA2-MECOM fusion and is observed in AML, primary myelofibrosis (PMF), and myelodysplastic syndrome (MDS)[6,23,24]. The inv(3)/ t(3;3) translocation repositions the distal GATA enhancer element and activates MECOM expression while simultaneously causing GATA2 haploinsufficiency[25].

Potential relevance: AML with MECOM rearrangement is considered a distinct molecular subtype of AML as defined by the World Health Organization (WHO)[26]. MECOM rearrangements, including GATA2-MECOM fusions, are associated with poor/adverse risk in AML[23,27]. Inv(3) is associated with poor cytogenetic risk in MDS as defined by the revised international prognostic scoring system (IPSS-R) scoring system[6]. In PMF, inv(3) is considered an unfavorable karyotype associated with intermediate risk as defined by the dynamic international prognostic scoring system (DIPSS)-Plus scoring system[24]. MECOM overexpression is observed in 10% of de novo AML associated with poor prognosis, and is commonly found in MLL-rearranged cases[28,29]. Amplification of MECOM is associated with favorable prognosis in ovarian cancer[30].

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[31]. 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[32]. 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[33,34]. RUNX1 is frequently mutated in various hematological malignancies[34]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[35,36]. 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)[34].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[37]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6-RUNX1 fusion and is observed in 20-25% of childhood ALL[38,39,40]. This translocation is also observed in adult ALL at a lower frequency (2%)[39,40]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1-RUNX1T1 fusion and is observed in 5-10% of AML[41]. The RUNX1-RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[34,41]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[34]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[6,11,23,34].

Potential relevance: AML with RUNX1-RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[23,26]. 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[27,42]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[6,15,27].

Relevant Therapy Summary

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

RUNX1::MECOM fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✖	●	✖	✖	✖
azacitidine	✖	●	✖	✖	✖
cytarabine	✖	●	✖	✖	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + daunorubicin + etoposide	✖	●	✖	✖	✖
cytarabine + etoposide + idarubicin	✖	●	✖	✖	✖
cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
liposomal cytarabine-daunorubicin CPX-351	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

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.

RUNX1::MECOM fusion

● azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 1

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

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

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 1

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

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

● cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 1

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

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

● cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 1

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

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

RUNX1::MECOM fusion (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 1

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

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

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

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 + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

RUNX1::MECOM fusion (continued)

decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

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liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

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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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

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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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

RUNX1::MECOM fusion (continued)

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

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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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2A

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

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

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2B

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

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

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2B

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

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

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2B

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

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

RUNX1::MECOM fusion (continued)

cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2B

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

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

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 2B

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

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

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venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 3

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

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

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** MECOM fusion

NCCN Recommendation category: 3

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

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

Diagnostic Details

Current ESMO Information

ESMO information is current as of 2023-09-01. For the most up-to-date information, search www.esmo.org.

RUNX1::MECOM fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: t(3;21)(q26.2;q22.1)

Diagnostic notes:

- AML with myelodysplasia-related changes; WHO classification of AML

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

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