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Sample Information

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Gender: Male
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History No.: 49211554
Age: 55

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Ordering REQ.: 0CERTWK
Signing in Date: 2023/01/12

Path No.: M112-00005
MP No.: MY23003
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/01/06

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	***CEBPA p.(H24Afs*84) c.68_69insC***	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	None detected
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	*CEBPA p.(H24Afs*84) c.68_69insC* CCAAT enhancer binding protein alpha Allele Frequency: 42.90% **Prognostic significance:** ELN 2017: Favorable **Diagnostic significance:** Acute Myeloid Leukemia	cytarabine + daunorubicin cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy	None	0

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
*DNMT3A p.(I471Lfs*180) c.1410delT, TET2 p.(P554Afs*13) c.1659_1660insG, CSF3R p.(T618I) c.1853C>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
CSF3R	p.(T618I)	c.1853C>T	COSM1737962	chr1:36933434	45.10%	NM_156039.3	missense	2000
DNMT3A	p.(I471Lfs*180)	c.1410delT	.	chr2:25469047	47.86%	NM_022552.4	frameshift Deletion	1987
TET2	p.(P554Afs*13)	c.1659_1660insG	.	chr4:106156757	49.00%	NM_001127208.2	frameshift Insertion	1992
CEBPA	p.(H24Afs*84)	c.68_69insC	COSM18922	chr19:33793252	42.90%	NM_004364.4	frameshift Insertion	1979
TET2	p.(A1876T)	c.5626G>A	.	chr4:106197293	47.90%	NM_001127208.2	missense	1998
CEBPA	p.(R297P)	c.890_891delGCinsCT	.	chr19:33792430	47.12%	NM_004364.4	missense	1995

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

Biomarker Descriptions (continued)

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: Biallelic CEBPA mutations are recognized as a diagnostic entity for AML by the World Health Organization (WHO)[15]. Biallelic CEBPA mutations are associated with favorable risk and improved prognosis in AML[11,15,16,17,18].

CSF3R (colony stimulating factor 3 receptor)

Background: The CSF3R gene encodes the colony stimulating factor 3 trans-membrane receptor for the granulocyte colony-stimulating factor (G-CSF) ligand. CSF3R is a class I membrane-bound cytokine receptor, which lacks intrinsic kinase activity and therefore must interact with downstream proteins for activation[19]. Upon ligand activation, CSF3R activates downstream oncogenic pathways by interacting with intracellular signaling proteins through its cytoplasmic tyrosine residues, including proteins from the JAK/STAT, MAPK/ERK, and PI3K/AKT pathways[19,20]. Nonsense and frameshift mutations in CSF3R target and truncate its cytoplasmic tail, subsequently impairing the internalization signal of the receptor and leading to an overexpression CSF3R on the cell surface[21,22,23]. Missense mutations in the proximal membrane lead to increased dimerization of the receptor, independent of G-CSF binding[21,22,23]. These mutations promote constitutive oncogenic JAK-STAT signaling, and increase granulocyte proliferation and survival signaling of hematopoietic progenitor cells[19,24].

Alterations and prevalence: CSF3R activating mutations are observed in up to 80% of patients with chronic neutrophilic leukemia (CNL), and in up to 59% of patients with atypical chronic myelogenous leukemia (aCML)[21,25]. CSF3R mutations occur in 0.5-1% of adult acute myeloid leukemia (AML) and in 2.4% of pediatric AML[25]. In solid malignancies, CSF3R mutations are observed in up to 5% of uterine carcinosarcoma and skin cutaneous melanoma[8,26]. Somatic mutations identified in CNL and AML include T615A, T618I, and T640N missense mutations, as well as truncating mutations at Q749, Q754, Y767, S783, Y787, and P820[25]. T618I mutation is the most frequent variant observed in CNL[27].

Potential relevance: CSF3R activating mutations including T618I are a diagnostic criteria for CNL as defined by the World Health Organization (WHO)[15]. Mutations in CSF3R are observed in patients with severe congenital neutropenia, which can progress to AML. CSF3R mutations frequently co-occur with CEBPA, and these co-mutations are associated with unfavorable prognosis in AML[25,28,29]. In independent reports, a CNL patient and an aCML patient with the proximal membrane T618I mutation demonstrated sensitivity to JAK1/2 inhibitor, ruxolitinib[21,30].

DNMT3A (DNA methyltransferase 3 alpha)

Background: The DNMT3A gene encodes the DNA methyltransferase 3 alpha which functions as a de novo methyltransferase (DNMT) with equal methylation efficiency for unmethylated and hemimethylated DNA[31]. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression[32,33].

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)[8,18,34,35,36,37,38]. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer[8,39]. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported[8,34]. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations[40,41]. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation[42,43]. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity[44].

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML[34,37,38,41]. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)[45].

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[46]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[47,48]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[49]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[46,47,48]

Biomarker Descriptions (continued)

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)[39]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[47,50]. 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[15,51]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[51,52]

Relevant Therapy Summary

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

CEBPA p.(H24Afs*84) c.68_69insC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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 2022-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

CEBPA p.(H24Afs*84) c.68_69insC

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia

Variant class: CEBPA mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

CEBPA p.(H24Afs*84) c.68_69insC (continued)

cytarabine + idarubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + mitoxantrone

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

CEBPA p.(H24Afs*84) c.68_69insC (continued)

gemtuzumab ozogamicin + cytarabine + daunorubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2022-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

CEBPA p.(H24Afs*84) c.68_69insC

Prognostic significance: ELN 2017: Favorable

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

NCCN Recommendation category: 2A

Summary:
- Genetic Abnormality: Biallelic mutated CEBPA.

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Current ESMO Information

ESMO information is current as of 2022-11-01. For the most up-to-date information, search www.esmo.org.

CEBPA p.(H24Afs*84) c.68_69insC

Prognostic significance: ELN 2017: Favorable

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

Summary:
- Double-mutant CEBPA

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

Diagnostic Details

Current ESMO Information

ESMO information is current as of 2022-11-01. For the most up-to-date information, search www.esmo.org.

CEBPA p.(H24Afs*84) c.68_69insC

Diagnostic significance: Acute Myeloid Leukemia

Variant class: CEBPA mutation

Diagnostic notes:

- CEBPA biallelic mutations; 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

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