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Sample Information

Patient Name: 廖天才
Gender: Male
ID No.: D100583455
History No.: 47530994
Age: 88

Ordering Doctor: DOC1751J 蕭樑材
Ordering REQ.: H46AEK8
Signing in Date: 2023/04/14

Path No.: M112-00065
MP No.: MY23021
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/04/10

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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Report Highlights

1 Relevant Biomarkers
4 Therapies Available
0 Clinical Trials

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	***NPM1 p.(W288Cfs*12) c.863_864insTCTG***
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	*NPM1 p.(W288Cfs*12) c.863_864insTCTG* nucleophosmin 1 Allele Frequency: 60.87% **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
TET2 p.(Q892) c.2674C>T, ZRSR2 p.(G438Afs*?) c.1313_1314delGCinsCAGCCGG, TET2 p.(K982*) c.2944A>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
TET2	p.(Q892*)	c.2674C>T	.	chr4:106157773	36.12%	NM_001127208.2	nonsense	227
TET2	p.(K982*)	c.2944A>T	.	chr4:106158043	35.96%	NM_001127208.2	nonsense	317
NPM1	p.(W288Cfs*12)	c.863_864insTCTG	COSM17559	chr5:170837547	60.87%	NM_002520.6	frameshift Insertion	23
ZRSR2	p.(G438Afs*?)	c.1313_1314delGCinsCAGCCGG	.	chrX:15841229	78.38%	NM_005089.3	frameshift Block Substitution	74
BRAF	p.(R239*)	c.715C>T	.	chr7:140501357	8.51%	NM_004333.6	nonsense	141

Biomarker Descriptions

NPM1 (nucleophosmin 1)

Background: The NPM1 gene encodes the nucleophosmin protein, a histone chaperone of the nucleophosmin/nucleoplasmin family, which also includes NPM2 and NPM3[1]. NPM1 functions as an oncogene and tumor suppressor, and is important in maintaining genomic stability, DNA repair, and apoptosis[1,2]. NPM1 has a highly conserved N-terminal region which constitutes the core domain responsible for oligomerization, an acidic domain, a nuclear localization signal, and a disorganized C-terminal region which is required for nucleolar localization[1]. Oligomerization of NPM1 localizes the protein in the nucleus of proliferating cells where it binds to Akt in response to growth factor stimulation and escapes proteolytic degradation by caspase activity, thereby promoting cell survival[1,2]. NPM1 is one of the most frequently altered genes in hematological cancers[3]. Most NPM1 mutations occur in the C-terminus, impacting protein folding or the nucleolar localization signal, and result in the localization of NPM1 to the cytoplasm (NPMc) instead of to the nucleus[1].

Alterations and prevalence: NPM1 mutations are observed in 45-60% of AML with a normal karyotype (NK-AML), 28-35% of de novo acute myeloid leukemia (AML) and are frequently co-mutated with DNMT3A and/or FLT3-ITD[4,5,6]. NPM1 fusions are associated with distinct partner genes in acute promyelocytic leukemia (APL), anaplastic large-cell lymphoma (ALCL), AML, and myelodysplasia[3]. Specifically, NPM1-ALK fusion is found in 30% of all ALCL and this specific fusion is observed in 85% of ALK-positive ALCL[1]. The t(5;17)(q35;q21) translocation that results in NPM1-RARA fusion is observed in APL[7].

Potential relevance: NPM1 mutated AML is recognized as a distinct diagnostic disease entity by the World Health Organization (WHO)[8]. NPM1 mutations are associated with better outcomes, increased complete remission, and improved overall survival in AML[4,6]. NPM1 without FLT3-ITD mutations or with <0.5 allelic ratio FLT3-ITD mutations are associated with favorable risk in AML[4]. Concurrent

Biomarker Descriptions (continued)

NPM1 and with >0.5 allelic ratio FLT3-ITD mutations confer intermediate risk in AML, whereas wild-type NPM1 confers poor/adverse risk[4]. The NPM1 frameshift mutation W288fs*12 is associated with poor prognosis in myelodysplastic syndrome (MDS)[9]. The ALK-NPM1 fusion, and translocation t(2;5)(p23;q35) which leads to an ALK-NPM1 fusion, is diagnostic of ALK-positive anaplastic large cell lymphoma[10,11].

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[12]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[13,14]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[15]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[12,13,14]

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)[9]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[13,16]. 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[8,17]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[17,18]

ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2)

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3' intron splice site[19]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[19,20]. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes[19,21].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[9,22].

Potential relevance: Nonsense or frameshift mutations in ZRSR2 are associated with poor prognosis in myelodysplastic syndromes[9].

Relevant Therapy Summary

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

NPM1 p.(W288Cfs*12) c.863_864insTCTG

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 2023-01-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NPM1 p.(W288Cfs*12) c.863_864insTCTG

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** NPM1 mutation

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 1

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

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

● cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** NPM1 mutation

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 1

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

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

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** NPM1 mutation

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 2A

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

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

NPM1 p.(W288Cfs*12) c.863_864insTCTG (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** NPM1 mutation

Other criteria: FLT3 ITD negative

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:** NPM1 mutation

Other criteria: FLT3 ITD negative

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:** NPM1 mutation

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 2A

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

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:** NPM1 mutation

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 2A

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

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

NPM1 p.(W288Cfs*12) c.863_864insTCTG (continued)

gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia

Variant class: NPM1 mutation

Other criteria: FLT3 ITD negative

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 2023-01-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

NPM1 p.(W288Cfs*12) c.863_864insTCTG

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant class:** NPM1 mutation

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 2A

Summary:
- Without FLT3-ITD or FLT-ITD^{low} defined as allelic ratio (<0.5).

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

Current ESMO Information

ESMO information is current as of 2023-01-03. For the most up-to-date information, search www.esmo.org.

NPM1 p.(W288Cfs*12) c.863_864insTCTG

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant class:** NPM1 mutation

Other criteria: FLT3 ITD negative

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 2023-01-03. For the most up-to-date information, search www.esmo.org.

NPM1 p.(W288Cfs*12) c.863_864insTCTG

Diagnostic significance: Acute Myeloid Leukemia

Variant class: NPM1 mutation

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.]

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