Taipei Veterans General Hospital

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Sample Information

Patient Name: 施玉圓
Gender: Female
ID No.: N203520469
History No.: 42621716
Age: 70

Ordering Doctor: DOC1483K 王浩元
Ordering REQ.: 0CPTBTE
Signing in Date: 2023/08/14

Path No.: M112-00215
MP No.: MY23056
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/08/14

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	*NPM1 p.(W288Cfs*12)* *c.863_864insTCTG* nucleophosmin 1 Allele Frequency: 19.79%	allogeneic stem cells cytarabine cytarabine + daunorubicin cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy	None	0

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

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
NPM1	p.(W288Cfs*12)	c.863_864insTCTG	COSM17559	chr5:170837547	19.79%	NM_002520.6	frameshift Insertion	1991
KIT	p.(A430=)	c.1290A>G	.	chr4:55589808	48.92%	NM_000222.3	synonymous	1999
TET2	p.(Y1294N)	c.3880T>A	.	chr4:106180852	34.15%	NM_001127208.2	missense	1997

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: Mutation of NPM1 is recognized as a diagnostic entity for AML with NPM1 mutation by the World Health Organization (WHO)[8]. NPM1 mutations are associated with better outcomes, increased complete remission, improved overall survival, and favorable risk in AML[4,6,9]. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML[4,9]. The NPM1 frameshift mutation W288fs*12 is associated with poor prognosis in myelodysplastic syndrome (MDS)[10]. 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[11,12].

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*
Allogeneic hematopoietic stem cell transplantation	✖	●	✖	✖	✖
cytarabine	✖	●	✖	✖	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	✖	✖

Relevant Therapy Summary (continued)

● 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 (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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 2023-06-01. 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.

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

● Allogeneic hematopoietic stem cell transplantation

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

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

● cytarabine

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

Other criteria: FLT3 ITD negative

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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

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):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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

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):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

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

Other criteria: CD33 positive, FLT3 ITD negative

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

Diagnostic Details

Current ESMO Information

ESMO information is current as of 2023-06-01. 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.]

References

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9. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
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