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Sample Information

Patient Name: 許雅雯
Gender: Female
ID No.: A224844561
History No.: 40944012
Age: 44

Ordering Doctor: DOC1483K 王浩元
Ordering REQ.: 0CUGUXV
Signing in Date: 2023/12/06

Path No.: M112-00311
MP No.: MY23082
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/12/04

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	*IDH2 p.(R140Q) c.419G>A* isocitrate dehydrogenase (NADP(+)) 2 Allele Frequency: 41.70%	**enasidenib** [1] azacitidine decitabine enasidenib + chemotherapy venetoclax + chemotherapy	None	0

Public data sources included in relevant therapies: FDA[1], 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
IA	*NPM1 p.(W288Cfs*12) c.863_864insTCTG* nucleophosmin 1 Allele Frequency: 37.51% **Diagnostic significance:** Acute Myeloid Leukemia	allogeneic stem cells cytarabine 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 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	37.51%	NM_002520.6	frameshift Insertion	1989
IDH2	p.(R140Q)	c.419G>A	COSM41590	chr15:90631934	41.70%	NM_002168.4	missense	2000
CEBPA	p.(H195_P196dup)	c.589_590insACCCGC	.	chr19:33792731	34.67%	NM_004364.4	nonframeshift Insertion	398

Biomarker Descriptions

IDH2 (isocitrate dehydrogenase (NADP(+)) 2)

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG)[1]. The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform.

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)[2]. Recurrent IDH2 variants include predominately R140Q and R172K plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[3]. Although wild-type enzymatic activity is ablated, recurrent IDH2 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair[1,4]. Recurrent IDH2 mutations are present in 10-20% of patients with AML and 5% of patients with MDS[5,6,7].

Potential relevance: Enasidenib[8] is FDA approved (2017) for the treatment of AML patients with IDH2 R140G/L/Q/W and R172G/K/M/S/W mutations. In AML, acquired resistance to enasidenib has been associated with the emergence of Q316E or I319M mutations[9]. IDH2 R172 and R140Q variants are associated with poor prognosis in MDS but have been shown to confer improved prognosis in lower grade gliomas[10,11,12]. Additionally, IDH2 mutations are associated with inferior overall survival in polycythemia vera (PV) and essential thrombocythemia (ET) as well as inferior leukemia-free survival in primary myelofibrosis (PMF)[13]. Mutations in IDH2 are diagnostic of astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q-codeleted subtypes of central nervous system (CNS) tumors[14]

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[15]. NPM1 functions as an oncogene and tumor suppressor, and is important in maintaining genomic stability, DNA repair, and apoptosis[15,16]. 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[15]. Oligomerization of NPM1 localizes the protein in the nucleus of proliferating cells where it binds to Akt in

Biomarker Descriptions (continued)

response to growth factor stimulation and escapes proteolytic degradation by caspase activity, thereby promoting cell survival[15,16]. NPM1 is one of the most frequently altered genes in hematological cancers[17]. 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[15].

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[18,19,20]. NPM1 fusions are associated with distinct partner genes in acute promyelocytic leukemia (APL), anaplastic large-cell lymphoma (ALCL), AML, and myelodysplasia[17]. Specifically, NPM1-ALK fusion is found in 30% of all ALCL and this specific fusion is observed in 85% of ALK-positive ALCL[15]. The t(5;17)(q35;q21) translocation that results in NPM1-RARA fusion is observed in APL[21].

Potential relevance: Mutation of NPM1 is recognized as a diagnostic entity for AML with NPM1 mutation by the World Health Organization (WHO)[22]. NPM1 mutations are associated with better outcomes, increased complete remission, improved overall survival, and favorable risk in AML[18,20,23]. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML[18,23]. 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[24,25].

Relevant Therapy Summary

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

IDH2 p.(R140Q) c.419G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
enasidenib	●	●	✖	●	✖
azacitidine	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
enasidenib + azacitidine	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

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	✖	●	✖	✖	✖
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 FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2023-09-13. For the most up-to-date information, search www.fda.gov.

IDH2 p.(R140Q) c.419G>A

● enasidenib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2020-11-24 **Variant class:** IDH2 R140Q mutation

Indications and usage:
IDHIFA® is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209606s004lbl.pdf

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.

IDH2 p.(R140Q) c.419G>A

● venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 R140 mutation

NCCN Recommendation category: 1

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

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

● enasidenib

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 R140 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Relapsed, Refractory (Line of therapy not specified)

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

● venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 R140 mutation

NCCN Recommendation category: 2A

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

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

● azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 mutation

NCCN Recommendation category: 2A

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

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

IDH2 p.(R140Q) c.419G>A (continued)

decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 mutation

NCCN Recommendation category: 2A

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

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

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enasidenib

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 mutation

NCCN Recommendation category: 2A

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

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

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 mutation

NCCN Recommendation category: 2A

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

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

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enasidenib + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy); Useful in certain circumstances

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

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 4.2023]

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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 4.2023]

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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):
- (Consolidation therapy)

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

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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 4.2023]

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):
- (Consolidation therapy)

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

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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 4.2023]

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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):
- (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:** 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 4.2023]

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

gemtuzumab ozogamicin + cytarabine

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)

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

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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 4.2023]

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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 4.2023]

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 2023-09-01. For the most up-to-date information, search www.esmo.org.

IDH2 p.(R140Q) c.419G>A

● enasidenib

Cancer type: Acute Myeloid Leukemia **Variant class:** IDH2 mutation

ESMO Level of Evidence/Grade of Recommendation: IV / B

Population segment (Line of therapy):
- Relapsed, Refractory (Second-line therapy)

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 2023-09-01. 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.]

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