Taipei Veterans General Hospital

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Sample Information

Patient Name: 賴朝慶
Gender: Male
ID No.: Y120211947
History No.: 49567693
Age: 56

Ordering Doctor: DOC1697J 蔡淳光
Ordering REQ.: 0CMDGYB
Signing in Date: 2023/06/16

Path No.: M112-00153
MP No.: MY23034
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/06/13

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

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	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: 16.92%	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

Prevalent cancer biomarkers without relevant evidence based on included data sources
DNMT3A p.(R882C) c.2644C>T, KRAS p.(G13D) c.38G>A

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
DNMT3A	p.(R882C)	c.2644C>T	COSM53042	chr2:25457243	18.61%	NM_022552.4	missense	1999
NPM1	p.(W288Cfs*12)	c.863_864insTCTG	COSM17559	chr5:170837547	16.92%	NM_002520.6	frameshift Insertion	1992
KRAS	p.(G13D)	c.38G>A	COSM532	chr12:25398281	16.32%	NM_033360.4	missense	1998
GATA2	p.(A372T)	c.1114G>A	.	chr3:128200691	16.70%	NM_032638.5	missense	2000

Biomarker Descriptions

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[1]. 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[2,3].

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)[4,5,6,7,8,9,10]. 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[9,11]. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported[4,9]. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations[12,13]. 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[14,15]. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity[16].

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML[4,7,8,13]. 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)[17].

Biomarker Descriptions (continued)

KRAS (KRAS proto-oncogene, GTPase)

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[18,19,20].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[9]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[9,21,22]. Mutations at A59, K117, and A146 have also been observed but are less frequent[23,24].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[25] (2021) and adagrasib[26] (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[27], for KRAS G12C mutation in non-small cell lung cancer. The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer[28]. The PLK1 inhibitor, onvansertib[29], was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). Additionally, the SHP2 inhibitor, BBP-398[30] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC.The EGFR antagonists, cetuximab[31] and panitumumab[32], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[24]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[33].

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[34]. NPM1 functions as an oncogene and tumor suppressor, and is important in maintaining genomic stability, DNA repair, and apoptosis[34,35]. 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[34]. 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[34,35]. NPM1 is one of the most frequently altered genes in hematological cancers[36]. 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[34].

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[10,37,38]. NPM1 fusions are associated with distinct partner genes in acute promyelocytic leukemia (APL), anaplastic large-cell lymphoma (ALCL), AML, and myelodysplasia[36]. Specifically, NPM1-ALK fusion is found in 30% of all ALCL and this specific fusion is observed in 85% of ALK-positive ALCL[34]. The t(5;17)(q35;q21) translocation that results in NPM1-RARA fusion is observed in APL[39].

Potential relevance: Mutation of NPM1 is recognized as a diagnostic entity for AML with NPM1 mutation by the World Health Organization (WHO)[40]. NPM1 mutations are associated with better outcomes, increased complete remission, improved overall survival, and favorable risk in AML[10,38,41]. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML[10,41]. The NPM1 frameshift mutation W288fs*12 is associated with poor prognosis in myelodysplastic syndrome (MDS)[11]. 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[17,42].

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	✖	●	✖	✖	✖

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

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 3.2022]

● 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 3.2022]

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):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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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 3.2022]

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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):
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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 3.2022]

Diagnostic Details

Current ESMO Information

ESMO information is current as of 2023-03-01. 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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