Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳建宏
Gender: Male
ID No.: N123742781
History No.: 48825474
Age: 41

Ordering Doctor: DOC1686E 陳玟均
Ordering REQ.: 0BYJTAD
Signing in Date: 2022/08/11

Path No.: S111-97831
MP No.: MY22022
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/08/03

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Acute Promyelocytic Leukemia

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Relevant Acute Promyelocytic Leukemia Variants

Gene	Finding
RARA	***PML-RARA fusion***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*PML-RARA fusion* PML nuclear body scaffold - retinoic acid receptor alpha	**arsenic trioxide** [1, 2] **arsenic trioxide + tretinoin** [1, 2] anthracycline + arsenic trioxide anthracycline + arsenic trioxide + tretinoin	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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		arsenic trioxide + idarubicin + tretinoin cytarabine + daunorubicin + tretinoin gemtuzumab ozogamicin gemtuzumab ozogamicin + chemotherapy idarubicin + tretinoin		
	Diagnostic significance: Acute Promyelocytic Leukemia			

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
*WT1 p.(V384Rfs*68) c.1149_1155delTGTACGG*

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
WT1	p.(V384Rfs*68)	c.1149_1155delTGTACGG	.	chr11:32417911	30.12%	NM_024426.6	frameshift Deletion	1989

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
PML-RARA	PML-RARA.P6del54R3	chr15:74325701 - chr17:38504568	22
PML-RARA	PML-RARA.P6del8ins8R3	chr15:74325747 - chr17:38503421	177
PML-RARA	PML-RARA.P6R3	chr15:74325755 - chr17:38504568	7624

Biomarker Descriptions

RARA (retinoic acid receptor alpha)

Background: The RARA gene encodes the retinoic acid receptor alpha, a transcription factor and a member of the retinoic acid (RA) nuclear receptor family. RARA binds DNA as a heterodimer with its cofactor the retinoid X receptor alpha (RXRA)[1]. Binding of the RARA/RXRA complex to specific RA response elements (RAREs) causes activation of transcription[1]. RARA is also involved in white blood cell (WBC) differentiation and hematopoietic stem cell specification[2,3]. RARA translocations are the genetic driver of acute promyelocytic leukemia (APL) where the 3' region of the RARA gene is translocated to the 5' region of partner genes such as the promyelocytic leukemia (PML) gene[4]. The PML-RARA fusion protein contributes to the pathogenesis of APL by blocking differentiation and promoting aberrant self-renewal of APL cells, leading to a buildup of immature white blood cells in the blood and bone marrow[5].

Alterations and prevalence: More than 95% of APL patients harbor the t(15;17)(q22;q21) translocation that results in PML-RARA fusion[1,6]. Other RARA fusion partners, including PLZF, NPM, NUMA, STAT5b, PRKAR1A, FIP1L1, TBLXR1, FNDC3B, GTF2I, IRF2BP2, account for the rest[6,7,8,9,10,11].

Potential relevance: The presence of PML-RARA fusion characterized by the presence of t(15;17)(q22;q21) translocation is diagnostic of APL[12]. Arsenic trioxide[13] is approved (2000) alone or in combination with tretinoin (ATRA) for the treatment of APL harboring PML-RARA fusions. Somatic missense mutations in PML-RARA fusion including A216V, S214L, A216T, L217F, and S220G are associated with acquired resistance to treatment with arsenic trioxide[14].

Biomarker Descriptions (continued)

WT1 (WT1 transcription factor)

Background: The WT1 gene encodes the Wilms tumor 1 homolog, a zinc-finger transcriptional regulator that plays an important role in cellular growth and metabolism[15,16]. WT1 is endogenously expressed in embryonic kidney cells as well as hematopoietic stem cells and regulates the process of filtration of blood through the kidneys[17]. WT1 protein contains N-terminal proline-glutamine rich regions that are involved in RNA and protein interaction while the C-terminal domain contains Kruppel link cysteine histidine zinc fingers that are involved in DNA binding[15]. WT1 interacts with various genes including TP53, STAT3, and epigenetic modifiers such as TET2 and TET3[15,18]. WT1 is primarily characterized as a tumor suppressor gene involved in the development of renal Wilm's tumor (WT), a rare pediatric kidney cancer[15,19]. Loss of function mutations observed in WT1, including large deletions and intragenic mutations, can impact the zinc finger domain, thereby decreasing the DNA binding activity[15]. WT1 overexpression is observed in acute myeloid leukemia (AML) and lymphoid cancers[15,20].

Alterations and prevalence: Somatic mutations of WT1 occur in 7% of AML, 5% of melanoma, and 1% of mesothelioma[21]. WT1 overexpression is observed in AML, acute lymphoblastic lymphoma (ALL), and myelodysplastic syndrome (MDS)[15]

Potential relevance: Somatic mutations in WT1, including nonsense, frameshift, and splice-site mutations, are associated with poor prognosis in MDS[22]. Overexpression of WT1 in MDS is associated with a higher risk of progression to AML. WT1 overexpression is also associated with poor prognosis, resistance to chemotherapy, and poor overall survival in AML[18].

Relevant Therapy Summary

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

PML-RARA fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
arsenic trioxide + tretinoin	●	●	●	●	✖
arsenic trioxide	●	●	●	✖	✖
anthracycline + arsenic trioxide + tretinoin	✖	●	✖	●	✖
idarubicin + tretinoin	✖	●	✖	●	✖
anthracycline + arsenic trioxide	✖	●	✖	✖	✖
arsenic trioxide + idarubicin + tretinoin	✖	●	✖	✖	✖
cytarabine + daunorubicin + tretinoin	✖	●	✖	✖	✖
gemtuzumab ozogamicin + arsenic trioxide	✖	●	✖	✖	✖
gemtuzumab ozogamicin + arsenic trioxide + tretinoin	✖	●	✖	✖	✖
gemtuzumab ozogamicin + tretinoin	✖	●	✖	✖	✖

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 2022-06-15. For the most up-to-date information, search www.fda.gov.

PML-RARA fusion

● arsenic trioxide, arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Label as of:** 2020-10-20 **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

Indications and usage:
TRISENOX® is an arsenical indicated:

- In combination with tretinoin for treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.
- For induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021248s019lbl.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 2022-06-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

PML-RARA fusion

● arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

● idarubicin + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

● anthracycline + arsenic trioxide

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

● anthracycline + arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

PML-RARA fusion (continued)

arsenic trioxide

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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arsenic trioxide + idarubicin + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + daunorubicin + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention
- Relapsed (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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gemtuzumab ozogamicin + arsenic trioxide

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

PML-RARA fusion (continued)

gemtuzumab ozogamicin + arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention
- Relapsed (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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gemtuzumab ozogamicin + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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idarubicin + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention
- Relapsed (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

Current EMA Information

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

EMA information is current as of 2022-06-15. For the most up-to-date information, search www.ema.europa.eu/ema.

PML-RARA fusion

● arsenic trioxide, arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Label as of:** 2022-03-10 **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

Reference:

https://www.ema.europa.eu/en/documents/product-information/trisenox-epar-product-information_en.pdf

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 2022-06-01. For the most up-to-date information, search www.esmo.org.

PML-RARA fusion

● arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

ESMO Level of Evidence/Grade of Recommendation: I / A

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

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

● anthracycline + arsenic trioxide + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

ESMO Level of Evidence/Grade of Recommendation: II / A

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

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

● idarubicin + tretinoin

Cancer type: Acute Promyelocytic Leukemia **Variant class:** PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

ESMO Level of Evidence/Grade of Recommendation: II / A

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

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

Diagnostic Details

Current NCCN Information

NCCN information is current as of 2022-06-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

PML-RARA fusion

Diagnostic significance: Acute Promyelocytic Leukemia

Variant class: PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

NCCN Recommendation category: 2A

Diagnostic notes:
- WHO 2016 classification

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

Current ESMO Information

ESMO information is current as of 2022-06-01. For the most up-to-date information, search www.esmo.org.

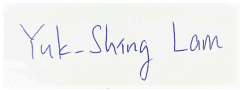
PML-RARA fusion

Diagnostic significance: Acute Promyelocytic Leukemia

Variant class: PML-RARA fusion [t(15;17)(q22;q21) or t(15;17)(q24;q21)]

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

Signatures

Testing Personnel:  2022.08.12 09:30:25 +08'00'

Laboratory Supervisor:  2022.08.12 09:30:45 +08'00'

Pathologist:  2022.08.12 09:30:57 +08'00'

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