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Sample Information

Patient Name: 張馨勻
Gender: Female
ID No.: A228948640
History No.: 22747086
Age: 28

Ordering Doctor: DOC1901H 高志平
Ordering REQ.: D61374E
Signing in Date: 2021/02/18

Path No.: S110-98251
MP No.: MY21001
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2021/02/09
Note:

Sample Cancer Type: Acute Promyelocytic Leukemia

Report Highlights

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7 Clinical Trials

Relevant Acute Promyelocytic Leukemia Variants

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

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
PML-RARA fusion promyelocytic leukemia - retinoic acid receptor alpha	**arsenic trioxide** [1, 2] **arsenic trioxide + tretinoin** [1, 2] anthracycline + arsenic trioxide anthracycline + arsenic trioxide + tretinoin arsenic trioxide + idarubicin + tretinoin cytarabine + daunorubicin + tretinoin gemtuzumab ozogamicin	None	7

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)

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
	gemtuzumab ozogamicin + chemotherapy idarubicin + tretinoin		

Prognostic significance: None
Diagnostic significance: Acute Promyelocytic Leukemia, Acute Myeloid Leukemia

Public data sources included in relevant therapies: FDA1, 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
ETV6 p.(Q413fs) c.1238_1239insCA

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
ETV6	p.(Q413fs)	c.1238_1239insCA	.	chr12:12038945	4.06%	NM_001987.4	frameshift Insertion	1994
SF3B1	p.(=)	c.2631T>C	.	chr2:198265526	99.95%	NM_012433.3	synonymous	1996
TET2	p.(V218M)	c.652G>A	.	chr4:106155751	49.75%	NM_001127208.2	missense	1998
TET2	p.(=)	c.4140T>C	.	chr4:106190862	47.67%	NM_001127208.2	synonymous	1999
HRAS	p.(=)	c.81T>C	.	chr11:534242	99.50%	NM_001130442.2	synonymous	1999
WT1	p.(=)	c.1107A>G	.	chr11:32417945	99.95%	NM_024426.4	synonymous	2000
ETV6	p.(=)	c.258G>A	.	chr12:11992168	51.35%	NM_001987.4	synonymous	1996
ETV6	p.(Y391N)	c.1171T>A	.	chr12:12038878	14.81%	NM_001987.4	missense	1999
KRAS	p.(=)	c.483G>A	.	chr12:25368462	99.90%	NM_033360.3	synonymous	2000
SH2B3	p.(F135V)	c.403T>G	.	chr12:111856352	48.61%	NM_005475.2	missense	1329
SH2B3	p.(W262R)	c.784T>C	.	chr12:111884608	99.90%	NM_005475.2	missense	1999
TP53	p.(P72R)	c.215C>G	.	chr17:7579472	81.23%	NM_000546.5	missense	1998
NF1	p.(=)	c.702G>A	.	chr17:29508775	44.79%	NM_001042492.2	synonymous	1085
NF1	p.(=)	c.2034G>A	.	chr17:29553485	51.33%	NM_001042492.2	synonymous	1999
SRSF2	p.(=)	c.144C>T	.	chr17:74733099	100.00%	NM_003016.4	synonymous	2000
ASXL1	p.(L815P)	c.2444T>C	.	chr20:31022959	99.95%	NM_015338.5	missense	1997
ASXL1	p.(=)	c.3759T>C	.	chr20:31024274	99.95%	NM_015338.5	synonymous	1999
ZRSR2	p.(=)	c.864C>T	.	chrX:15838366	100.00%	NM_005089.3	synonymous	1996
BCOR	p.(=)	c.1692A>G	.	chrX:39932907	47.42%	NM_001123385.1	synonymous	1976
BCOR	p.(=)	c.1260T>C	.	chrX:39933339	99.95%	NM_001123385.1	synonymous	1999

Variant Details (continued)

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
PML-RARA	PML-RARA.P3R3	chr15:74315749 - chr17:38504568	70849

Biomarker Descriptions

ETV6 (ETS variant 6)

Background: The ETV6 gene encodes the E twenty-six (ETS) variant 1 transcription factor. ETV6 contains an N-terminal pointed (PNT) domain responsible for protein-protein interactions and a C-terminal ETS domain involved in DNA binding[1]. ETV6 plays a critical role in embryonic development as well as hematopoiesis and is the target of chromosomal rearrangement and missense mutations in hematological malignancies as well as solid tumors[2,3]. Hereditary mutations in ETV6 are associated with a predisposition to hematological cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS)[4,5,6].

Alterations and prevalence: ETV6 translocations are prevalent in hematological malignancies and have been observed with numerous fusion partners[7]. The most recurrent translocation is t(12;21)(q34;q11) which results in ETV6-RUNX1 fusion and is observed in 20-25% childhood acute lymphoblastic leukemia (ALL)[7,8,9]. ETV6-RUNX1 fusions are also observed in adult ALL (2%)[8,9]. The t(5;12)(q33;p13) translocation which results in the ETV6-PDGFRB fusion is recurrent in chronic myelomonocytic leukemia (CMML)[7,10]. Other ETV6 fusions including ETV6-PDGFRA, ETV6-NTRK2, ETV6-NTRK3, and ETV6-ABL1 are reported in hematological malignancies as well as solid tumors[3,7,11]. ETV6 fusions involving a receptor tyrosine kinase (RTK) fusion partner retains the ETV6 PNT domain and the tyrosine kinase domain of the RTK, leading to constitutive kinase activation[7,11]. Mutations in ETV6 are primarily missense, nonsense, or frameshift and are observed in about 1-5% of select myeloid malignancies and solid tumors, including chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), MDS, AML, ALL, melanoma, lung, bladder, stomach, colorectal, and uterine cancers[1,12,13]. ETV6 mutations occur in the PNT and ETS domain of ETV6 and may impair ETV6 oligomerization or DNA-binding, respectively[1].

Potential relevance: ETV6-NTRK3 fusions are used as an ancillary diagnostic marker in congenital/infantile fibrosarcoma[14]. Nonsense or frameshift mutations in ETV6 are independently associated with poor prognosis in MDS[6]. However, ETV6-RUNX1 fusions are associated with favorable outcomes in ALL and good risk in B-cell ALL (B-ALL)[9]. ETV6 fusions that partner with a RTKs demonstrate response to various tyrosine kinase inhibitors such as imatinib, nilotinib, and entrectinib. Specifically, individual case reports of an ETV6-PDGFRA fusion chronic eosinophilic leukemia patient and an ETV6-PDGFRB fusion CMML patient treated with imatinib demonstrated complete cytogenetic response (CCyR) and complete hematological responses, respectively[15,16]. Additionally, an ETV6-ABL1 fusion Ph-negative CML patient treated with nilotinib demonstrated CCyR and major molecular response (MMR) at 22 months from diagnosis[17]. In another case report, an ETV6-NTRK3 fusion mammary analogue secretory carcinoma (MASC) patient demonstrated partial response to entrectinib with 89% reduction in tumor burden[18].

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)[19]. Binding of the RARA/RXRA complex to specific RA response elements (RAREs) causes activation of transcription[19]. RARA is also involved in white blood cell (WBC) differentiation and hematopoietic stem cell specification[20,21]. 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[22]. 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[23].

Alterations and prevalence: More than 95% of APL patients harbor the t(15;17)(q22;q21) translocation that results in PML-RARA fusion[19,24]. Other RARA fusion partners, including PLZF, NPM, NUMA, STAT5b, PRKAR1A, FIP1L1, TBLXR1, FNDC3B, GTF2I, IRF2BP2, account for the rest[24,25,26,27,28,29].

Potential relevance: The presence of PML-RARA fusion characterized by the presence of t(15;17)(q22;q21) translocation is diagnostic of APL[30]. Arsenic trioxide[31] 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[32].

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	✖	●	✖	✖	✖
chemotherapy	✖	✖	✖	✖	● (IV)
chemotherapy, supplement	✖	✖	✖	✖	● (IV)
gemtuzumab ozogamicin, ganetespib, chemotherapy, allogeneic stem cells, supplement	✖	✖	✖	✖	● (III)
supplement, chemotherapy	✖	✖	✖	✖	● (III)
chemotherapy, valproic acid	✖	✖	✖	✖	● (II)
T-cell therapy	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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 2020-12-16. 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 2020-12-01. 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 2.2021]

● 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 2.2021]

● 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 2.2021]

● 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 2.2021]

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 2.2021]

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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 2.2021]

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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 2.2021]

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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 2.2021]

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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 2.2021]

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 2.2021]

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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); Preferred intervention, Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2021]

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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 2.2021]

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 2020-12-16. 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:** 2019-11-26 **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 2020-12-01. 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 2020-12-01. 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 2.2021]

Diagnostic significance: Acute Myeloid Leukemia

Variant class: t(15;17)

NCCN Recommendation category: 2A

Diagnostic notes:
- Karyotypes t(8;21), inv16, and t(15;17) are considered to be Acute Myeloid Leukemia even if the marrow blast count is less than 20%

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2021]

Current ESMO Information

ESMO information is current as of 2020-12-01. 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: Shin-Ying Lin 2021.02.22 10:32:16 +08'00'

Laboratory Supervisor: 2021.02.22 10:32:30 +08'00'

Pathologist: 2021.02.22 10:32:45 +08'00'

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