Taipei Veterans General Hospital

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Sample Information

Patient Name: 董文瑞
Gender: Male
ID No.: X120309192
History No.: 23094555
Age: 53

Ordering Doctor: DOC1697J 蔡淳光
Ordering REQ.: 0CSLUFY
Signing in Date: 2023/10/25

Path No.: M112-00273
MP No.: MY23069
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/10/20

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	*KMT2A::MLLT4 fusion* lysine methyltransferase 2A	allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine liposomal cytarabine-daunorubicin CPX-351	None	0

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		venetoclax + chemotherapy		

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], 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
NF1	p.(C2062=)	c.6186C>T	.	chr17:29663691	47.12%	NM_001042492.3	synonymous	1997
CEBPA	p.(T230=)	c.690G>T	.	chr19:33792631	58.04%	NM_004364.4	synonymous	1356

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
KMT2A-MLLT4	KMT2A-MLLT4.K7M2	chr11:118352807 - chr6:168265231	8310
KMT2A-MLLT4	KMT2A-MLLT4.K8M2	chr11:118353210 - chr6:168265231	26378

Biomarker Descriptions

KMT2A (lysine methyltransferase 2A)

Background: The KMT2A gene encodes the lysine methyltransferase 2A protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily. KMT2A influences epigenetic regulation by means of its methyltransferase activity, which regulates a variety of cellular functions including neurogenesis, hematopoiesis, and osteogenesis[1]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[2]. Such translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[2]. Loss of methyltransferase activity along with partner gene gain of function contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[2,3,4,5].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[2,6,7]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1-KMT2A, t(9;11)(p22;q23)/MLLT3-KMT2A, t(11;19)(q23;p13.3)/KMT2A-MLLT1, t(10;11)(p12;q23)/MLLT10-KMT2A, and t(6;11)(q27;q23)/AFDN-KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[2]. In infant acute leukemic cases, KMT2A rearrangement is reported in up to 70% of those diagnosed with either AML or ALL[2,8,9]. Mutations in KMT2A are also reported in diverse solid tumors including 10-20% of melanoma, stomach, bladder, and uterine cancers and around 5% of lung and head and neck cancers[10]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations which result in KMT2A truncation and loss of methyltransferase activity[10,11].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[7,12]. For example, t(6;11)(q27;q23)/AFDN-KMT2A fusions are associated with poor prognosis whereas, t(9;11)(p22;q23)/MLLT3-KMT2A fusions confer more favorable or intermediate prognosis in AML[13,14,15]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[16]. KMT2A fusion is also associated with poor risk in ALL[17]. In 2022, the FDA granted breakthrough therapy designation to the oral menin inhibitor, revumenib[18], for the treatment of patients with relapsed or refractory acute leukemia harboring a KMT2A rearrangement.

Relevant Therapy Summary

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

KMT2A::MLLT4 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✖	●	✖	✖	✖
azacitidine	✖	●	✖	✖	✖
cytarabine	✖	●	✖	✖	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + daunorubicin + etoposide	✖	●	✖	✖	✖
cytarabine + etoposide + idarubicin	✖	●	✖	✖	✖
cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
liposomal cytarabine-daunorubicin CPX-351	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

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 2023-08-01. 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.

KMT2A::MLLT4 fusion

● azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 1

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

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

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 1

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

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

● cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 1

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

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

KMT2A::MLLT4 fusion (continued)

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 1

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

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

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 1

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

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

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD 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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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

KMT2A::MLLT4 fusion (continued)

cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD 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:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

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liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

KMT2A::MLLT4 fusion (continued)

venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD 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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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

KMT2A::MLLT4 fusion (continued)

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2A

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

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

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2B

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

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

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2B

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

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

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2B

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

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

KMT2A::MLLT4 fusion (continued)

cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2B

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

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

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 2B

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

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

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venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 3

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

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

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

Other criteria: KMT2A PTD negative

NCCN Recommendation category: 3

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

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

KMT2A::MLLT4 fusion

revumenib

Cancer type: Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia

Variant class: KMT2A fusion

Supporting Statement:
The FDA has granted Breakthrough designation to menin inhibitor, revumenib, for KMT2A rearrangement in adult and pediatric patients with relapsed or refractory (R/R) acute leukemia.

Reference:

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-to-revumenib-for-relapsed-refractory-kmt2ar-acute-leukemia

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