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## Sample Information

**Patient Name:** 許書璟
**Gender:** Male
**ID No.:** A101401164
**History No.:** 12498769
**Age:** 84

**Ordering Doctor:** DOC1697J 蔡淳光
**Ordering REQ.:** 0CMYWZR
**Signing in Date:** 2023/07/06

**Path No.:** M112-00170
**MP No.:** MY23038
**Assay:** Oncomine Myeloid Assay
**Sample Type:** Bone Marrow
**Bone Marrow Aspirating Date:** 2023/07/03

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

**Note:**

## Sample Cancer Type: Acute Myeloid Leukemia

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### Report Highlights

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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 | None detected |
| FLT3 | None detected | NUP214 | None detected |
| IDH1 | None detected | RARA | None detected |
| IDH2 | None detected | RUNX1 | None detected |
| KMT2A | ***KMT2A::ELL fusion*** | TP53 | None detected |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IA | *KMT2A::ELL fusion*<br>lysine methyltransferase 2A - elongation factor for RNA polymerase II | allogeneic stem cells<br>azacitidine<br>cytarabine<br>cytarabine + daunorubicin + etoposide<br>cytarabine + etoposide + idarubicin<br>cytarabine + fludarabine + idarubicin + filgrastim<br>daunorubicin<br>decitabine<br>idarubicin<br>liposomal cytarabine-daunorubicin CPX-351<br>mitoxantrone<br>venetoclax + chemotherapy | None | 0 |

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

**Prevalent cancer biomarkers without relevant evidence based on included data sources**
*DNMT3A c.1936+2T>G*

## 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.(?) | c.1936+2T>G | . | chr2:25466765 | 45.32% | NM_022552.4 | unknown | 1999 |
| ASXL1 | p.(N986S) | c.2957A>G | . | chr20:31023472 | 48.62% | NM_015338.6 | missense | 1999 |

### Gene Fusions (RNA)

| Genes | Variant ID | Locus | Read Count |
|---|---|---|---|
| KMT2A-ELL | KMT2A-ELL.K8E2 | chr11:118353210 - chr19:18583692 | 15967 |
| KMT2A-ELL | KMT2A-ELL.K7E2.Non-Targeted | chr11:118352807 - chr19:18583692 | 1275 |
| KMT2A-ELL | KMT2A-ELL.K8E3.Non-Targeted | chr11:118353210 - chr19:18576728 | 478 |

## 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

## Biomarker Descriptions (continued)

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].

**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[18]. 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)[19]. Such translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[19]. 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[19,20,21,22].

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%)[10,19,23]. 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[19]. In infant acute leukemic cases, KMT2A rearrangement is reported in up to 70% of those diagnosed with either AML or ALL[19,24,25]. 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[9]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations which result in KMT2A truncation and loss of methyltransferase activity[9,26].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[10,27]. 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[28,29,30]. 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[31]. KMT2A fusion is also associated with poor risk in ALL[32]. In 2022, the FDA granted breakthrough therapy designation to the oral menin inhibitor, revumenib[33], 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::ELL fusion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| Allogeneic hematopoietic stem cell transplantation | ✖ | ● | ✖ | ✖ | ✖ |
| azacitidine | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + daunorubicin + etoposide | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + etoposide + idarubicin | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + fludarabine + idarubicin + filgrastim | ✖ | ● | ✖ | ✖ | ✖ |
| daunorubicin | ✖ | ● | ✖ | ✖ | ✖ |

## Relevant Therapy Summary (continued)

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

### KMT2A::ELL fusion (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| decitabine | ✖ | ● | ✖ | ✖ | ✖ |
| idarubicin | ✖ | ● | ✖ | ✖ | ✖ |
| liposomal cytarabine-daunorubicin CPX-351 | ✖ | ● | ✖ | ✖ | ✖ |
| mitoxantrone | ✖ | ● | ✖ | ✖ | ✖ |
| 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 2023-05-01. 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::ELL 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); Preferred intervention
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

## KMT2A::ELL fusion (continued)

### 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):**
- (Maintenance therapy); Preferred intervention
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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### cytarabine + etoposide + idarubicin

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

**Other criteria:** KMT2A PTD negative

**NCCN Recommendation category:** 1

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

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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### daunorubicin

**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); Preferred intervention
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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### idarubicin

**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); Preferred intervention
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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## KMT2A::ELL fusion (continued)

### 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):**
- (Maintenance therapy)
- (Consolidation therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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)
- (Consolidation therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

---

### cytarabine

**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)
- (Consolidation therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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 3.2023]

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## KMT2A::ELL fusion (continued)

### 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):**
- (Maintenance therapy)
- (Consolidation therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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### 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 3.2023]

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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 3.2023]

---

### 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):**
- (Maintenance therapy)
- (Consolidation therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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## KMT2A::ELL fusion (continued)

### 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 3.2023]

---

### 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 3.2023]

---

### 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):**
- (Maintenance therapy)
- (Consolidation therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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):**
- (Maintenance therapy)
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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## KMT2A::ELL fusion (continued)

### 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):**
- (Maintenance therapy)
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

---

### 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):**
- (Maintenance therapy)
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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### 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):**
- (Maintenance therapy)
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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)
- (Induction therapy)

**Reference:** NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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## KMT2A::ELL fusion (continued)

### 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 3.2023]

### 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 3.2023]

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-05-17. For the most up-to-date information, search www.fda.gov.

## KMT2A::ELL 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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