Taipei Veterans General Hospital

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Sample Information

Patient Name: 莊詩婷
Gender: Female
ID No.: G221383227
History No.: 49384078
Age: 43

Ordering Doctor: DOC4205A 柯博伸
Ordering REQ.: 0CHULDE
Signing in Date: 2023/03/29

Path No.: M112-00051
MP No.: MY23018
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/03/24

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	None detected
FLT3	***FLT3 ITD mutation***	NUP214	None detected
IDH1	None detected	RARA	None detected
IDH2	None detected	RUNX1	None detected
KMT2A	***KMT2A-MLLT4 fusion***	TP53	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*FLT3 ITD mutation* fms related receptor tyrosine kinase 3 Allele Frequency: 0.20%	**gilteritinib** [1, 2] **midostaurin + chemotherapy** [1, 2] azacitidine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine gemtuzumab ozogamicin + chemotherapy sorafenib sorafenib + chemotherapy venetoclax + chemotherapy	None	0
	Prognostic significance: ELN 2017: Adverse			
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 gemtuzumab ozogamicin + chemotherapy midostaurin + chemotherapy venetoclax + chemotherapy	None	0
	Prognostic significance: ELN 2017: Adverse			

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

*NRAS p.(G13R) c.37G>C, TET2 p.(Q538Kfs*4) c.1612delC*

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
NRAS	p.(G13R)	c.37G>C	COSM569	chr1:115258745	40.15%	NM_002524.5	missense	2000
TET2	p.(Q538Kfs*4)	c.1612delC	.	chr4:106156710	48.32%	NM_001127208.2	frameshift Deletion	1995
FLT3	p.(R595_L601dup)	c.1803_1804insAGAGAATATGAATATGATCTC	.	chr13:28608252	0.20%	NM_004119.3	nonframeshift Insertion	

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
DNMT3A	p.(L639P)	c.1916T>C	.	chr2:25466787	45.62%	NM_022552.4	missense	1999

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
KMT2A-MLLT4	KMT2A-MLLT4.K9M2	chr11:118355029 - chr6:168265231	16615

Biomarker Descriptions

FLT3 (fms related receptor tyrosine kinase 3)

Background: The FLT3 gene encodes the fms related tyrosine kinase 3, a tyrosine kinase receptor that is a member of the class III receptor tyrosine kinase family that also includes PDGFR, FMS, and KIT[1]. FLT3 is highly expressed in hematopoietic progenitor cells[2]. Genomic alterations in FLT3 activate downstream oncogenic pathways including PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways which promote cellular proliferation, survival, and inhibition of differentiation[1].

Alterations and prevalence: Somatic mutations occur in approximately 30% of acute myeloid leukemia (AML), 7-10% of melanoma, and up to 8% of uterine cancer[3,4,5,6]. The most common activating FLT3 mutations are internal tandem duplications (ITD) that range from 3 to 400 base pairs in length within exons 14 and 15 in the juxtamembrane (JM) domain[7]. The second most frequent mutations are point mutations in exon 20 within the tyrosine kinase domain (TKD)[8]. FLT3 is amplified in up to 8% of colorectal cancer, 3% of stomach cancer, and is commonly overexpressed in AML[5,6,9].

Potential relevance: The presence of FLT3-ITD confers poor prognosis in myelodysplastic syndrome (MDS) and AML[10,11]. Similarly, the FLT3 TKD mutation D835 confers poor prognosis in MDS[10]. Midostaurin[12] (2017) and gilteritinib[13] (2018) are kinase inhibitors approved for AML patients with FLT3-ITD and TKD mutations including D835 and I836 mutations. The FDA granted fast track designations in 2017 to crenolanib[14] and in 2022 to tuspetinib (HM43239)[15] for FLT3 mutation-positive relapsed or refractory AML. In 2018 the FDA granted breakthrough therapy designation to quizartinib[16] for AML with FLT3-ITD. A phase II trial testing crenolanib in 34 patients with FLT3-ITD and TKD mutated relapsed/refractory AML, reported that FLT3 inhibitor naïve patients demonstrated a longer overall survival (OS) and event free survival (EFS) in comparison to previously treated patients (median OS: 55 weeks vs 13 weeks; median EFS: 13 weeks vs 7 weeks)[17]. Another phase II trial of crenolanib with chemotherapy in newly diagnosed FLT3 mutated AML reported complete remission in 24/29 (83%) patients[18]. Several multi-targeted tyrosine kinase inhibitors such as sorafenib (2005), sunitinib (2006), cabozantinib (2012), and ponatinib (2012) are FDA approved and include FLT3 as a target. Sorafenib is recommended in combination with chemotherapy in FLT3-ITD mutated AML[11].

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[19]. 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)[20]. Such translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[20]. 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[20,21,22,23].

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%)[11,20,24]. 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[20]. In infant acute leukemic cases, KMT2A rearrangement is reported in up to 70% of those diagnosed with either AML or ALL[20,25,26]. 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[6].

Biomarker Descriptions (continued)

KMT2A alterations observed in solid tumors include nonsense or frameshift mutations which result in KMT2A truncation and loss of methyltransferase activity[6,27].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[11]. 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.

NRAS (NRAS proto-oncogene, GTPase)

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS 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[34,35,36].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[6,37]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[6,38]. Mutations at A59, K117, and A146 have also been observed but are less frequent[5,39].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[40] and panitumumab[41], are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[39]. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787[42], for the treatment of NRAS mutation positive metastatic or unresectable melanoma. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[10] as well as melanoma[43]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[44].

TET2 (tet methylcytosine dioxygenase 2)

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[45]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[46,47]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[48]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[45,46,47]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[10]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[46,49]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[31,50]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[31,51]

Relevant Therapy Summary

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

FLT3 ITD mutation

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
gilteritinib	●	●	●	●	✖

Relevant Therapy Summary (continued)

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

FLT3 ITD mutation (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
midostaurin + cytarabine + daunorubicin	●	●	●	●	✖
azacitidine	✖	●	✖	✖	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + daunorubicin + etoposide	✖	●	✖	✖	✖
cytarabine + etoposide + idarubicin	✖	●	✖	✖	✖
cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	✖	✖
midostaurin + cytarabine	✖	●	✖	✖	✖
sorafenib	✖	●	✖	✖	✖
sorafenib + azacitidine	✖	●	✖	✖	✖
sorafenib + decitabine	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

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	✖	●	✖	✖	✖

Relevant Therapy Summary (continued)

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

KMT2A-MLLT4 fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
decitabine	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	✖	✖
midostaurin + cytarabine + daunorubicin	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

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 2023-01-18. For the most up-to-date information, search www.fda.gov.

FLT3 ITD mutation

● gilteritinib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2022-01-12 **Variant class:** FLT3 ITD mutation

Indications and usage:
XOSPATA® is a kinase inhibitor indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211349s003lbl.pdf

● midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Label as of:** 2021-11-15 **Variant class:** FLT3 ITD mutation

Indications and usage:

RYDAPT® is a kinase inhibitor indicated for the treatment of adult patients with:

- Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

  Limitations of Use: RYDAPT® is not indicated as a single-agent induction therapy for the treatment of patients with AML.
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207997s008lbledt.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 2023-01-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

FLT3 ITD mutation + KMT2A-MLLT4 fusion

● midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & KMT2A fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

● cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation (continued)

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gilteritinib

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

---

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

---

cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation (continued)

midostaurin + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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sorafenib

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation (continued)

sorafenib + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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sorafenib + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation (continued)

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

---

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

FLT3 ITD mutation (continued)

cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

---

venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

---

venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

KMT2A-MLLT4 fusion

cytarabine + daunorubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin + etoposide

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + etoposide + idarubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + idarubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Allogeneic hematopoietic stem cell transplantation

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

KMT2A-MLLT4 fusion (continued)

cytarabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + idarubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + mitoxantrone

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

KMT2A-MLLT4 fusion (continued)

decitabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + azacitidine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + cytarabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + decitabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

KMT2A-MLLT4 fusion (continued)

azacitidine

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin + etoposide

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + etoposide + idarubicin

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + fludarabine + idarubicin + filgrastim

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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 2023-01-18. For the most up-to-date information, search www.ema.europa.eu/ema.

FLT3 ITD mutation

● gilteritinib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2021-09-08 **Variant class:** FLT3 ITD mutation

Reference:

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

● midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Label as of:** 2022-09-23 **Variant class:** FLT3 ITD mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/rydapt-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 2023-01-03. For the most up-to-date information, search www.esmo.org.

FLT3 ITD mutation

● gilteritinib

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

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

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

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

● midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

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.]

Prognostic Details

Current NCCN Information

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

FLT3 ITD mutation

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

Summary:
- FLT3-ITD^{high}; High defined as allelic ratio (≥0.5)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

KMT2A-MLLT4 fusion

Prognostic significance: ELN 2017: Adverse

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

NCCN Recommendation category: 2A

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Current ESMO Information

ESMO information is current as of 2023-01-03. For the most up-to-date information, search www.esmo.org.

FLT3 ITD mutation

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 ITD mutation

Other criteria: NPM1 wild type

Summary:
- FLT3-ITD^{High}; High defined as allelic ratio (≥0.5)

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

KMT2A-MLLT4 fusion

Prognostic significance: ELN 2017: Adverse

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

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-01-18. For the most up-to-date information, search www.fda.gov.

FLT3 ITD mutation

crenolanib

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 mutation

Supporting Statement:

The FDA has granted Fast Track Designation to the benzimidazole type I kinase inhibitor, crenolanib, for:

- FLT3 mutation-positive relapsed or refractory acute myeloid leukemia (AML)
- PDGFRA D842V mutated unresectable or metastatic gastrointestinal stromal tumors (GIST)

Reference:

https://www.globenewswire.com/news-release/2017/12/01/1216122/0/en/Arog-Pharmaceuticals-Receives-FDA-Fast-Track-Designation-for-Crenolanib-in-Relapsed-or-Refractory-FLT3-Positive-AML.html

tuspetinib

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 mutation

Supporting Statement:
The FDA has granted Fast Track Designation to tuspetinib (HM43239), a myeloid kinome inhibitor, for relapsed or refractory (R/R) acute myeloid leukemia (AML) with FLT3 mutation.

Reference:

https://www.aptose.com/news-media/press-releases/detail/230/aptose-receives-fast-track-designation-for-hm43239-in

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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