Taipei Veterans General Hospital

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Sample Information

Patient Name: 盧秋香
Gender: Female
ID No.: H200007161
History No.: 24289290
Age: 91

Ordering Doctor: DOC1751J 蕭樑材
Ordering REQ.: 0CYBAUF
Signing in Date: 2024/03/06

Path No.: M113-00064
MP No.: MY24008
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2024/03/05

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	*FLT3 ITD mutation* fms related receptor tyrosine kinase 3 Allele Frequency: 36.10%	**gilteritinib** [1, 2] **midostaurin + chemotherapy** [1, 2] **quizartinib** [1, 2] **quizartinib + chemotherapy** [1, 2] allogeneic stem cells azacitidine decitabine gilteritinib + chemotherapy midostaurin sorafenib sorafenib + chemotherapy venetoclax + chemotherapy	None	0

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*RUNX1 p.(R201Q) c.602G>A* RUNX family transcription factor 1 Allele Frequency: 45.40%	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 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

*TET2 p.(G1187Afs*39) c.3558delA, TET2 p.(Q731*) c.2191C>T*

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
TET2	p.(Q731*)	c.2191C>T	.	chr4:106157290	49.50%	NM_001127208.2	nonsense	2000
TET2	p.(G1187Afs*39)	c.3558delA	.	chr4:106164046	45.81%	NM_001127208.2	frameshift Deletion	1563
FLT3	p.(E598delinsDGWVRSTH)	c.1794_1794delAinsTGGTTGGGTGAGGAGTACTCAT	.	chr13:28608262	36.10%	NM_004119.3	nonframeshift Block Substitution	
RUNX1	p.(R201Q)	c.602G>A	COSM24805	chr21:36231782	45.40%	NM_001754.4	missense	1998
EZH2	p.(L149P)	c.446T>C	.	chr7:148526858	42.60%	NM_004456.5	missense	2000

Biomarker Descriptions

RUNX1 p.(R201Q) c.602G>A

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[1]. All RUNX proteins share several conserved regions with similar functionality including a highly conserved N-terminal 'runt' domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[2]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[3,4]. RUNX1 is frequently mutated in various hematological malignancies[4]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[5,6]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in

Biomarker Descriptions (continued)

myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[4].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[7]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 20-25% of childhood ALL[8,9,10]. This translocation is also observed in adult ALL at a lower frequency (2%)[9,10]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[11]. The RUNX1::RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[4,11]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[4]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[4,12,13,14].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[12,15]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1 in AML and t(12;21)(q34;q11)/ETV6::RUNX1 in ALL, are associated with favorable risk[16,17]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[13,16,18].

FLT3 ITD mutation

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[19]. FLT3 is highly expressed in hematopoietic progenitor cells[20]. 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[19].

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[14,21,22,23]. 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[24]. The second most frequent mutations are point mutations in exon 20 within the tyrosine kinase domain (TKD)[25]. FLT3 is amplified in up to 8% of colorectal cancer, 3% of stomach cancer, and is commonly overexpressed in AML[14,23,26].

Potential relevance: FLT3 rearrangements are recognized by the World Health Organization (WHO) as one of the possible molecular abnormality requirements that define myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions[15].The presence of FLT3-ITD confers poor prognosis in myelodysplastic syndrome (MDS)[13]. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML[12,16]. FLT3 TKD mutation at D835 confers poor prognosis in MDS[13]. Midostaurin[27] (2017) and gilteritinib[28] (2018) are kinase inhibitors approved for AML patients with FLT3-ITD and TKD mutations including D835 and I836 mutations. Quizartinib dihydrochloride[29] (2023) is also a kinase inhibitor approved for AML patients with FLT3-ITD mutations. The FDA granted fast track designations in 2017 to crenolanib[30] and in 2022 to tuspetinib (HM43239)[31] for FLT3 mutation-positive relapsed or refractory AML. 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)[32]. Another phase II trial of crenolanib with chemotherapy in newly diagnosed FLT3 mutated AML reported complete remission in 24/29 (83%) patients[33]. 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[12].

TET2 p.(G1187Afs*39) c.3558delA, TET2 p.(Q731*) c.2191C>T

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[34]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[35,36]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[37]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[34,35,36]

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)[13]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[35,38]. 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).

Biomarker Descriptions (continued)

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[39]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[39,40]

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	●	●	●	●	✖
midostaurin + cytarabine + daunorubicin	●	●	●	●	✖
quizartinib	●	●	●	✖	✖
quizartinib + cytarabine	●	●	●	✖	✖
quizartinib + anthracycline + cytarabine	●	✖	●	✖	✖
Allogeneic hematopoietic stem cell transplantation	✖	●	✖	✖	✖
azacitidine	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
gilteritinib + azacitidine	✖	●	✖	✖	✖
midostaurin	✖	●	✖	✖	✖
midostaurin + cytarabine	✖	●	✖	✖	✖
midostaurin + cytarabine + idarubicin	✖	●	✖	✖	✖
quizartinib + cytarabine + daunorubicin	✖	●	✖	✖	✖
quizartinib + cytarabine + idarubicin	✖	●	✖	✖	✖
sorafenib	✖	●	✖	✖	✖
sorafenib + azacitidine	✖	●	✖	✖	✖
sorafenib + decitabine	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

RUNX1 p.(R201Q) c.602G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✖	●	✖	✖	✖
azacitidine	✖	●	✖	✖	✖

Relevant Therapy Summary (continued)

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

RUNX1 p.(R201Q) c.602G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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 FDA Information

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

FDA information is current as of 2024-01-17. 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

FLT3 ITD mutation (continued)

midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Label as of:** 2023-05-22 **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/2023/207997s010lbl.pdf

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quizartinib, quizartinib + cytarabine, quizartinib + anthracycline + cytarabine

Cancer type: Acute Myeloid Leukemia **Label as of:** 2023-07-20 **Variant class:** FLT3 ITD mutation

Indications and usage:
VANFLYTA® is a kinase inhibitor indicated in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216993s000lbl.pdf

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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 2024-01-02. To view the most recent and complete version of the guideline, go online to 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.

FLT3 ITD mutation

● 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 6.2023]

● midostaurin + cytarabine + daunorubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

● midostaurin + 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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

FLT3 ITD mutation (continued)

midostaurin + 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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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midostaurin + cytarabine + idarubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib + 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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib + cytarabine + daunorubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

FLT3 ITD mutation (continued)

quizartinib + cytarabine + idarubicin

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib + 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)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + azacitidine

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

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

Allogeneic hematopoietic stem cell transplantation

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 6.2023]

FLT3 ITD mutation (continued)

Allogeneic hematopoietic stem cell transplantation

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

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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midostaurin + 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):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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 6.2023]

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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):
- Residual (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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midostaurin + cytarabine + idarubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib

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 6.2023]

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quizartinib + 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 6.2023]

FLT3 ITD mutation (continued)

quizartinib + 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):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib + cytarabine + daunorubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib + cytarabine + idarubicin

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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sorafenib

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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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 6.2023]

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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sorafenib + azacitidine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + cytarabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

FLT3 ITD mutation (continued)

venetoclax + decitabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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gilteritinib

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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gilteritinib + azacitidine

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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midostaurin

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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quizartinib

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

FLT3 ITD mutation (continued)

quizartinib

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

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

RUNX1 p.(R201Q) c.602G>A

azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

RUNX1 p.(R201Q) c.602G>A (continued)

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

RUNX1 p.(R201Q) c.602G>A (continued)

cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

RUNX1 p.(R201Q) c.602G>A (continued)

venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

RUNX1 p.(R201Q) c.602G>A (continued)

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 3

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 3

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

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 2024-01-17. 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:** 2023-11-07 **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:** 2023-07-26 **Variant class:** FLT3 ITD mutation

Reference:

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

● quizartinib, quizartinib + cytarabine, quizartinib + anthracycline + cytarabine

Cancer type: Acute Myeloid Leukemia **Label as of:** 2023-11-21 **Variant class:** FLT3 ITD mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vanflyta-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 2024-01-02. 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.]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2024-01-17. 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

FLT3 ITD mutation (continued)

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

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