



Sample Information

Patient Name: 吳侯山  
Gender: Male  
ID No.: W100003217  
History No.: 49596023  
Age: 82

Ordering Doctor: DOC4205A 柯博仲  
Ordering REQ.: 0CMMFWE  
Signing in Date: 2023/06/27

Path No.: M112-00155  
MP No.: MY23036  
Assay: Oncomine Myeloid Assay  
Sample Type: Bone Marrow  
Bone Marrow Aspirating Date: 2023/06/20

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	<b>NPM1 p.(W288Cfs*12) c.863_864insTCTG</b>
FLT3	<b>FLT3 ITD mutation</b>	NUP214	None detected
IDH1	None detected	RARA	None detected
IDH2	None detected	RUNX1	None detected
KMT2A	None detected	TP53	None detected

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<b>FLT3 ITD mutation</b> fms related receptor tyrosine kinase 3 Allele Frequency: 35.65%	<b>gilteritinib</b> <sup>1,2</sup> <b>midostaurin + chemotherapy</b> <sup>1,2</sup> allogeneic stem cells azacitidine cytarabine cytarabine + fludarabine + idarubicin + filgrastim daunorubicin decitabine gemtuzumab ozogamicin + chemotherapy gilteritinib + chemotherapy idarubicin midostaurin mitoxantrone sorafenib sorafenib + chemotherapy venetoclax + chemotherapy	None	0
IA	<b>NPM1 p.(W288Cfs*12)</b> <b>c.863_864insTCTG</b> nucleophosmin 1 Allele Frequency: 45.73%	allogeneic stem cells azacitidine cytarabine cytarabine + fludarabine + idarubicin + filgrastim daunorubicin decitabine gemtuzumab ozogamicin + chemotherapy idarubicin mitoxantrone venetoclax + chemotherapy	None	0
<b>Diagnostic significance:</b> Acute Myeloid Leukemia				

Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

Public data sources included in diagnostic significance: NCCN, ESMO

### Prevalent cancer biomarkers without relevant evidence based on included data sources

DNMT3A p.(R882C) c.2644C>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
DNMT3A	p.(R882C)	c.2644C>T	COSM53042	chr2:25457243	45.87%	NM_022552.4	missense	1999
NPM1	p.(W288Cfs*12)	c.863_864insTCTG	COSM17559	chr5:170837547	45.73%	NM_002520.6	frameshift Insertion	1990
FLT3	p.(D586_R595dup)	c.1787_1788insTAAT GAGTACTTCTACGT TGATTTTCAGAGA	.	chr13:28608268	35.65%	NM_004119.3	nonframeshift Insertion	1972
NRAS	p.(L53=)	c.159G>A	.	chr1:115256552	50.35%	NM_002524.5	synonymous	2000

## 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<sup>1</sup>. 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<sup>2,3</sup>.

**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)<sup>4,5,6,7,8,9,10</sup>. 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<sup>9,11</sup>. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported<sup>4,9</sup>. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations<sup>12,13</sup>. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation<sup>14,15</sup>. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity<sup>16</sup>.

**Potential relevance:** DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML<sup>4,7,8,13</sup>. 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)<sup>17</sup>.

### 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<sup>18</sup>. FLT3 is highly expressed in hematopoietic progenitor cells<sup>19</sup>. 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<sup>18</sup>.

**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<sup>9,20,21,22</sup>. 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<sup>23</sup>. The second most frequent mutations are point mutations in exon 20 within the tyrosine kinase domain (TKD)<sup>24</sup>. FLT3 is amplified in up to 8% of colorectal cancer, 3% of stomach cancer, and is commonly overexpressed in AML<sup>9,22,25</sup>.

**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<sup>26</sup>. The presence of FLT3-ITD confers poor prognosis in myelodysplastic syndrome (MDS)<sup>11</sup>. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML<sup>10,27</sup>. FLT3 TKD mutation at D835 confers poor prognosis in MDS<sup>11</sup>. Midostaurin<sup>28</sup> (2017) and gilteritinib<sup>29</sup> (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<sup>30</sup> and in 2022 to tuspentinib (HM43239)<sup>31</sup> for FLT3 mutation-positive relapsed or refractory AML. In 2018 the FDA granted breakthrough therapy designation to quizartinib<sup>32</sup> 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)<sup>33</sup>. Another phase II trial of crenolanib with chemotherapy in newly diagnosed FLT3 mutated AML reported complete remission in 24/29 (83%) patients<sup>34</sup>. 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<sup>10</sup>.

### NPM1 (nucleophosmin 1)

**Background:** The NPM1 gene encodes the nucleophosmin protein, a histone chaperone of the nucleophosmin/nucleoplasmin family, which also includes NPM2 and NPM3<sup>35</sup>. NPM1 functions as an oncogene and tumor suppressor, and is important in maintaining genomic stability, DNA repair, and apoptosis<sup>35,36</sup>. NPM1 has a highly conserved N-terminal region which constitutes the core domain responsible for oligomerization, an acidic domain, a nuclear localization signal, and a disorganized C-terminal region which is required for nucleolar localization<sup>35</sup>. Oligomerization of NPM1 localizes the protein in the nucleus of proliferating cells where it binds to Akt in response to growth factor stimulation and escapes proteolytic degradation by caspase activity, thereby promoting cell survival<sup>35,36</sup>. NPM1 is one of the most frequently altered genes in hematological cancers<sup>37</sup>. Most NPM1 mutations occur in the C-terminus, impacting protein folding or the nucleolar localization signal, and result in the localization of NPM1 to the cytoplasm (NPMc) instead of to the nucleus<sup>35</sup>.

## Biomarker Descriptions (continued)

Alterations and prevalence: NPM1 mutations are observed in 45-60% of AML with a normal karyotype (NK-AML), 28-35% of de novo acute myeloid leukemia (AML) and are frequently co-mutated with DNMT3A and/or FLT3-ITD<sup>10,38,39</sup>. NPM1 fusions are associated with distinct partner genes in acute promyelocytic leukemia (APL), anaplastic large-cell lymphoma (ALCL), AML, and myelodysplasia<sup>37</sup>. Specifically, NPM1-ALK fusion is found in 30% of all ALCL and this specific fusion is observed in 85% of ALK-positive ALCL<sup>35</sup>. The t(5;17)(q35;q21) translocation that results in NPM1-RARA fusion is observed in APL<sup>40</sup>.

Potential relevance: Mutation of NPM1 is recognized as a diagnostic entity for AML with NPM1 mutation by the World Health Organization (WHO)<sup>26</sup>. NPM1 mutations are associated with better outcomes, increased complete remission, improved overall survival, and favorable risk in AML<sup>10,27,39</sup>. Concurrent expression of FLT-ITD with mutant or wild-type NPM1 (when lacking adverse risk genetic lesions) confers intermediate risk in AML<sup>10,27</sup>. The NPM1 frameshift mutation W288fs\*12 is associated with poor prognosis in myelodysplastic syndrome (MDS)<sup>11</sup>. The ALK-NPM1 fusion and translocation t(2;5)(p23;q35) which leads to an ALK-NPM1 fusion is diagnostic of ALK-positive anaplastic large cell lymphoma<sup>17,41</sup>.

## 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	●	×	●	●	×
Allogeneic hematopoietic stem cell transplantation	×	●	×	×	×
azacitidine	×	●	×	×	×
cytarabine	×	●	×	×	×
cytarabine + fludarabine + idarubicin + filgrastim	×	●	×	×	×
daunorubicin	×	●	×	×	×
decitabine	×	●	×	×	×
gemtuzumab ozogamicin + cytarabine + daunorubicin	×	●	×	×	×
gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim	×	●	×	×	×
gemtuzumab ozogamicin + daunorubicin	×	●	×	×	×
gilteritinib + azacitidine	×	●	×	×	×
idarubicin	×	●	×	×	×
midostaurin	×	●	×	×	×
midostaurin + cytarabine	×	●	×	×	×
midostaurin + daunorubicin	×	●	×	×	×
mitoxantrone	×	●	×	×	×
sorafenib	×	●	×	×	×
sorafenib + azacitidine	×	●	×	×	×

## 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*
sorafenib + decitabine	✕	●	✕	✕	✕
venetoclax + azacitidine	✕	●	✕	✕	✕
venetoclax + cytarabine	✕	●	✕	✕	✕
venetoclax + cytarabine + fludarabine + idarubicin + filgrastim	✕	●	✕	✕	✕
venetoclax + decitabine	✕	●	✕	✕	✕

### NPM1 p.(W288Cfs\*12) c.863\_864insTCTG

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✕	●	✕	✕	✕
azacitidine	✕	●	✕	✕	✕
cytarabine	✕	●	✕	✕	✕
cytarabine + fludarabine + idarubicin + filgrastim	✕	●	✕	✕	✕
daunorubicin	✕	●	✕	✕	✕
decitabine	✕	●	✕	✕	✕
gemtuzumab ozogamicin + cytarabine + daunorubicin	✕	●	✕	✕	✕
gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim	✕	●	✕	✕	✕
gemtuzumab ozogamicin + daunorubicin	✕	●	✕	✕	✕
idarubicin	✕	●	✕	✕	✕
mitoxantrone	✕	●	✕	✕	✕
venetoclax + cytarabine + fludarabine + idarubicin + filgrastim	✕	●	✕	✕	✕

## 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 2023-04-19. For the most up-to-date information, search [www.fda.gov](https://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](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/2021/207997s008lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207997s008lbl.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 2023-04-03. For the most up-to-date information, search [www.nccn.org](http://www.nccn.org).  
For NCCN International Adaptations & Translations, search [www.nccn.org/global/international\\_adaptations.aspx](http://www.nccn.org/global/international_adaptations.aspx).

### FLT3 ITD mutation + NPM1 p.(W288Cfs\*12) c.863\_864insTCTG

#### ● azacitidine

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- (Maintenance therapy)
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

#### ● daunorubicin

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- (Maintenance therapy)
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

#### ● idarubicin

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- (Maintenance therapy)
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**FLT3 ITD mutation + NPM1 p.(W288Cfs\*12) c.863\_864insTCTG (continued)****● gemtuzumab ozogamicin + cytarabine + daunorubicin**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

Other criteria: CD33 positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Induction therapy); Other recommended intervention
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● gemtuzumab ozogamicin + daunorubicin**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

Other criteria: CD33 positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Induction therapy); Other recommended intervention
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● mitoxantrone**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● cytarabine + fludarabine + idarubicin + filgrastim**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]



**FLT3 ITD mutation + NPM1 p.(W288Cfs\*12) c.863\_864insTCTG (continued)****● decitabine**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● venetoclax + cytarabine + fludarabine + idarubicin + filgrastim**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 ITD mutation &amp; NPM1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● Allogeneic hematopoietic stem cell transplantation**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 &amp; NPM1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

**● cytarabine**

Cancer type: Acute Myeloid Leukemia

Variant classes: FLT3 &amp; NPM1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

## 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 2.2023]

### ● 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 2.2023]

### ● Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia

Variant class: FLT3 ITD mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Residual (Recurrence therapy)
- (Induction therapy, Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

### ● 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 2.2023]

## FLT3 ITD mutation (continued)

### ● midostaurin + daunorubicin

Cancer type: Acute Myeloid Leukemia

Variant class: FLT3 ITD mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Residual (Recurrence therapy)
- (Induction therapy, Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

### ● 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 2.2023]

### ● 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 2.2023]

### ● 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 2.2023]

## 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 2.2023]

### ● gilteritinib

Cancer type: Acute Myeloid Leukemia

Variant class: FLT3 ITD mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Maintenance therapy)
- (Induction therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

### ● gilteritinib + azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: FLT3 ITD mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Maintenance therapy)
- (Induction therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

### ● midostaurin

Cancer type: Acute Myeloid Leukemia

Variant class: FLT3 ITD mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Maintenance therapy)
- (Induction therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2023]

## FLT3 ITD mutation (continued)

### ● azacitidine

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 2.2023]

### ● decitabine

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 2.2023]

### ● sorafenib

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 2.2023]

### ● sorafenib + azacitidine

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 2.2023]

### ● sorafenib + decitabine

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 2.2023]

## FLT3 ITD mutation (continued)

### ● 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 2.2023]

## 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 2023-04-19. For the most up-to-date information, search [www.ema.europa.eu/ema](https://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](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](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 2023-04-03. For the most up-to-date information, search [www.esmo.org](http://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.]



## Diagnostic Details

### Current ESMO Information

ESMO information is current as of 2023-04-03. For the most up-to-date information, search [www.esmo.org](http://www.esmo.org).

#### NPM1 p.(W288Cfs\*12) c.863\_864insTCTG

### Diagnostic significance: Acute Myeloid Leukemia

Variant class: NPM1 mutation

#### Diagnostic notes:

- AML with recurrent genetic abnormalities; WHO classification of AML

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 2023-04-19. For the most up-to-date information, search [www.fda.gov](http://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>

### tuspentinib

Cancer type: Acute Myeloid Leukemia

Variant class: FLT3 mutation

#### Supporting Statement:

The FDA has granted Fast Track Designation to tuspentinib (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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