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## Sample Information

**Patient Name:** 江奕峰
**Gender:** Male
**ID No.:** F122873807
**History No.:** 30290085
**Age:** 48

**Ordering Doctor:** DOC1483K 王浩元
**Ordering REQ.:** 0CGFFTM
**Signing in Date:** 2023/02/21

**Path No.:** M112-00031
**MP No.:** MY23008
**Assay:** Oncomine Myeloid Assay
**Sample Type:** Bone Marrow
**Bone Marrow Aspirating Date:** 2023/02/16

**Reporting Doctor:** DOC5466K 葉奕成 (Phone: 8#5466)

**Note:**

## Sample Cancer Type: Myelodysplastic Syndrome

### Table of Contents



### Report Highlights

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## Relevant Myelodysplastic Syndrome Variants

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| ASXL1 | None detected | NPM1 | None detected |
| BCOR | None detected | NRAS | None detected |
| CBL | None detected | NUP214 | None detected |
| CREBBP | None detected | RUNX1 | None detected |
| ETV6 | None detected | SF3B1 | None detected |
| EZH2 | None detected | SRSF2 | None detected |
| FLT3 | ***FLT3 ITD mutation*** | STAG2 | None detected |
| GATA2 | None detected | TP53 | None detected |
| IDH2 | None detected | U2AF1 | None detected |
| KIT | None detected | WT1 | None detected |
| KMT2A | None detected | ZRSR2 | None detected |

## Relevant Myelodysplastic Syndrome Variants (continued)

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| MECOM | 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*<br>fms related receptor tyrosine kinase 3<br>Allele Frequency: 1.80% | None | **gilteritinib** [1, 2]<br>**midostaurin + chemotherapy** [1, 2]<br>azacitidine<br>cytarabine + daunorubicin<br>cytarabine + daunorubicin + etoposide<br>cytarabine + etoposide + idarubicin<br>cytarabine + fludarabine + idarubicin + filgrastim<br>cytarabine + idarubicin<br>cytarabine + mitoxantrone<br>decitabine<br>gemtuzumab ozogamicin + chemotherapy<br>sorafenib<br>sorafenib + chemotherapy<br>venetoclax + chemotherapy | 0 |
| | **Prognostic significance:** NCCN: Poor | | | |

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

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

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect | Coverage |
|---|---|---|---|---|---|---|---|---|
| FLT3 | p.(Y597_E598insDYNEYFYVDFREY) | c.1792_1793insATTATAATGAGTACTTCTACGTTGATTTCAGAGAATATG | . | chr13:28608263 | 1.80% | NM_004119.3 | nonframeshift Insertion | |
| EZH2 | p.(Y311=) | c.933T>C | . | chr7:148516754 | 48.97% | NM_004456.5 | synonymous | 1999 |

## 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

## Biomarker Descriptions (continued)

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].

## 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 | ○ | ○ | ○ | ○ | ✖ |
| 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 | ✖ | ○ | ✖ | ✖ | ✖ |

# 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

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### ○ 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

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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 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

### ○ 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]

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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:** 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:** 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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## FLT3 ITD mutation (continued)

### 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]

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### 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]

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### 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]

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## FLT3 ITD mutation (continued)

### 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]

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### 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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## FLT3 ITD mutation (continued)

### 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]

---

### 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]

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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):**
- (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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## FLT3 ITD mutation (continued)

### 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]

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### 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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## FLT3 ITD mutation (continued)

### 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]

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### 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]

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## FLT3 ITD mutation (continued)

### 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]

### 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]

## 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.]

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### ○ 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.]

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# 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: NCCN: Poor

**Cancer type:** Myelodysplastic Syndrome **Variant class:** FLT3 ITD mutation

**NCCN Recommendation category:** 2A

**Summary:**
- NCCN Guidelines® associate the biomarker with poor prognosis

**Reference:** NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

# 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

## Signatures

**Testing Personnel:** Shu-Ying Wang 2023.03.02 14:53:18 +08'00'

**Laboratory Supervisor:** 2023.03.02 14:53:31 +08'00'

**Pathologist:** Yi-Chu Yeh 2023.03.02 14:53:42 +08'00'

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