Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 王佳豪
Gender: Male
ID No.: Y120223983
History No.: 14880003
Age: 50

Ordering Doctor: DOC8919E 周逸峰
Ordering REQ.: 0CBMPCA
Signing in Date: 2022/11/1

Path No.: S111-97964
MP No.: MY22032
Assay: 2022/10/21
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: Oncomine Myeloid Assay

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

Table of Contents

Report Highlights

2 Relevant Biomarkers
12 Therapies Available
0 Clinical Trials

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	***NPM1 p.(W288Cfs*12) c.863_864insTCTG***
FLT3	***FLT3 ITD mutation***	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	*FLT3 ITD mutation* fms related receptor tyrosine kinase 3 Allele Frequency: 26.30%	**gilteritinib** [1, 2] **midostaurin + chemotherapy** [1, 2] cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy sorafenib sorafenib + chemotherapy venetoclax + chemotherapy	None	0
	Prognostic significance: ELN 2017: Favorable to Intermediate			
IA	*NPM1 p.(W288Cfs*12) c.863_864insTCTG* nucleophosmin 1 Allele Frequency: 49.33%	cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy midostaurin + chemotherapy	None	0
	Prognostic significance: ELN 2017: Favorable to Intermediate **Diagnostic significance:** Acute Myeloid Leukemia			

Public data sources included in relevant therapies: FDA[1], 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

PHF6 p.(K21) c.60_61insT, PHF6 p.(R198Sfs*20) c.594delG, 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	48.12%	NM_022552.4	missense	1999
NPM1	p.(W288Cfs*12)	c.863_864insTCTG	COSM17559	chr5:170837547	49.33%	NM_002520.6	frameshift Insertion	1778
FLT3	p.(Y572_D593dup)	c.1779_1780insTATGAAAGCCAGCTACAGATGGTACAGGTGACCGGCTCCTCAGATAATGAGTACTTCTACGTTGAT	.	chr13:28608276	26.30%	NM_004119.3	nonframeshift Insertion	
PHF6	p.(K21*)	c.60_61insT	.	chrX:133511706	45.42%	NM_032458.3	nonsense	1843

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
PHF6	p.(R198Sfs*20)	c.594delG	.	chrX:133547859	38.10%	NM_032458.3	frameshift Deletion	1433
GATA2	p.(A372T)	c.1114G>A	.	chr3:128200691	48.10%	NM_032638.5	missense	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[1]. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression[2,3].

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)[4,5,6,7,8,9,10]. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer[9,11]. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported[4,9]. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations[12,13]. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation[14,15]. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity[16].

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML[4,7,8,13]. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)[17].

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[18]. FLT3 is highly expressed in hematopoietic progenitor cells[19]. 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[18].

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

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[11]. Midostaurin[26] (2017) and gilteritinib[27] (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[28] for FLT3 mutation-positive relapsed or refractory AML and in 2018 to quizartinib[29] 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)[30]. Another phase II trial of crenolanib with chemotherapy in newly diagnosed FLT3 mutated AML reported complete remission in 24/29 (83%) patients[31]. 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[10].

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[32]. NPM1 functions as an oncogene and tumor suppressor, and is important in maintaining

Biomarker Descriptions (continued)

genomic stability, DNA repair, and apoptosis[32,33]. 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[32]. 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[32,33]. NPM1 is one of the most frequently altered genes in hematological cancers[34]. 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[32].

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[10,35,36]. NPM1 fusions are associated with distinct partner genes in acute promyelocytic leukemia (APL), anaplastic large-cell lymphoma (ALCL), AML, and myelodysplasia[34]. Specifically, NPM1-ALK fusion is found in 30% of all ALCL and this specific fusion is observed in 85% of ALK-positive ALCL[32]. The t(5;17)(q35;q21) translocation that results in NPM1-RARA fusion is observed in APL[37].

Potential relevance: NPM1 mutated AML is recognized as a distinct diagnostic disease entity by the World Health Organization (WHO)[38]. NPM1 mutations are associated with better outcomes, increased complete remission, and improved overall survival in AML[10,36]. NPM1 without FLT3-ITD mutations or with <0.5 allelic ratio FLT3-ITD mutations are associated with favorable risk in AML[10]. Concurrent NPM1 and with >0.5 allelic ratio FLT3-ITD mutations confer intermediate risk in AML, whereas wild-type NPM1 confers poor/adverse risk[10]. The NPM1 frameshift mutation W288fs*12 is associated with poor prognosis in myelodysplastic syndrome (MDS)[11]. 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[17,39].

PHF6 (PHD finger protein 6)

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[40,41].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[40,42,43,44]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[42,44]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[42]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[40,42].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[45].

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	●	●	●	●	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + daunorubicin + etoposide	✖	●	✖	✖	✖
cytarabine + etoposide + idarubicin	✖	●	✖	✖	✖
cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖

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*
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	✖	✖
midostaurin + cytarabine	✖	●	✖	✖	✖
sorafenib	✖	●	✖	✖	✖
sorafenib + azacitidine	✖	●	✖	✖	✖
sorafenib + decitabine	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

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

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

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 2022-08-17. 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

---

● 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 2022-08-01. 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 + NPM1 p.(W288Cfs*12) c.863_864insTCTG

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

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 classes:** FLT3 ITD mutation & NPM1 mutation

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 + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

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 + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

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 + NPM1 p.(W288Cfs*12) c.863_864insTCTG (continued)

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2A

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

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

---

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

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 classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2A

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

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

---

gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2A

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

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

---

midostaurin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2A

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

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

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

cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2B

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

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

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2B

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

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

cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

NCCN Recommendation category: 2B

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

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

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 2.2022]

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]

---

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]

---

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]

---

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]

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]

---

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 2022-08-17. 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:** 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:** 2022-07-01 **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 2022-08-01. For the most up-to-date information, search www.esmo.org.

FLT3 ITD mutation

● 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.]

● gilteritinib

Cancer type: Acute Myeloid Leukemia **Variant class:** FLT3 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.]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2022-08-01. 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 + NPM1 p.(W288Cfs*12) c.863_864insTCTG

Prognostic significance: ELN 2017: Intermediate

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

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]

Current ESMO Information

ESMO information is current as of 2022-08-01. For the most up-to-date information, search www.esmo.org.

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

Prognostic significance: ELN 2017: Intermediate

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

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.]

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant classes:** FLT3 ITD mutation & NPM1 mutation

Summary:
- FLT3-ITD^{Low}; Low 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.]

Diagnostic Details

Current ESMO Information

ESMO information is current as of 2022-08-01. For the most up-to-date information, search 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 2022-08-17. 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:

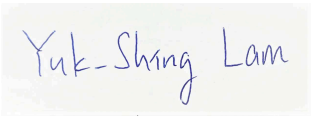
The FDA has granted Fast Track Designation to the benzimidazole type I kinase inhibitor, crenolanib, for:

- 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

Signatures

Testing Personnel: 

2022.11.07
13:47:09 +08'00'

Laboratory Supervisor: 
2022.11.07
13:47:33 +08'00'

Pathologist: 
2022.11.07
13:48:12 +08'00'

References

1. Okano et al. Cloning and characterization of a family of novel mammalian DNA (cytosine-5) methyltransferases. Nat Genet. 1998 Jul;19(3):219-20. PMID: 9662389
2. Fernandez et al. A DNA methylation fingerprint of 1628 human samples. Genome Res. 2012 Feb;22(2):407-19. PMID: 21613409
3. Jones et al. The epigenomics of cancer. Cell. 2007 Feb 23;128(4):683-92. PMID: 17320506
4. Ley et al. DNMT3A mutations in acute myeloid leukemia. N. Engl. J. Med. 2010 Dec 16;363(25):2424-33. PMID: 21067377
5. Marková et al. Prognostic impact of DNMT3A mutations in patients with intermediate cytogenetic risk profile acute myeloid leukemia. Eur. J. Haematol. 2012 Feb;88(2):128-35. PMID: 21967546
6. Yang et al. DNMT3A in haematological malignancies. Nat. Rev. Cancer. 2015 Mar;15(3):152-65. PMID: 25693834
7. Renneville et al. Prognostic significance of DNA methyltransferase 3A mutations in cytogenetically normal acute myeloid leukemia: a study by the Acute Leukemia French Association. Leukemia. 2012 Jun;26(6):1247-54. PMID: 22289988
8. Marcucci et al. Age-related prognostic impact of different types of DNMT3A mutations in adults with primary cytogenetically normal acute myeloid leukemia. J. Clin. Oncol. 2012 Mar 1;30(7):742-50. PMID: 22291079
9. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
10. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]
11. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2022]
12. Kumar et al. DNMT3A (R882) mutation features and prognostic effect in acute myeloid leukemia in Coexistent with NPM1 and FLT3 mutations. Hematol Oncol Stem Cell Ther. 2018 Jun;11(2):82-89. PMID: 29079128
13. Thol et al. Incidence and prognostic influence of DNMT3A mutations in acute myeloid leukemia. J. Clin. Oncol. 2011 Jul 20;29(21):2889-96. PMID: 21670448
14. Sandoval et al. Mutations in the DNMT3A DNA methyltransferase in acute myeloid leukemia patients cause both loss and gain of function and differential regulation by protein partners. J. Biol. Chem. 2019 Mar 29;294(13):4898-4910. PMID: 30705090
15. Holz-Schietinger et al. Mutations in DNA methyltransferase (DNMT3A) observed in acute myeloid leukemia patients disrupt processive methylation. J. Biol. Chem. 2012 Sep 7;287(37):30941-51. PMID: 22722925
16. Russler-Germain et al. The R882H DNMT3A mutation associated with AML dominantly inhibits wild-type DNMT3A by blocking its ability to form active tetramers. Cancer Cell. 2014 Apr 14;25(4):442-54. PMID: 24656771
17. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2022]
18. Grafone et al. An overview on the role of FLT3-tyrosine kinase receptor in acute myeloid leukemia: biology and treatment. Oncol Rev. 2012 Mar 5;6(1):e8. PMID: 25992210
19. Short et al. Emerging treatment paradigms with FLT3 inhibitors in acute myeloid leukemia. Ther Adv Hematol. 2019; 10: 2040620719827310. PMID: 30800259
20. Small. FLT3 mutations: biology and treatment. Hematology Am Soc Hematol Educ Program. 2006:178-84. PMID: 17124058
21. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013 May 30;368(22):2059-74. doi: 10.1056/NEJMoa1301689. Epub 2013 May 1. PMID: 23634996
22. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
23. Nakao et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996 Dec;10(12):1911-8. PMID: 8946930
24. Yamamoto et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood. 2001 Apr 15;97(8):2434-9. PMID: 11290608
25. Carow et al. Expression of the hematopoietic growth factor receptor FLT3 (STK-1/Flk2) in human leukemias. Blood. 1996 Feb 1;87(3):1089-96. PMID: 8562934
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207997s008lbledt.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211349s003lbl.pdf
28. 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
29. https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/006896.html
30. Jasleen et al. Results of a Phase II Study of Crenolanib in Relapsed/Refractory Acute Myeloid Leukemia Patients (Pts) with Activating FLT3 Mutations. Blood. 124:389

References (continued)

31. Bartus et al. Crenolanib in combination with standard chemotherapy in newly diagnosed FLT3-mutated AML patients. ASH 2017. Abstract #566
32. Box et al. Nucleophosmin: from structure and function to disease development. 2016 Aug 24;17(1):19. PMID: 27553022
33. Koike et al. Recruitment of phosphorylated NPM1 to sites of DNA damage through RNF8-dependent ubiquitin conjugates. Cancer Res. 2010 Sep 1;70(17):6746-56. PMID: 20713529
34. Sportoletti. How does the NPM1 mutant induce leukemia?. Pediatr Rep. 2011 Jun 22;3 Suppl 2:e6. PMID: 22053282
35. Hourigan et al. Accurate Medicine: Indirect Targeting of NPM1-Mutated AML. 2016 Oct;6(10):1087-1089. PMID: 27698101
36. Jain et al. Mutated NPM1 in patients with acute myeloid leukemia in remission and relapse. Leuk. Lymphoma. 2014 Jun;55(6):1337-44. PMID: 24004182
37. Redner et al. The t(5;17) acute promyelocytic leukemia fusion protein NPM-RAR interacts with co-repressor and co-activator proteins and exhibits both positive and negative transcriptional properties. Blood. 2000 Apr 15;95(8):2683-90. PMID: 10753851
38. Arber et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. PMID: 27069254
39. NCCN Guidelines® - NCCN-Primary Cutaneous Lymphomas [Version 2.2022]
40. Wendorff et al. Phf6 Loss Enhances HSC Self-Renewal Driving Tumor Initiation and Leukemia Stem Cell Activity in T-ALL. Cancer Discov. 2019 Mar;9(3):436-451. PMID: 30567843
41. Lower et al. Mutations in PHF6 are associated with Börjeson-Forssman-Lehmann syndrome. Nat. Genet. 2002 Dec;32(4):661-5. PMID: 12415272
42. Van et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. Nat. Genet. 2010 Apr;42(4):338-42. PMID: 20228800
43. Van et al. PHF6 mutations in adult acute myeloid leukemia. Leukemia. 2011 Jan;25(1):130-4. PMID: 21030981
44. Yoo et al. Somatic mutation of PHF6 gene in T-cell acute lymphoblatic leukemia, acute myelogenous leukemia and hepatocellular carcinoma. Acta Oncol. 2012 Jan;51(1):107-11. PMID: 21736506
45. Patel et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N. Engl. J. Med. 2012 Mar 22;366(12):1079-89. PMID: 22417203