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Date: 30 Mar 2023 1 of 17

Sample Information

Patient Name: 羅雅楹 Gender: Female ID No.: H222318896 History No.: 49383359

Age: 43

Ordering Doctor: DOC6266E 徐千富 Ordering REQ.: 0CHTWVQ Signing in Date: 2023/03/29

Path No.: M112-00050 **MP No.:** MY23017

Assay: Oncomine Myeloid Assay **Sample Type:** Bone Marrow

Bone Marrow Aspirating Date: 2023/03/24

Reporting Doctor: DOC5444B 楊靜芬 (Phone: 8#5444)

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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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	None detected
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: 4.10%	gilteritinib 1,2 midostaurin + chemotherapy 1,2 azacitidine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine gemtuzumab ozogamicin + chemotherapy sorafenib sorafenib + chemotherapy venetoclax + chemotherapy	None	0
	Prognostic significance: ELN 201	17: Adverse		

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

WT1 p.(A387Vfs*4) c.1159_1160insTCGG

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
WT1	p.(A387Vfs*4)	c.1159_1160insTCG G	COSM21392	chr11:32417907	35.89%	NM_024426.6	frameshift Insertion	1995
FLT3	p.(Q575_D600dup)	c.1722_1723insCAG CTACAGATGGTACA GGTGACCGGCTCCT CAGATAATGAGTAC TTCTACGTTGATTT CAGAGAATATGAAT ATGAT		chr13:28608333	4.10%	NM_004119.3	nonframeshift Insertion	
IKZF1	p.(A434G)	c.1301C>G		chr7:50468066	51.33%	NM_006060.6	missense	1999

Biomarker Descriptions

FLT3 (fms related receptor tyrosine kinase 3)

<u>Background:</u> 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 KIT¹. FLT3 is highly expressed in hematopoietic progenitor cells². 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 differentiation¹.

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) domain⁷. 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 MDS¹⁰. Midostaurin¹² (2017) and gilteritinib¹³ (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 crenolanib¹⁴ and in 2022 to tuspetinib (HM43239)¹⁵ for FLT3 mutation-positive relapsed or refractory AML. In 2018 the FDA granted breakthrough therapy designation to quizartinib¹⁶ 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%) patients¹⁸. 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 AML¹¹.

WT1 (WT1 transcription factor)

Background: The WT1 gene encodes the Wilms tumor 1 homolog, a zinc-finger transcriptional regulator that plays an important role in cellular growth and metabolism^{19,20}. WT1 is endogenously expressed in embryonic kidney cells as well as hematopoietic stem cells and regulates the process of filtration of blood through the kidneys²¹. WT1 protein contains N-terminal proline-glutamine rich regions that are involved in RNA and protein interaction while the C-terminal domain contains Kruppel link cysteine histidine zinc fingers that are involved in DNA binding¹⁹. WT1 interacts with various genes including TP53, STAT3, and epigenetic modifiers such as TET2 and TET3^{19,22}. WT1 is primarily characterized as a tumor suppressor gene involved in the development of renal Wilm's tumor (WT), a rare pediatric kidney cancer^{19,23}. Loss of function mutations observed in WT1, including large deletions and intragenic mutations, can impact the zinc finger domain, thereby decreasing the DNA binding activity¹⁹. WT1 overexpression is observed in acute myeloid leukemia (AML) and lymphoid cancers^{19,24}.

<u>Alterations and prevalence:</u> Somatic mutations of WT1 occur in 7% of AML, 5% of melanoma, and 1% of mesothelioma⁵. WT1 overexpression is observed in AML, acute lymphoblastic lymphoma (ALL), and myelodysplastic syndrome (MDS)¹⁹

Potential relevance: Somatic mutations in WT1, including nonsense, frameshift, and splice-site mutations, are associated with poor prognosis in MDS¹⁰. Overexpression of WT1 in MDS is associated with a higher risk of progression to AML. WT1 overexpression is also associated with poor prognosis, resistance to chemotherapy, and poor overall survival in AML²².

Relevant Therapy Summary

In this cancer type	In this cancer type In other cancer type In this cancer			other cancer types X No evidence		
FLT3 ITD mutat	tion					
Relevant Therapy		FDA	NCCN	EMA	ESMO	Clinical Trial
gilteritinib		•	•	•	•	×

Relevant Therapy	FUA	NCCN	LIVIA	ESIVIO	Cillical Illais
gilteritinib					×
midostaurin + cytarabine + daunorubicin			•		×
azacitidine	×	•	×	×	×
cytarabine + daunorubicin	×		×	×	×
cytarabine + daunorubicin + etoposide	×	•	×	×	×
cytarabine + etoposide + idarubicin	×	•	×	×	×
cytarabine + fludarabine + idarubicin + filgrastim	×	•	×	×	×
cytarabine + idarubicin	×	•	×	×	×

Relevant Therapy Summary (continued)

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

FLT3 ITD mutation (continued)					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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

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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FLT3 ITD mutation (continued)

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

O 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]

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]

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

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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]

gilteritinib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):

Relapsed, Refractory (Line of therapy not specified)

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

cytarabine + daunorubicin

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

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

Population segment (Line of therapy):

■ (Induction therapy); Preferred intervention

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

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

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]

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]

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]

midostaurin + cytarabine

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

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]

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)

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 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]

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]

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)

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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]

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]

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

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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

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Current EMA Information

In this cancer type

O 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

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Current ESMO Information

In this cancer type
In other cancer type
In this cancer type and other cancer types

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

FLT3 ITD mutation

gilteritinib

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

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

Population segment (Line of therapy):

■ Relapsed, Refractory (Line of therapy not specified)

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

midostaurin + cytarabine + daunorubicin

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

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

Population segment (Line of therapy):

■ (Induction therapy)

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

Prognostic Details

Current NCCN Information

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

FLT3 ITD mutation

Prognostic significance: ELN 2017: Adverse

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

Other criteria: NPM1 wild type

NCCN Recommendation category: 2A

Summary:

■ FLT3-ITDhigh; 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 2023-01-03. For the most up-to-date information, search www.esmo.org.

FLT3 ITD mutation

Prognostic significance: ELN 2017: Adverse

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

Other criteria: NPM1 wild type

Summary:

■ FLT3-ITDHigh; 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.]

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Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended

Resistance



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

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