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## Sample Information

**Patient Name:** 何瑞源
**Gender:** Male
**ID No.:** A110972818
**History No.:** 50117469
**Age:** 65

**Ordering Doctor:** DOC8131B 呂鍇東
**Ordering REQ.:** 0CVDXTC
**Signing in Date:** 2023/12/28

**Path No.:** M112-00341
**MP No.:** MY23086
**Assay:** Oncomine Myeloid Assay
**Sample Type:** Bone Marrow
**Bone Marrow Aspirating Date:** 2023/12/25

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

**Note:**

## Sample Cancer Type: Acute Myeloid Leukemia

### Table of Contents


| | Page |
|---|---|
| Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) | 2 |
| Biomarker Descriptions | 3 |
| Relevant Therapy Summary | 4 |
| Relevant Therapy Details | 6 |
| Alert Details | 21 |


### Report Highlights

4 Relevant Biomarkers
15 Therapies Available
0 Clinical Trials

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IA | *IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T*<br>isocitrate dehydrogenase (NADP(+)) 1<br>Allele Frequency: 4.10%, 9.51% (2 variants) | **ivosidenib** [1]<br>**ivosidenib + chemotherapy** [1, 2]<br>**olutasidenib** [1]<br>azacitidine<br>decitabine<br>venetoclax + chemotherapy | **ivosidenib** [1]<br>**ivosidenib + chemotherapy** [1] | 0 |

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

## Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IA | *RUNX1 p.(R204*) c.610C>T*<br>RUNX family transcription factor 1<br>Allele Frequency: 12.85% | allogeneic stem cells<br>azacitidine<br>cytarabine<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>liposomal cytarabine-daunorubicin<br>CPX-351<br>venetoclax + chemotherapy | None | 0 |
| IA | *ZRSR2 p.(R30Vfs*8) c.88delC*<br>zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2<br>Allele Frequency: 10.47% | allogeneic stem cells<br>azacitidine<br>cytarabine<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>liposomal cytarabine-daunorubicin<br>CPX-351<br>venetoclax + chemotherapy | None | 0 |

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

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

*PHF6 p.(K241*) c.721A>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 |
|---|---|---|---|---|---|---|---|---|
| IDH1 | p.(R132L) | c.395G>T | COSM28750 | chr2:209113112 | 9.51% | NM_005896.3 | missense | 1998 |
| IDH1 | p.(R132C) | c.394C>T | COSM28747 | chr2:209113113 | 4.10% | NM_005896.3 | missense | 1998 |
| RUNX1 | p.(R204*) | c.610C>T | . | chr21:36231774 | 12.85% | NM_001754.4 | nonsense | 2000 |
| ZRSR2 | p.(R30Vfs*8) | c.88delC | . | chrX:15809102 | 10.47% | NM_005089.3 | frameshift Deletion | 1996 |
| PHF6 | p.(K241*) | c.721A>T | . | chrX:133547988 | 28.20% | NM_032458.3 | nonsense | 2000 |
| EZH2 | p.(Y741C) | c.2222A>G | . | chr7:148504772 | 20.35% | NM_004456.5 | missense | 2000 |
| ETV6 | p.(N90_L96dup) | c.288_289insAATGGCAAAGCTCTCCTGCTG | . | chr12:11992175 | 13.67% | NM_001987.5 | nonframeshift Insertion | 1990 |

## 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 |
|---|---|---|---|---|---|---|---|---|
| ETV6 | p.(R103=) | c.309C>T | . | chr12:11992219 | 14.45% | NM_001987.5 | synonymous | 2000 |

## Biomarker Descriptions

**IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T**

*isocitrate dehydrogenase (NADP(+)) 1*

Background: The IDH1 and IDH2 genes encode homologous isocitrate dehydrogenase enzymes that catalyze the conversion of isocitrate to α-ketoglutarate (α-KG)[1]. The IDH1 gene encodes the NADP+ dependent cytoplasmic isocitrate dehydrogenase enzyme; IDH2 encodes the mitochondrial isoform.

Alterations and prevalence: Recurrent somatic mutations in IDH1 and IDH2 are mutually exclusive and observed in several malignancies including glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS)[2]. Recurrent IDH1 variants include predominately R132H/C plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[3]. Although wild-type enzymatic activity is ablated, recurrent IDH1 variants catalyze the conversion of α-KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair[1,4]. Recurrent IDH1 mutations are present in 5-10% of patients with AML and 5% of patients with MDS[5,6,7]. Recurrent IDH1 mutations are present in nearly 80% of lower grade diffuse gliomas[8,9].

Potential relevance: The IDH1 inhibitor, olutasidenib[10] is approved (2022) for the treatment of IDH1 R132C/G/H/L/S variants in AML. Ivosidenib[11] is also FDA approved (2018) for the treatment of AML or cholangiocarcinoma patients with IDH1 R132C/G/H/L/S variants[12]. Ivosidenib was granted breakthrough therapy designation (2020) for the treatment of IDH1 mutated relapsed or refractory myelodysplastic syndrome (MDS)[13]. IDH1 mutations are associated with inferior leukemia-free survival in primary myelofibrosis (PMF) and inferior overall survival in polycythemia vera (PV) but have been shown to confer improved prognosis in lower grade gliomas[14,15,16]. Mutations in IDH1 are diagnostic of astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q-codeleted subtypes of central nervous system (CNS) tumors[17].

**RUNX1 p.(R204*) c.610C>T**

*RUNX family transcription factor 1*

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[18]. All RUNX proteins share several conserved regions with similar functionality including a highly conserved N-terminal 'runt' domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[19]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[20,21]. RUNX1 is frequently mutated in various hematological malignancies[21]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[22,23]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[21].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[24]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6-RUNX1 fusion and is observed in 20-25% of childhood ALL[25,26,27]. This translocation is also observed in adult ALL at a lower frequency (2%)[26,27]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1-RUNX1T1 fusion and is observed in 5-10% of AML[28]. The RUNX1-RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[21,28]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[21]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[8,21,29,30].

Potential relevance: AML with RUNX1-RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[29,31]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1-RUNX1T1 in AML and t(12;21)(q34;q11)/ETV6-

## Biomarker Descriptions (continued)

RUNX1 in ALL, are associated with favorable risk[32,33]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[30,32,34].

**ZRSR2 p.(R30Vfs*8) c.88delC**

*zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2*

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3' intron splice site[35]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[35,36]. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes[35,37].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[9,30].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[29,30,32].

**PHF6 p.(K241*) c.721A>T**

*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[38,39].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[38,40,41,42]. 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)[40,42]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[40]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[38,40].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[43].

## Relevant Therapy Summary

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

### IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ivosidenib + azacitidine | ◑ | ● | ● | ✖ | ✖ |
| ivosidenib | ◑ | ● | ✖ | ● | ✖ |
| olutasidenib | ● | ● | ✖ | ✖ | ✖ |
| azacitidine | ✖ | ● | ✖ | ✖ | ✖ |
| decitabine | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + azacitidine | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + cytarabine | ✖ | ● | ✖ | ✖ | ✖ |

## Relevant Therapy Summary (continued)

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

### IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| venetoclax + decitabine | ✖ | ● | ✖ | ✖ | ✖ |

### RUNX1 p.(R204*) c.610C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| Allogeneic hematopoietic stem cell transplantation | ✖ | ● | ✖ | ✖ | ✖ |
| azacitidine | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + daunorubicin | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + daunorubicin + etoposide | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + etoposide + idarubicin | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + fludarabine + idarubicin + filgrastim | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + idarubicin | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + mitoxantrone | ✖ | ● | ✖ | ✖ | ✖ |
| decitabine | ✖ | ● | ✖ | ✖ | ✖ |
| liposomal cytarabine-daunorubicin CPX-351 | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + azacitidine | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + cytarabine | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + cytarabine + fludarabine + idarubicin + filgrastim | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + decitabine | ✖ | ● | ✖ | ✖ | ✖ |

### ZRSR2 p.(R30Vfs*8) c.88delC

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

### ZRSR2 p.(R30Vfs*8) c.88delC (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| cytarabine + idarubicin | ✖ | ● | ✖ | ✖ | ✖ |
| cytarabine + mitoxantrone | ✖ | ● | ✖ | ✖ | ✖ |
| decitabine | ✖ | ● | ✖ | ✖ | ✖ |
| liposomal cytarabine-daunorubicin CPX-351 | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + azacitidine | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + cytarabine | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + cytarabine + fludarabine + idarubicin + filgrastim | ✖ | ● | ✖ | ✖ | ✖ |
| venetoclax + decitabine | ✖ | ● | ✖ | ✖ | ✖ |

## Relevant Therapy Details

### Current FDA Information

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

FDA information is current as of 2023-11-15. For the most up-to-date information, search www.fda.gov.

### IDH1 p.(R132C) c.394C>T

#### ◑ ivosidenib, ivosidenib + azacitidine

**Cancer type:** Acute Myeloid Leukemia, Myelodysplastic Syndrome

**Label as of:** 2023-10-24

**Variant class:** IDH1 R132C mutation

**Indications and usage:**

TIBSOVO® is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

Newly Diagnosed Acute Myeloid Leukemia (AML)

- In combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Relapsed or refractory AML

- For the treatment of adult patients with relapsed or refractory AML.

Relapsed or refractory Myelodysplastic Syndromes (MDS)

- For the treatment of adult patients with relapsed or refractory myelodysplastic syndromes.

Locally Advanced or Metastatic Cholangiocarcinoma

- For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211192s011lbl.pdf

## IDH1 p.(R132C) c.394C>T (continued)

### olutasidenib

**Cancer type:** Acute Myeloid Leukemia **Label as of:** 2022-12-01 **Variant class:** IDH1 R132C mutation

**Indications and usage:**
REZLIDHIA™ is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215814s000lbl.pdf

## IDH1 p.(R132L) c.395G>T

### ivosidenib, ivosidenib + azacitidine

**Cancer type:** Acute Myeloid Leukemia, Myelodysplastic Syndrome **Label as of:** 2023-10-24 **Variant class:** IDH1 R132L mutation

**Indications and usage:**

TIBSOVO® is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

Newly Diagnosed Acute Myeloid Leukemia (AML)

- In combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Relapsed or refractory AML

- For the treatment of adult patients with relapsed or refractory AML.

Relapsed or refractory Myelodysplastic Syndromes (MDS)

- For the treatment of adult patients with relapsed or refractory myelodysplastic syndromes.

Locally Advanced or Metastatic Cholangiocarcinoma

- For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211192s011lbl.pdf

### olutasidenib

**Cancer type:** Acute Myeloid Leukemia **Label as of:** 2022-12-01 **Variant class:** IDH1 R132L mutation

**Indications and usage:**
REZLIDHIA™ is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215814s000lbl.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 2023-11-01. To view the most recent and complete version of the guideline, go online to NCCN.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.



## IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T

### ● ivosidenib + azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 R132 mutation

**NCCN Recommendation category:** 1

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

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

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### ● venetoclax + azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 R132 mutation

**NCCN Recommendation category:** 1

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

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

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### ● ivosidenib

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 R132 mutation

**NCCN Recommendation category:** 2A

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

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

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## IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T (continued)

### olutasidenib

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 R132 mutation

**NCCN Recommendation category:** 2A

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

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

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### venetoclax + decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 R132 mutation

**NCCN Recommendation category:** 2A

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

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

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### azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 mutation

**NCCN Recommendation category:** 2A

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

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

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### decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 mutation

**NCCN Recommendation category:** 2A

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

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

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### ivosidenib

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 mutation

**NCCN Recommendation category:** 2A

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

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

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## IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T (continued)

### venetoclax + cytarabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 mutation

**NCCN Recommendation category:** 2A

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

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

## RUNX1 p.(R204*) c.610C>T

### azacitidine

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

**NCCN Recommendation category:** 1

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

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

### cytarabine + daunorubicin

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

**NCCN Recommendation category:** 1

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

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

### cytarabine + daunorubicin + etoposide

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

**NCCN Recommendation category:** 1

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

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

## RUNX1 p.(R204*) c.610C>T (continued)

### cytarabine + etoposide + idarubicin

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

**NCCN Recommendation category:** 1

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

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

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### cytarabine + idarubicin

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

**NCCN Recommendation category:** 1

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

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

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### Allogeneic hematopoietic stem cell transplantation

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

**NCCN Recommendation category:** 2A

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

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

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### azacitidine

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

**NCCN Recommendation category:** 2A

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

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

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### cytarabine

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

**NCCN Recommendation category:** 2A

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

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

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## RUNX1 p.(R204*) c.610C>T (continued)

### cytarabine + mitoxantrone

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

**NCCN Recommendation category:** 2A

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

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

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### decitabine

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

**NCCN Recommendation category:** 2A

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

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

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### liposomal cytarabine-daunorubicin CPX-351

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

**NCCN Recommendation category:** 2A

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

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

---

### venetoclax + azacitidine

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

**NCCN Recommendation category:** 2A

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

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

---

### venetoclax + azacitidine

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

**NCCN Recommendation category:** 2A

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

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

---

## RUNX1 p.(R204*) c.610C>T (continued)

### venetoclax + cytarabine

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

**NCCN Recommendation category:** 2A

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

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

---

### venetoclax + decitabine

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

**NCCN Recommendation category:** 2A

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

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

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### venetoclax + decitabine

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

**NCCN Recommendation category:** 2A

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

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

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### azacitidine

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

**NCCN Recommendation category:** 2B

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

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

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### cytarabine + daunorubicin + etoposide

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

**NCCN Recommendation category:** 2B

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

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

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## RUNX1 p.(R204*) c.610C>T (continued)

### cytarabine + etoposide + idarubicin

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

**NCCN Recommendation category:** 2B

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

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

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### cytarabine + fludarabine + idarubicin + filgrastim

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

**NCCN Recommendation category:** 2B

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

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

---

### decitabine

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

**NCCN Recommendation category:** 2B

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

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

---

### venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

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

**NCCN Recommendation category:** 3

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

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

---

### venetoclax + decitabine

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

**NCCN Recommendation category:** 3

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

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

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## ZRSR2 p.(R30Vfs*8) c.88delC

### azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 1

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

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

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### cytarabine + daunorubicin

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 1

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

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

---

### cytarabine + daunorubicin + etoposide

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 1

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

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

---

### cytarabine + etoposide + idarubicin

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 1

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

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

---

### cytarabine + idarubicin

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 1

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

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

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## ZRSR2 p.(R30Vfs*8) c.88delC (continued)

### Allogeneic hematopoietic stem cell transplantation

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### cytarabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### cytarabine + mitoxantrone

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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## ZRSR2 p.(R30Vfs*8) c.88delC (continued)

### liposomal cytarabine-daunorubicin CPX-351

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### venetoclax + azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### venetoclax + azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### venetoclax + cytarabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### venetoclax + decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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## ZRSR2 p.(R30Vfs*8) c.88delC (continued)

### venetoclax + decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2A

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

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

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### azacitidine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2B

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

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

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### cytarabine + daunorubicin + etoposide

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2B

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

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

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### cytarabine + etoposide + idarubicin

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2B

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

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

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### cytarabine + fludarabine + idarubicin + filgrastim

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2B

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

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

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## ZRSR2 p.(R30Vfs*8) c.88delC (continued)

### decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 2B

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

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

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### venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 3

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

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

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### venetoclax + decitabine

**Cancer type:** Acute Myeloid Leukemia **Variant class:** ZRSR2 mutation

**NCCN Recommendation category:** 3

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

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

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## 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 2023-11-15. For the most up-to-date information, search www.ema.europa.eu/ema.

## IDH1 p.(R132C) c.394C>T

### ● ivosidenib + azacitidine

**Cancer type:** Acute Myeloid Leukemia **Label as of:** 2023-05-12 **Variant class:** IDH1 R132C mutation

**Reference:**

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

## IDH1 p.(R132L) c.395G>T

### ● ivosidenib + azacitidine

**Cancer type:** Acute Myeloid Leukemia **Label as of:** 2023-05-12 **Variant class:** IDH1 R132L mutation

**Reference:**

https://www.ema.europa.eu/en/documents/product-information/tibsovo-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 2023-11-01. For the most up-to-date information, search www.esmo.org.

### IDH1 p.(R132C) c.394C>T, IDH1 p.(R132L) c.395G>T

#### ivosidenib

**Cancer type:** Acute Myeloid Leukemia **Variant class:** IDH1 mutation

**ESMO Level of Evidence/Grade of Recommendation:** IV / B

**Population segment (Line of therapy):**
- Relapsed, Refractory (Second-line therapy)

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

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-11-15. For the most up-to-date information, search www.fda.gov.

### IDH1 p.(R132C) c.394C>T

#### ivosidenib

**Cancer type:** Myelodysplastic Syndrome **Variant class:** IDH1 mutation

**Supporting Statement:**
The FDA has granted Breakthrough Designation to the isocitrate dehydrogenase-1 inhibitor, ivosidenib, for the treatment of adult patients with relapsed or refractory myelodysplastic syndrome (MDS) with a susceptible IDH1 mutation as detected by an FDA-approved test.

**Reference:**

https://investor.agios.com/news-releases/news-release-details/agios-receives-fda-breakthrough-therapy-designation-tibsovor-0

### IDH1 p.(R132L) c.395G>T

#### ivosidenib

**Cancer type:** Myelodysplastic Syndrome **Variant class:** IDH1 mutation

**Supporting Statement:**
The FDA has granted Breakthrough Designation to the isocitrate dehydrogenase-1 inhibitor, ivosidenib, for the treatment of adult patients with relapsed or refractory myelodysplastic syndrome (MDS) with a susceptible IDH1 mutation as detected by an FDA-approved test.

**Reference:**

https://investor.agios.com/news-releases/news-release-details/agios-receives-fda-breakthrough-therapy-designation-tibsovor-0

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