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: 王賢德
Gender: Male
ID No.: W100051633
History No.: 41049972
Age: 69

Ordering Doctor: DOC1697J 蔡淳光
Ordering REQ.: 0CTAWCD
Signing in Date: 2023/11/10

Path No.: M112-00290
MP No.: MY23072
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/11/06

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*IDH1 p.(R132H) c.395G>A* isocitrate dehydrogenase (NADP(+)) 1 Allele Frequency: 42.72%	None	**ivosidenib** [1] **ivosidenib + chemotherapy** [2] **olutasidenib** [1] azacitidine decitabine venetoclax + chemotherapy	0

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004). The content of this report has not been evaluated or approved by FDA, EMA or other regulatory agencies.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*SRSF2 p.(P95R) c.284C>G* serine and arginine rich splicing factor 2 Allele Frequency: 45.25%	None	allogeneic stem cells 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 + chemotherapy	0
IIC	*STAG2 p.(N1223Mfs*11) c.3668delA* STAG2 cohesin complex component Allele Frequency: 31.54%	None	allogeneic stem cells 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 + chemotherapy	0

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

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

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
IDH1	p.(R132H)	c.395G>A	COSM28746	chr2:209113112	42.72%	NM_005896.3	missense	1999
SRSF2	p.(P95R)	c.284C>G	COSM211661	chr17:74732959	45.25%	NM_003016.4	missense	1916
STAG2	p.(N1223Mfs*11)	c.3668delA	.	chrX:123227955	31.54%	NM_001042749.2	frameshift Deletion	1994

Biomarker Descriptions

IDH1 (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

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Biomarker Descriptions (continued)

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].

SRSF2 (serine and arginine rich splicing factor 2)

Background: The SRFS2 gene encodes the serine/arginine (SR)-rich splicing factor 2, a member of the SR-rich family of pre-mRNA splicing factors which make up part of the spliceosome. SRFS2 contains an RNA recognition motif (RRM) that recognizes and binds exonic splicing enhancers (ESE) in a sequence-specific manner[18]. SR proteins are essential regulators of alternative RNA splicing due to their ability to bind RNA and interact with other splicing factors. These proteins can influence the exclusion of cassette exons, a form of alternative splicing also known as exon skipping, which allows for the production of different protein isoforms[18,19]. SRSF2 is the target of somatic missense mutations and in-frame deletions in hematological malignancies, particularly myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), and myeloproliferative neoplasms (MPN)[20,21,22]. Such mutations in SRSF2 result in a differential gain of function which influences cassette exon exclusion, thereby supporting an oncogenic role in cancer[23].

Alterations and prevalence: Mutations in SRSF2 are observed in approximately 10% of MDS cases and 30-40% of CMML[21,24,25]. Missense mutations at P95 are most recurrent, which leads to an amino acid change from proline to histidine (H), leucine (L), or arginine (R)[25]. Specifically, the P95H substitution alters SRSF2 affinity for ESEs and drives preferential recognition of cassette exons containing C- versus G-rich ESEs[22,23]. Although less prevalent, recurrent in-frame deletions (P95H_R102del) are observed in primary myelofibrosis (PMF)[26]. This mutation results in the deletion of 8 amino acids which has been shown to exhibit greater variation of splicing events relative to the P95 missense mutation alone[27].

Potential relevance: Mutation of SRSF2 considered is one of the molecular abnormalities that defines acute myeloid leukemia, myelodysplasia related (AML-MR) according to the World Health Organization (WHO)[28]. SRSF2 mutations confer poor prognosis and risk in MDS, systemic mastocytosis (SM), and acute myeloid leukemia (AML) and are associated with decreased overall survival (OS)[29,30,31,32,33]. In MPN, SRSF2 mutations are considered high-risk mutations and are independently associated with inferior OS as well as leukemia-free survival[14,34]. Additionally, SRSF2 mutations are predictive of leukemic transformation in patients with PMF[14].

STAG2 (STAG2 cohesin complex component)

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[35,36]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[37,38]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[37,39].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[29]. Somatic mutations in STAG2 are observed in various solid tumors including 14% of bladder cancer, 10% of uterine cancer, 3% of stomach cancer, and 4% of lung adenocarcinoma[9]. In addition, mutations in STAG2 are observed in 5-10% of myelodysplastic syndrome(MDS), 3% of acute myeloid leukemia, and 2% of diffuse large B-cell lymphoma[9,29].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and Acute Myeloid Leukemia[29,31,33]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[40].

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Relevant Therapy Summary

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

IDH1 p.(R132H) c.395G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ivosidenib	○	○	✖	○	✖
olutasidenib	○	○	✖	✖	✖
ivosidenib + azacitidine	✖	○	○	✖	✖
azacitidine	✖	○	✖	✖	✖
decitabine	✖	○	✖	✖	✖
venetoclax + azacitidine	✖	○	✖	✖	✖
venetoclax + cytarabine	✖	○	✖	✖	✖
venetoclax + decitabine	✖	○	✖	✖	✖

SRSF2 p.(P95R) c.284C>G

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	✖	○	✖	✖	✖

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Relevant Therapy Summary (continued)

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

STAG2 p.(N1223Mfs*11) c.3668delA

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	✖	○	✖	✖	✖

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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 2023-09-13. For the most up-to-date information, search www.fda.gov.

IDH1 p.(R132H) c.395G>A

○ ivosidenib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2022-05-25 **Variant class:** IDH1 R132H 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.

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/2022/211192s009lbl.pdf

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○ olutasidenib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2022-12-01 **Variant class:** IDH1 R132H 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

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Current NCCN Information

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

NCCN information is current as of 2023-09-01. For the most up-to-date information, search www.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.(R132H) c.395G>A

○ 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 4.2023]

○ 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 4.2023]

○ 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 4.2023]

○ 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 4.2023]

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IDH1 p.(R132H) c.395G>A (continued)

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 4.2023]

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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 4.2023]

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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 4.2023]

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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 4.2023]

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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 4.2023]

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SRSF2 p.(P95R) c.284C>G

azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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SRSF2 p.(P95R) c.284C>G (continued)

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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SRSF2 p.(P95R) c.284C>G (continued)

liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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SRSF2 p.(P95R) c.284C>G (continued)

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

SRSF2 p.(P95R) c.284C>G (continued)

decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 3

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** SRSF2 mutation

NCCN Recommendation category: 3

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

STAG2 p.(N1223Mfs*11) c.3668delA

azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

STAG2 p.(N1223Mfs*11) c.3668delA (continued)

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

STAG2 p.(N1223Mfs*11) c.3668delA (continued)

azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

STAG2 p.(N1223Mfs*11) c.3668delA (continued)

venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

STAG2 p.(N1223Mfs*11) c.3668delA (continued)

azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

STAG2 p.(N1223Mfs*11) c.3668delA (continued)

○ venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 3

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

○ venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** STAG2 mutation

NCCN Recommendation category: 3

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

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 2023-09-13. For the most up-to-date information, search www.ema.europa.eu/ema.

IDH1 p.(R132H) c.395G>A

○ ivosidenib + azacitidine

Cancer type: Acute Myeloid Leukemia **Label as of:** 2023-05-12 **Variant class:** IDH1 R132H mutation

Reference:

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

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 2023-09-01. For the most up-to-date information, search www.esmo.org.

IDH1 p.(R132H) c.395G>A

○ 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 2023-09-13. For the most up-to-date information, search www.fda.gov.

IDH1 p.(R132H) c.395G>A

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.10(004).

References

1. Molenaar et al. Wild-type and mutated IDH1/2 enzymes and therapy responses. Oncogene. 2018 Apr;37(15):1949-1960. PMID: 29367755
2. Yan et al. IDH1 and IDH2 mutations in gliomas. N. Engl. J. Med. 2009 Feb 19;360(8):765-73. PMID: 19228619
3. Dang et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009 Dec 10;462(7274):739-44. PMID: 19935646
4. Ward et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell. 2010 Mar 16;17(3):225-34. PMID: 20171147
5. Paschka et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J. Clin. Oncol. 2010 Aug 1;28(22):3636-43. PMID: 20567020
6. Chou et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia. 2011 Feb;25(2):246-53. PMID: 21079611
7. Marcucci et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J. Clin. Oncol. 2010 May 10;28(14):2348-55. PMID: 20368543
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. 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
10. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215814s000lbl.pdf
11. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211192s009lbl.pdf
12. Abou et al. The role of enasidenib in the treatment of mutant IDH2 acute myeloid leukemia. Ther Adv Hematol. 2018 Jul;9(7):163-173. PMID: 30013764
13. https://investor.agios.com/news-releases/news-release-details/agios-receives-fda-breakthrough-therapy-designation-tibsovor-0
14. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2023]
15. Cancer Genome Atlas Research Network. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med. 2015 Jun 25;372(26):2481-98. doi: 10.1056/NEJMoa1402121. Epub 2015 Jun 10. PMID: 26061751
16. Houillier et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010 Oct 26;75(17):1560-6. PMID: 20975057
17. Louis et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. PMID: 34185076
18. Liang et al. SRSF2 mutations drive oncogenesis by activating a global program of aberrant alternative splicing in hematopoietic cells. Leukemia. 2018 Dec;32(12):2659-2671. PMID: 29858584
19. Cui et al. Comparative Analysis and Classification of Cassette Exons and Constitutive Exons. Biomed Res Int. 2017;2017:7323508. doi: 10.1155/2017/7323508. Epub 2017 Dec 4. PMID: 29349080
20. Meggendorfer et al. The mutational landscape of 18 investigated genes clearly separates four subtypes of myelodysplastic/ myeloproliferative neoplasms. Haematologica. 2018 May;103(5):e192-e195. PMID: 29700173
21. Arbab et al. Prognostic significance of SRSF2 mutations in myelodysplastic syndromes and chronic myelomonocytic leukemia: a meta-analysis. Hematology. 2018 Dec;23(10):778-784. PMID: 29757120
22. Kim et al. SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition. Cancer Cell. 2015 May 11;27(5):617-30. PMID: 25965569
23. Zhang et al. Disease-associated mutation in SRSF2 misregulates splicing by altering RNA-binding affinities. Proc. Natl. Acad. Sci. U.S.A. 2015 Aug 25;112(34):E4726-34. PMID: 26261309
24. Ethan et al. AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 2017 Aug;7(8):818-831. PMID: 28572459
25. Thol et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood. 2012 Apr 12;119(15):3578-84. PMID: 22389253
26. Lasho et al. SRSF2 mutations in primary myelofibrosis: significant clustering with IDH mutations and independent association with inferior overall and leukemia-free survival. Blood. 2012 Nov 15;120(20):4168-71. PMID: 22968464
27. Komeno et al. SRSF2 Is Essential for Hematopoiesis, and Its Myelodysplastic Syndrome-Related Mutations Dysregulate Alternative Pre-mRNA Splicing. Mol. Cell. Biol. 2015 Sep 1;35(17):3071-82. PMID: 26124281
28. Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719. PMID: 35732831

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References (continued)

29. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]
30. NCCN Guidelines® - NCCN-Systemic Mastocytosis [Version 1.2020]
31. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 4.2023]
32. Jawhar et al. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. Leukemia. 2016 Dec;30(12):2342-2350. PMID: 27416984
33. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
34. Vannucchi et al. Mutations and prognosis in primary myelofibrosis. Leukemia. 2013 Sep;27(9):1861-9. PMID: 23619563
35. Mehta et al. Cohesin: functions beyond sister chromatid cohesion. FEBS Lett. 2013 Aug 2;587(15):2299-312. PMID: 23831059
36. Aquila et al. The role of STAG2 in bladder cancer. Pharmacol. Res. 2018 May;131:143-149. PMID: 29501732
37. Mullegama et al. De novo loss-of-function variants in STAG2 are associated with developmental delay, microcephaly, and congenital anomalies. Am. J. Med. Genet. A. 2017 May;173(5):1319-1327. PMID: 28296084
38. van et al. Synthetic lethality between the cohesin subunits STAG1 and STAG2 in diverse cancer contexts. Elife. 2017 Jul 10;6. PMID: 28691904
39. Solomon et al. Mutational inactivation of STAG2 causes aneuploidy in human cancer. Science. 2011 Aug 19;333(6045):1039-43. PMID: 21852505
40. Solomon et al. Frequent truncating mutations of STAG2 in bladder cancer. Nat. Genet. 2013 Dec;45(12):1428-30. PMID: 24121789

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