Taipei Veterans General Hospital

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Sample Information

Patient Name: 周昌杰
Gender: Male
ID No.: Q120235165
History No.: 16995883
Age: 65

Ordering Doctor: DOC1686E 陳玟均
Ordering REQ.: 0CBJCNQ
Signing in Date: 2022/10/18

Path No.: S111-97946
MP No.: MY22031
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/10/18

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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Relevant Acute Myeloid Leukemia Variants

Gene	Finding	Gene	Finding
ABL1	None detected	MECOM	None detected
ASXL1	***ASXL1 p.(W796*) c.2388G>A***	MLLT3	None detected
CEBPA	None detected	MYH11	None detected
CREBBP	None detected	NPM1	None detected
FLT3	None detected	NUP214	None detected
IDH1	***IDH1 p.(R132S) c.394C>A***	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	*IDH1 p.(R132S) c.394C>A* isocitrate dehydrogenase (NADP(+)) 1 Allele Frequency: 42.02%	**ivosidenib** [1] azacitidine decitabine ivosidenib + chemotherapy venetoclax + chemotherapy	None	1
IA	*ASXL1 p.(W796*) c.2388G>A* ASXL transcriptional regulator 1 Allele Frequency: 38.90%	allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine gemtuzumab ozogamicin + chemotherapy venetoclax + chemotherapy	None	0

Prognostic significance: ELN 2017: Adverse

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

Prevalent cancer biomarkers without relevant evidence based on included data sources
STAG2 p.(E383) c.1147G>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.(R132S)	c.394C>A	COSM28748	chr2:209113113	42.02%	NM_005896.3	missense	1999
ASXL1	p.(W796*)	c.2388G>A	.	chr20:31022903	38.90%	NM_015338.6	nonsense	2000
STAG2	p.(E383*)	c.1147G>T	.	chrX:123185195	75.21%	NM_001042749.2	nonsense	476
MPL	p.(R592Q)	c.1775G>A	.	chr1:43818310	38.17%	NM_005373.3	missense	1999
DNMT3A	p.(I681F)	c.2041A>T	.	chr2:25464472	42.64%	NM_022552.4	missense	1998
CALR	p.(?)	c.-72C>T	.	chr19:13049422	49.04%	NM_004343.4	unknown	1972

Biomarker Descriptions

ASXL1 (ASXL transcriptional regulator 1)

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,2]. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3[2]. ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and histones[2,3]. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors[2,4]. In cancer, ASXL1 is the target of somatic mutations which

Biomarker Descriptions (continued)

often result in a truncated ASXL1 protein and loss of its PHD[5,6,7]. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1[8].

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)[4,9,10,11,12,13,14,15,16]. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies[6,11,17]. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence[18]. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing[19]. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation[9,18,20].

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic[21]. Mutations in ASXL1 confer poor/adverse risk in AML and are associated with poor outcomes and adverse risk[16]. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML[22]. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM[23,24].

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)[25]. 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)[26]. Recurrent IDH1 variants include predominately R132H/C plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[27]. 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[25,28]. Recurrent IDH1 mutations are present in 5-10% of patients with AML and 5% of patients with MDS[29,30,31]. Recurrent IDH1 mutations are present in nearly 80% of lower grade diffuse gliomas[12,32].

Potential relevance: Ivosidenib[33] is FDA approved (2018) for the treatment of AML patients with IDH1 R132C/G/H/L/S variants[34]. Ivosidenib has also been granted breakthrough designation (2020) for IDH1 mutated relapsed or refractory myelodysplastic syndrome (MDS)[35]. 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[23,36,37].

STAG2 (stromal antigen 2)

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[38,39]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[40,41]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[40,42].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[22]. 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[32]. 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[22,32].

Potential relevance: Nonsense, frameshift, and splice site STAG2 mutations are associated with poor prognosis in MDS[22]. 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[43].

Relevant Therapy Summary

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

IDH1 p.(R132S) c.394C>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ivosidenib	●	●	✖	●	✖
azacitidine	✖	●	✖	✖	✖
decitabine	✖	●	✖	✖	✖
ivosidenib + azacitidine	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖
LY-3410738	✖	✖	✖	✖	● (I)

ASXL1 p.(W796*) c.2388G>A

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	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	✖	✖
venetoclax + azacitidine	✖	●	✖	✖	✖
venetoclax + cytarabine	✖	●	✖	✖	✖
venetoclax + decitabine	✖	●	✖	✖	✖

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Details

Current FDA Information

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

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

IDH1 p.(R132S) c.394C>A

● ivosidenib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2022-05-25 **Variant class:** IDH1 R132S 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

Current NCCN Information

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

NCCN information is current as of 2022-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

IDH1 p.(R132S) c.394C>A

ivosidenib + azacitidine

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

NCCN Recommendation category: 1

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

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

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venetoclax + azacitidine

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

NCCN Recommendation category: 1

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

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

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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 2.2022]

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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 2.2022]

IDH1 p.(R132S) c.394C>A (continued)

ivosidenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention
- Relapsed, Refractory (Line of therapy not specified)

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

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 2.2022]

venetoclax + decitabine

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 2.2022]

ASXL1 p.(W796*) c.2388G>A

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

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

ASXL1 p.(W796*) c.2388G>A (continued)

cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

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

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

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

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

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

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

ASXL1 p.(W796*) c.2388G>A (continued)

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

ASXL1 p.(W796*) c.2388G>A (continued)

gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

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

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

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

ASXL1 p.(W796*) c.2388G>A (continued)

cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

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

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

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

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cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

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

Current ESMO Information

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

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

IDH1 p.(R132S) c.394C>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.]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2022-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ASXL1 p.(W796*) c.2388G>A

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Summary:
- Do not use as an adverse prognostic marker if it co-occurs with favorable-risk AML subtypes.

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

Current ESMO Information

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

ASXL1 p.(W796*) c.2388G>A

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

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

Clinical Trials Summary

IDH1 p.(R132S) c.394C>A

NCT ID	Title	Phase
NCT04603001	A Phase I Study of Oral LY3410738 in Patients With Advanced Hematologic Malignancies With IDH1 or IDH2 Mutations.	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

IDH1 p.(R132S) c.394C>A

ivosidenib

Cancer type: Myelodysplastic Syndrome

Variant class: IDH1 mutation

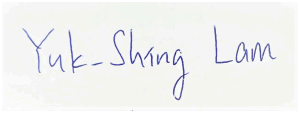
Supporting Statement:
The FDA has granted Breakthrough Designation to the isocitrate dehydrogenase-1 inhibitor, ivosidenib, for the treatment of adult patients with relapsed or refractory myelodysplastic syndrome (MDS) with a susceptible IDH1 mutation as detected by an FDA-approved test.

Reference:

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

Signatures

Testing Personnel:



2022.11.03
12:02:54 +08'00'

Laboratory Supervisor:

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Pathologist:

2022.11.03
12:03:27 +08'00'

References

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