Taipei Veterans General Hospital

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Sample Information

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Gender: Male
ID No.: F122798390
History No.: 19605653
Age: 59

Ordering Doctor: DOC4205A 柯博伸
Ordering REQ.: 0CNCQMS
Signing in Date: 2023/07/14

Path No.: M112-00182
MP No.: MY23042
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/07/06

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Myelodysplastic Syndrome Variants

Gene	Finding	Gene	Finding
ASXL1	None detected	NPM1	None detected
BCOR	None detected	NRAS	None detected
CBL	None detected	NUP214	None detected
CREBBP	None detected	RUNX1	None detected
ETV6	None detected	SF3B1	None detected
EZH2	None detected	SRSF2	None detected
FLT3	None detected	STAG2	None detected
GATA2	None detected	TP53	None detected
IDH2	None detected	U2AF1	None detected
KIT	None detected	WT1	None detected
KMT2A	None detected	ZRSR2	None detected
MECOM	None detected		

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.06(005). The content of this report has not been evaluated or approved by FDA, EMA or other regulatory agencies.

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*IDH1 p.(R132S) c.394C>A* isocitrate dehydrogenase (NADP(+)) 1 Allele Frequency: 14.75%	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

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	14.75%	NM_005896.3	missense	2000

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 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].

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	○	○	✖	○	✖

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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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olutasidenib	○	○	✖	✖	✖
ivosidenib + azacitidine	✖	○	○	✖	✖
azacitidine	✖	○	✖	✖	✖
decitabine	✖	○	✖	✖	✖
venetoclax + azacitidine	✖	○	✖	✖	✖
venetoclax + cytarabine	✖	○	✖	✖	✖
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 2023-05-17. 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

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

olutasidenib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2022-12-01 **Variant class:** IDH1 R132S 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 2023-05-01. 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.(R132S) c.394C>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 3.2023]

○ 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 3.2023]

○ 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 3.2023]

○ 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 3.2023]

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IDH1 p.(R132S) c.394C>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 3.2023]

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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); Preferred intervention
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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); Preferred intervention
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.06(005).

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

venetoclax + cytarabine

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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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 2023-05-17. For the most up-to-date information, search www.ema.europa.eu/ema.

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

○ ivosidenib + azacitidine

Cancer type: Acute Myeloid Leukemia **Label as of:** 2023-05-12 **Variant class:** IDH1 R132S 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 2023.06(005).

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 2023-05-01. 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.]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-05-17. 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

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