



Sample Information

Patient Name: 陳美慧
Gender: Female
ID No.: H200322716
History No.: 46221630
Age: 80

Ordering Doctor: DOC8284E 鄧齡喬
Ordering REQ.: 0CFQVJF
Signing in Date: 2023/02/04

Path No.: M112-00022
MP No.: MY23007
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/02/02

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	None detected	MLLT3	None detected
CEBPA	None detected	MYH11	None detected
CREBBP	None detected	NPM1	None detected
FLT3	None detected	NUP214	None detected
IDH1	None detected	RARA	None detected
IDH2	IDH2 p.(R140Q) c.419G>A	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	<i>IDH2 p.(R140Q) c.419G>A</i> isocitrate dehydrogenase (NADP(+)) 2 Allele Frequency: 45.47%	enasidenib ¹ azacitidine decitabine venetoclax + chemotherapy	None	1

Public data sources included in relevant therapies: FDA¹, NCCN, EMA², ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

SRSF2 p.(P95H) c.284C>A

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
IDH2	p.(R140Q)	c.419G>A	COSM41590	chr15:90631934	45.47%	NM_002168.4	missense	1999
SRSF2	p.(P95H)	c.284C>A	COSM211504	chr17:74732959	51.41%	NM_003016.4	missense	142

Biomarker Descriptions

IDH2 (isocitrate dehydrogenase (NADP(+)) 2)

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 IDH2 variants include predominately R140Q and R172K plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity³. Although wild-type enzymatic activity is ablated, recurrent IDH2 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 IDH2 mutations are present in 10-20% of patients with AML and 5% of patients with MDS^{5,6,7}.

Potential relevance: Enasidenib⁸ is FDA approved (2017) for the treatment of AML patients with IDH2 R140G/L/Q/W and R172G/K/M/S/W mutations. In AML, acquired resistance to enasidenib has been associated with the emergence of Q316E or I319M mutations⁹. IDH2 R172 and R140Q variants are associated with poor prognosis in MDS but have been shown to confer improved prognosis in lower grade gliomas^{10,11,12}. Additionally, IDH2 mutations are associated with inferior overall survival in polycythemia vera (PV) and essential thrombocythemia (ET) as well as inferior leukemia-free survival in primary myelofibrosis (PMF)¹³.

SRSF2 (serine and arginine rich splicing factor 2)

Background: The SRSF2 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. SRSF2 contains an RNA recognition motif (RRM) that recognizes and binds exonic splicing enhancers (ESE) in a sequence-specific manner¹⁴. 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^{14,15}. 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)^{16,17,18}. Such mutations in SRSF2 result in a differential gain of function which influences cassette exon exclusion, thereby supporting an oncogenic role in cancer¹⁹.

Alterations and prevalence: Mutations in SRSF2 are observed in approximately 10% of MDS cases and 30-40% of CMML^{17,20,21}. Missense mutations at P95 are most recurrent, which leads to an amino acid change from proline to histidine (H), leucine (L), or

Biomarker Descriptions (continued)

arginine (R)²¹. Specifically, the P95H substitution alters SRSF2 affinity for ESEs and drives preferential recognition of cassette exons containing C- versus G-rich ESEs^{18,19}. Although less prevalent, recurrent in-frame deletions (P95H_R102del) are observed in primary myelofibrosis (PMF)²². 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 alone²³.

Potential relevance: In CMML, SRSF2 mutations are often enriched and can be used to support diagnosis^{10,24}. SRSF2 mutations confer poor prognosis in MDS and systemic mastocytosis (SM) and are associated with decreased overall survival (OS)^{10,25,26}. In MPN, SRSF2 mutations are considered high-risk mutations and are independently associated with inferior OS as well as leukemia-free survival^{13,27}. Additionally, SRSF2 mutations are predictive of leukemic transformation in patients with PMF¹³.

Relevant Therapy Summary

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

IDH2 p.(R140Q) c.419G>A

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

* 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 2022-12-14. For the most up-to-date information, search www.fda.gov.

IDH2 p.(R140Q) c.419G>A

● enasidenib

Cancer type: Acute Myeloid Leukemia

Label as of: 2020-11-24

Variant class: IDH2 R140Q mutation

Indications and usage:

IDHIFA® is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209606s004lbl.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 2022-12-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

IDH2 p.(R140Q) c.419G>A

☒ venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- (Induction therapy); Preferred intervention

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

☒ azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 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]

☒ decitabine

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 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]

☒ enasidenib

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 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]

IDH2 p.(R140Q) c.419G>A (continued)**● venetoclax + cytarabine**

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 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: IDH2 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Induction therapy); Preferred 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 2022-12-01. For the most up-to-date information, search www.esmo.org.

IDH2 p.(R140Q) c.419G>A

☒ enasidenib

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 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.]

Clinical Trials Summary

IDH2 p.(R140Q) c.419G>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

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

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