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: 李勝光
Gender: Male
ID No.: F102882275
History No.: 18340471
Age: 76

Ordering Doctor: DOC1697J 蔡淳光
Ordering REQ.: H448JMB
Signing in Date: 2022/09/08

Path No.: S111-97878
MP No.: MY22024
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/09/01

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

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	***IDH2 p.(R140Q) c.419G>A***	U2AF1	None detected
KIT	None detected	WT1	None detected

Relevant Myelodysplastic Syndrome Variants (continued)

Gene	Finding	Gene	Finding
KMT2A	None detected	ZRSR2	***ZRSR2 p.(E365*) c.1093G>T, ZRSR2 p.(E11Rfs*12) c.24delG***
MECOM	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*IDH2 p.(R140Q) c.419G>A* isocitrate dehydrogenase (NADP(+)) 2 Allele Frequency: 37.30% **Prognostic significance:** NCCN: Poor	None	**enasidenib** [1] azacitidine decitabine venetoclax + chemotherapy	1
IA	*ZRSR2 p.(E365*) c.1093G>T, ZRSR2 p.(E11Rfs*12) c.24delG* zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2 Allele Frequency: 17.10%, 37.60% (2 variants) **Prognostic significance:** NCCN: Poor	None	None	0

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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
IDH2	p.(R140Q)	c.419G>A	COSM41590	chr15:90631934	37.30%	NM_002168.4	missense	2000
ZRSR2	p.(E11Rfs*12)	c.24delG	.	chrX:15808641	37.60%	NM_005089.3	frameshift Deletion	1992
ZRSR2	p.(E365*)	c.1093G>T	.	chrX:15841009	17.10%	NM_005089.3	nonsense	2000

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 activity[3]. 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].

Biomarker Descriptions (continued)

Potential relevance: Enasidenib[8] 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 mutations[9]. 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].

ZRSR2 (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[14]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[14,15]. 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[14,16].

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[10,17].

Potential relevance: Nonsense or frameshift mutations in ZRSR2 are associated with poor prognosis in myelodysplastic syndromes[10].

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 2022-08-17. 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 2022-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

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 2022-08-01. 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.]

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.

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

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** IDH2 R140Q mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® associate the biomarker with poor prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2022]

ZRSR2 p.(E365*) c.1093G>T, ZRSR2 p.(E11Rfs*12) c.24delG

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** ZRSR2 truncating mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® associate the biomarker with poor prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2022]

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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