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Sample Information

Patient Name: 林加旺
Gender: Male
ID No.: V100126937
History No.: 15300784
Age: 73

Ordering Doctor: DOC1901H 高志平
Ordering REQ.: H3M1D63
Signing in Date: 2021/12/23

Path No.: S110-94927
MP No.: MY21008
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2021/12/14

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	***SRSF2 p.(P95L) c.284C>T***
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
KMT2A	None detected	ZRSR2	None detected

Relevant Myelodysplastic Syndrome Variants (continued)

Gene	Finding	Gene	Finding
MECOM	None detected		

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IDH2 p.(R140Q) c.419G>A isocitrate dehydrogenase (NADP(+)) 2 Allele Frequency: 29.11% **Prognostic significance:** NCCN: Poor **Diagnostic significance:** None	None	**enasidenib** [1] azacitidine decitabine venetoclax + chemotherapy	1
SRSF2 p.(P95L) c.284C>T serine and arginine rich splicing factor 2 Allele Frequency: 16.07% **Prognostic significance:** NCCN: Poor **Diagnostic significance:** None	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

Prevalent cancer biomarkers without relevant evidence based on included data sources
TET2 p.(Q1553) c.4657C>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
TET2	p.(Q1553*)	c.4657C>T	.	chr4:106196324	30.53%	NM_001127208.2	nonsense	1998
IDH2	p.(R140Q)	c.419G>A	COSM41590	chr15:90631934	29.11%	NM_002168.4	missense	1999
SRSF2	p.(P95L)	c.284C>T	COSM146288	chr17:74732959	16.07%	NM_003016.4	missense	1966

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].

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[14]. 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 cancer[19].

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 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 alone[23].

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 PMF[13].

TET2 (tet methylcytosine dioxygenase 2)

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[28]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[29,30]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[31]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[28,29,30]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[10]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[29,32]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[13,24]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[13,33]

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	○	○	✖	○	✖

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

Relevant Therapy Summary (continued)

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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 2021-10-13. 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 2021-10-01. 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 3.2021]

○ 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 3.2021]

○ 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 3.2021]

○ 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 3.2021]

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 3.2021]

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 3.2021]

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 2021-10-01. 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 2021-10-01. 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 3.2021]

SRSF2 p.(P95L) c.284C>T

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** SRSF2 P95 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2021]

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:

Shin-Ying Lin 2021.12.24 08:59:58 +08'00'

Laboratory Supervisor:

2021.12.24 09:00:09 +08'00'

Pathologist:

Yi-Chu Yeh 2021.12.24 09:00:20 +08'00'

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