



Sample Information

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Gender: Female  
ID No.: A221627273  
History No.: 25156596  
Age: 64  
  
Ordering Doctor: DOC4205A 柯博伸  
Ordering REQ.: H47P228  
Signing in Date: 2023/09/20

Path No.: M112-00251  
MP No.: MY23068  
Assay: Oncomine Myeloid Assay  
Sample Type: Bone Marrow  
Bone Marrow Aspirating Date: 2023/09/14

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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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: 18.46%	enasidenib <sup>1</sup> azacitidine decitabine enasidenib + chemotherapy venetoclax + chemotherapy	None	0

Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources

NRAS p.(G12D) c.35G>A

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.08(005). The content of this report has not been evaluated or approved by FDA, EMA or other regulatory agencies.

## 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
NRAS	p.(G12D)	c.35G>A	COSM564	chr1:115258747	18.43%	NM_002524.5	missense	1997
IDH2	p.(R140Q)	c.419G>A	COSM41590	chr15:90631934	18.46%	NM_002168.4	missense	1999
IKZF1	p.(S506P)	c.1516T>C	.	chr7:50468281	18.90%	NM_006060.6	missense	2000
CEBPA	p.(H195_P196dup)	c.589_590insACCCG C	.	chr19:33792731	38.75%	NM_004364.4	nonframeshift Insertion	1489
CEBPA	p.(G122E)	c.365G>A	.	chr19:33792956	52.03%	NM_004364.4	missense	1868

## 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  $\alpha$ -ketoglutarate ( $\alpha$ -KG)<sup>1</sup>. The IDH1 gene encodes the NADP<sup>+</sup> 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)<sup>2</sup>. Recurrent IDH2 variants include predominately R140Q and R172K plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity<sup>3</sup>. Although wild-type enzymatic activity is ablated, recurrent IDH2 variants catalyze the conversion of  $\alpha$ -KG to D-2-hydroxyglutarate, an oncometabolite with diverse effects on cellular metabolism, epigenetic regulation, redox states, and DNA repair<sup>1,4</sup>. Recurrent IDH2 mutations are present in 10-20% of patients with AML and 5% of patients with MDS<sup>5,6,7</sup>.

**Potential relevance:** Enasidenib<sup>8</sup> 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<sup>9</sup>. IDH2 R172 and R140Q variants are associated with poor prognosis in MDS but have been shown to confer improved prognosis in lower grade gliomas<sup>10,11,12</sup>. 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)<sup>13</sup>. Mutations in IDH2 are diagnostic of astrocytoma IDH-mutant and oligodendroglioma IDH-mutant and 1p/19q-codeleted subtypes of central nervous system (CNS) tumors<sup>14</sup>.

### NRAS (NRAS proto-oncogene, GTPase)

**Background:** The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival<sup>15,16,17</sup>.

**Alterations and prevalence:** Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers<sup>18,19</sup>. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61<sup>18,20</sup>. Mutations at A59, K117, and A146 have also been observed but are less frequent<sup>21,22</sup>.

**Potential relevance:** Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab<sup>23</sup> and panitumumab<sup>24</sup>, are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)<sup>22</sup>. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787<sup>25</sup>, for the treatment of NRAS mutation positive metastatic or unresectable melanoma. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome<sup>10</sup> as well as melanoma<sup>26</sup>. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively<sup>27</sup>.

## 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	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>
azacitidine	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
decitabine	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
enasidenib + azacitidine	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
venetoclax + azacitidine	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
venetoclax + cytarabine	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
venetoclax + decitabine	<input checked="" type="checkbox"/>	<input checked="" type="radio"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

## 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 2023-07-19. For the most up-to-date information, search [www.fda.gov](https://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](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 2023-07-03. For the most up-to-date information, search [www.nccn.org](http://www.nccn.org). For NCCN International Adaptations & Translations, search [www.nccn.org/global/what-we-do/international-adaptations](http://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.

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

#### ● venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 R140 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- (Induction therapy); Preferred intervention

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

#### ● enasidenib

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 R140 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]

#### ● venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 R140 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- (Induction therapy); Preferred intervention

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

#### ● 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 3.2023]

**IDH2 p.(R140Q) c.419G>A (continued)****● 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 3.2023]

**● enasidenib**

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 3.2023]

**● 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 3.2023]

**● enasidenib + azacitidine**

Cancer type: Acute Myeloid Leukemia

Variant class: IDH2 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- (Induction therapy); Useful in certain circumstances

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

## 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 2023-07-03. For the most up-to-date information, search [www.esmo.org](http://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.]

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