Taipei Veterans General Hospital

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Sample Information

Patient Name: 楊美容
Gender: Female
ID No.: F226876959
History No.: 33972553
Age: 64

Ordering Doctor: DOC14863K 王浩元
Ordering REQ.: 0CHPVXC
Signing in Date: 2023/03/24

Path No.: M112-00049
MP No.: MY23016
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/03/20

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

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.(R172K) c.515G>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	*IDH2 p.(R172K) c.515G>A* isocitrate dehydrogenase (NADP(+)) 2 Allele Frequency: 19.35%	**enasidenib** [1] azacitidine decitabine venetoclax + chemotherapy	None	1

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
*BCOR p.(G1034Afs*21) c.3101delG*

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.(R172K)	c.515G>A	COSM33733	chr15:90631838	19.35%	NM_002168.4	missense	1995
BCOR	p.(G1034Afs*21)	c.3101delG	.	chrX:39930362	17.32%	NM_001123385.2	frameshift Deletion	1992
DNMT3A	p.(D857G)	c.2570A>G	.	chr2:25458603	24.92%	NM_022552.4	missense	1998
DNMT3A	p.(L647H)	c.1940T>A	.	chr2:25464573	30.31%	NM_022552.4	missense	1996
WT1	p.([R374=;R375H])	c.1122_1124delACGinsGCA	.	chr11:32417943	50.93%	NM_024426.6	synonymous, missense	1995
TP53	p.(A86V)	c.257C>T	.	chr17:7579430	50.30%	NM_000546.5	missense	2000

Biomarker Descriptions

BCOR (BCL6 corepressor)

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) corepressor protein which potentiates transcriptional repression by BCL6[1,2]. BCOR also associates with class I and II histone deacetylases (HDACs) suggesting an alternate mechanism for BCOR mediated transcriptional repression independent of BCL6[2]. Genetic alterations in BCOR result in protein dysfunction which suggests BCOR functions as a tumor suppressor gene[3,4,5].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[6,7,8,9]. Higher mutational frequencies are reported in some solid tumors, including up to 15% of uterine cancer and 5-10% of colorectal cancer, stomach cancer, cholangiocarcinoma, and melanoma. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[10,11,12]. Specifically, BCOR-CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR-CCNB3 sarcomas (BCS)[13,14]. In clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, one study described the presence of BCOR ITDs in more than 90% of cases[10].

Potential relevance: BCOR rearrangement, including inv(X)(p11.4p11.22) resulting in BCOR-CCNB3 fusion, is diagnostic of sarcoma with BCOR genetic alterations, a subset of undifferentiated round cell sarcomas[15,16]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B-BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[15]. Nonsense, frameshift, and splice site mutations in BCOR are associated with poor prognosis in myelodysplastic syndromes[6,7]. In FLT3-ITD negative AML patients under 65 with intermediate cytogenetic prognosis, mutations in BCOR confer inferior overall survival (OS) as well as relapse free survival (RFS) compared to those without BCOR abnormalities (OS= 13.6% vs. 55%; RFS= 14.3% vs. 44.5%)[9].

Biomarker Descriptions (continued)

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)[17]. 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)[18]. Recurrent IDH2 variants include predominately R140Q and R172K plus other substitutions at lower frequencies. These gain of function variants confer neomorphic enzyme activity[19]. 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[17,20]. Recurrent IDH2 mutations are present in 10-20% of patients with AML and 5% of patients with MDS[21,22,23].

Potential relevance: Enasidenib[24] 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[25]. IDH2 R172 and R140Q variants are associated with poor prognosis in MDS but have been shown to confer improved prognosis in lower grade gliomas[6,26,27]. 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)[28].

Relevant Therapy Summary

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

IDH2 p.(R172K) c.515G>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 2023-01-18. For the most up-to-date information, search www.fda.gov.

IDH2 p.(R172K) c.515G>A

● enasidenib

Cancer type: Acute Myeloid Leukemia **Label as of:** 2020-11-24 **Variant class:** IDH2 R172K 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 2023-01-03. 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.(R172K) c.515G>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.(R172K) c.515G>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 2023-01-03. For the most up-to-date information, search www.esmo.org.

IDH2 p.(R172K) c.515G>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.(R172K) c.515G>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

References

1. Gearhart et al. Polycomb group and SCF ubiquitin ligases are found in a novel BCOR complex that is recruited to BCL6 targets. Mol. Cell. Biol. 2006 Sep;26(18):6880-9. PMID: 16943429
2. Huynh et al. BCoR, a novel corepressor involved in BCL-6 repression. Genes Dev. 2000 Jul 15;14(14):1810-23. PMID: 10898795
3. Kelly et al. Bcor loss perturbs myeloid differentiation and promotes leukaemogenesis. Nat Commun. 2019 Mar 22;10(1):1347. PMID: 30902969
4. Cao et al. BCOR regulates myeloid cell proliferation and differentiation. Leukemia. 2016 May;30(5):1155-65. PMID: 26847029
5. Yamamoto et al. Clarifying the impact of polycomb complex component disruption in human cancers. Mol. Cancer Res. 2014 Apr;12(4):479-84. PMID: 24515802
6. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]
7. Damm et al. BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. Blood. 2013 Oct 31;122(18):3169-77. PMID: 24047651
8. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
9. Terada et al. Usefulness of BCOR gene mutation as a prognostic factor in acute myeloid leukemia with intermediate cytogenetic prognosis. Genes Chromosomes Cancer. 2018 Aug;57(8):401-408. PMID: 29663558
10. Wong et al. Clear cell sarcomas of the kidney are characterised by BCOR gene abnormalities, including exon 15 internal tandem duplications and BCOR-CCNB3 gene fusion. Histopathology. 2018 Jan;72(2):320-329. PMID: 28833375
11. Cramer et al. Successful Treatment of Recurrent Primitive Myxoid Mesenchymal Tumor of Infancy With BCOR Internal Tandem Duplication. J Natl Compr Canc Netw. 2017 Jul;15(7):868-871. PMID: 28687574
12. Peters et al. BCOR-CCNB3 fusions are frequent in undifferentiated sarcomas of male children. Mod. Pathol. 2015 Apr;28(4):575-86. PMID: 25360585
13. Puls et al. BCOR-CCNB3 (Ewing-like) sarcoma: a clinicopathologic analysis of 10 cases, in comparison with conventional Ewing sarcoma. Am. J. Surg. Pathol. 2014 Oct;38(10):1307-18. PMID: 24805859
14. Kao et al. BCOR-CCNB3 Fusion Positive Sarcomas: A Clinicopathologic and Molecular Analysis of 36 Cases With Comparison to Morphologic Spectrum and Clinical Behavior of Other Round Cell Sarcomas. Am. J. Surg. Pathol. 2018 May;42(5):604-615. PMID: 29300189
15. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2022]
16. NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2023]
17. Molenaar et al. Wild-type and mutated IDH1/2 enzymes and therapy responses. Oncogene. 2018 Apr;37(15):1949-1960. PMID: 29367755
18. Yan et al. IDH1 and IDH2 mutations in gliomas. N. Engl. J. Med. 2009 Feb 19;360(8):765-73. PMID: 19228619
19. Dang et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009 Dec 10;462(7274):739-44. PMID: 19935646
20. Ward et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell. 2010 Mar 16;17(3):225-34. PMID: 20171147
21. Paschka et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J. Clin. Oncol. 2010 Aug 1;28(22):3636-43. PMID: 20567020
22. Chou et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia. 2011 Feb;25(2):246-53. PMID: 21079611
23. Marcucci et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J. Clin. Oncol. 2010 May 10;28(14):2348-55. PMID: 20368543
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209606s004lbl.pdf
25. Intlekofer et al. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. Nature. 2018 Jul;559(7712):125-129. PMID: 29950729
26. Cancer Genome Atlas Research Network. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med. 2015 Jun 25;372(26):2481-98. doi: 10.1056/NEJMoa1402121. Epub 2015 Jun 10. PMID: 26061751
27. Houillier et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010 Oct 26;75(17):1560-6. PMID: 20975057
28. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 3.2022]