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Sample Information

Patient Name: 江欽思
Gender: Male
ID No.: F104017141
History No.: 48438239
Age: 70

Ordering Doctor: DOC1050C 劉嘉仁
Ordering REQ.: 0CLCTNF
Signing in Date: 2023/05/25

Path No.: M112-00113
MP No.: MY23028
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marro
Bone Marrow Aspirating Date: 2023/05/19

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	***CEBPA p.(G123Efs*37) c.368delG***	MYH11	None detected
CREBBP	None detected	NPM1	None detected
FLT3	None detected	NUP214	None detected
IDH1	None detected	RARA	None detected
IDH2	None detected	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	*CEBPA p.(G123Efs*37) c.368delG* CCAAT enhancer binding protein alpha Allele Frequency: 45.04%	cytarabine + daunorubicin cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy	None	0
	Diagnostic significance: Acute Myeloid Leukemia			

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

BCOR p.(R810) c.2428C>T, NRAS p.(G12D) c.35G>A, EZH2 c.2110+1G>A, KRAS p.(K117N) c.351A>C, TET2 p.(N281*) c.840_841insT, KRAS p.(A146T) c.436G>A, NRAS p.(G12S) c.34G>A, NRAS p.(G13C) c.37G>T, TET2 p.(S1087*) c.3260_3269delCTTCAGAAAA*

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.(G13C)	c.37G>T	COSM570	chr1:115258745	4.46%	NM_002524.5	missense	1996
NRAS	p.(G12D)	c.35G>A	COSM564	chr1:115258747	12.30%	NM_002524.5	missense	2000
NRAS	p.(G12S)	c.34G>A	COSM563	chr1:115258748	5.20%	NM_002524.5	missense	2000
TET2	p.(N281*)	c.840_841insT	.	chr4:106155938	47.17%	NM_001127208.2	nonsense	1993
TET2	p.(S1087*)	c.3260_3269delCTTCAGAAAA	.	chr4:106158358	45.15%	NM_001127208.2	nonsense	1980
EZH2	p.(?)	c.2110+1G>A	.	chr7:148506401	46.65%	NM_004456.5	unknown	2000
KRAS	p.(A146T)	c.436G>A	COSM19404	chr12:25378562	8.30%	NM_033360.4	missense	2000
KRAS	p.(K117N)	c.351A>C	COSM19940	chr12:25378647	7.45%	NM_033360.4	missense	2000
CEBPA	p.(G123Efs*37)	c.368delG	.	chr19:33792952	45.04%	NM_004364.4	frameshift Deletion	897
BCOR	p.(R810*)	c.2428C>T	.	chrX:39932171	88.40%	NM_001123385.2	nonsense	1810
EZH2	p.(R732T)	c.2195G>C	.	chr7:148506163	47.90%	NM_004456.5	missense	2000
SH2B3	p.(H541Y)	c.1621C>T	.	chr12:111885999	48.72%	NM_005475.3	missense	1995

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].

Biomarker Descriptions (continued)

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].

CEBPA (CCAAT enhancer binding protein alpha)

Background: The CEBPA gene encodes the enhancer binding protein alpha, a member of the basic region leucine zipper family of transcription factors that recognizes the CCAAT promoter[17]. CEBPA gives rise to two protein isoforms— p42 and p30, where p30 is the shorter isoform lacking the N-terminal 117 amino acids that is present in p42. Both isoforms contain the basic leucine zipper (bZip) domain involved in hetero/homo-dimerization with other CEBP family members and are required for DNA binding[17]. CEBPA is a tumor suppressor gene that plays a critical role in the development of granulocytes[17]. Specifically, CEBPA can influence the expression of granulocyte colony-stimulating factor (G-CSF) and interleukin 6 (IL-6), which are required for neutrophil maturation[18,19]. CEBPA also directly interacts and inhibits cell cycle kinases, including CDK2 and CDK4, thereby hindering cell proliferation[20]. CEBPA is the target of monoallelic or biallelic mutations leading to a loss of function, which can promote the development of cancers such as acute myeloid leukemia (AML)[21]. Germline mutations in CEBPA are also frequent among AML patients and are associated with predisposition to the disease[22,23].

Alterations and prevalence: Mutations in CEBPA are reported in 6-18% of all AML cases[8,24,25,26]. In AML, CEBPA mutations are observed to occur as either monoallelic (single mutant) or bi-allelic (double mutant)[26,27,28]. Biallelic CEBPA mutations are heterozygous and occur as a specific combination of an N-terminal frameshift on one allele and a C-terminal in frame mutation on the other, referred to as an N/C mutant[28,29]. Frameshift mutations result in the N-terminal truncation of approximately 120 amino acids while preserving the remaining 300 amino acids that are initiated further downstream[29]. C-terminal in-frame mutations disrupt the bZip domain which interferes with DNA binding and hetero/homo-dimerization with other CEBP family members. Specifically, N/C mutants possess one N-terminal truncated allele coding for the p30 isoform while the other allele codes for either p30 or p42 isoforms harboring C-terminal mutations[28].

Potential relevance: Single mutations located in the basic leucine zipper (bZIP) region of the gene (smbZIP-CEBPA) as well as biallelic CEBPA mutations are recognized as a diagnostic entity for AML with CEBPA mutation by the World Health Organization (WHO)[30]. Both smbZIP-CEBPA and biallelic CEBPA mutations are associated with a favorable prognosis in AML[31].

EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit)

Background: The EZH2 gene encodes the enhancer of zeste homolog 2 protein, a histone methyltransferase that functions as both a transcriptional suppressor and co-activator[32]. EZH2 mediates methylation of histone H3 at Lys 27 (H3K27me3) and promotes tumor growth and metastasis through regulation of the cell cycle[32,33]. Since EZH2 loss-of-function is associated with the development of cancer, it is considered a tumor suppressor. EZH2 is overexpressed in various cancer types, consequently, it can also function as an oncogene[32].

Alterations and prevalence: Diverse EZH2 alterations including missense, nonsense, frameshift mutations, and inactivating deletions are observed in 18-25% of T-cell acute lymphocytic leukemia (T-ALL), 3-13% of myeloproliferative neoplasms (MPN), 8-12% of myelodysplastic/myeloproliferative neoplasms overlap disorders (MDS/MPN), and 6% of diverse MDS[33,34]. Heterozygous gain-of-function mutations at tyrosine 641 (Y641) are observed in 22% of germinal center B-cell (GBC) and diffuse large B-cell lymphoma (DLBCL), and 7-17% of follicular lymphoma (FL)[33,35]. In solid tumors, EZH2 mutations are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 3% of cholangiocarcinoma[8,36]. Amplifications are observed in up to 7% of ovarian carcinoma[8,36]. Increased EZH2 copy number corresponds with enhanced protein expression and is observed in over 50% of hormone-refractory prostate cancers[37].

Potential relevance: The methyltransferase inhibitor tazemetostat[38] was FDA approved (2020) for EZH2 mutated relapsed or refractory follicular lymphoma after at least 2 prior systemic therapies. Tazemetostat was also granted FDA fast track designation in 2016

Biomarker Descriptions (continued)

for DLBCL harboring EZH2 activating mutations[39]. EZH2 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and MDS/MPN[6]. EZH2 mutations confer poor prognosis in essential thrombocythemia (ET) and primary myelofibrosis (PMF)[40]. EZH2 overexpression correlates with malignancy, poor prognosis, and poor survival, and has been detected in MDS and acute myeloid leukemia (AML)[32,41]. Several studies have shown EZH2 overexpression enhances chemoresistance in solid tumor types[42,43].

KRAS (KRAS proto-oncogene, GTPase)

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS 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[44,45,46].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[8]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[8,47,48]. Mutations at A59, K117, and A146 have also been observed but are less frequent[36,49].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[50] (2021) and adagrasib[51] (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[52], for KRAS G12C mutation in non-small cell lung cancer. The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer[53]. The PLK1 inhibitor, onvansertib[54], was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). Additionally, the SHP2 inhibitor, BBP-398[55] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC.The EGFR antagonists, cetuximab[56] and panitumumab[57], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[49]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[58].

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[44,45,46].

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[8,59]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[8,60]. Mutations at A59, K117, and A146 have also been observed but are less frequent[36,49].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[56] and panitumumab[57], 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)[49]. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787[61], 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[6] as well as melanoma[62]. 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[63].

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[64]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[65,66]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[67]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[64,65,66]

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)[6]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[65,68]. 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).

Biomarker Descriptions (continued)

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[40,69]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[40,70]

Relevant Therapy Summary

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

CEBPA p.(G123Efs*37) c.368delG

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim	✖	●	✖	✖	✖

Relevant Therapy Details

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 2023-03-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

CEBPA p.(G123Efs*37) c.368delG

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia

Variant class: CEBPA mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

CEBPA p.(G123Efs*37) c.368delG (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

CEBPA p.(G123Efs*37) c.368delG (continued)

gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

Other criteria: CD33 positive

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** CEBPA mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

Diagnostic Details

Current ESMO Information

ESMO information is current as of 2023-03-01. For the most up-to-date information, search www.esmo.org.

CEBPA p.(G123Efs*37) c.368delG

Diagnostic significance: Acute Myeloid Leukemia

Variant class: CEBPA mutation

Diagnostic notes:

- CEBPA biallelic mutations; AML with recurrent genetic abnormalities; WHO classification of AML

Reference: ESMO Clinical Practice Guidelines - ESMO-Acute Myeloblastic Leukaemia in Adult Patients [Ann Oncol (2020); 31(6): 697-712.]

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