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Sample Information

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Gender: Female
ID No.: F221164632
History No.: 23446244
Age: 66

Ordering Doctor: DOC6266E 徐千富
Ordering REQ.: 0CGGRLW
Signing in Date: 2023/02/21

Path No.: M112-00033
MP No.: MY23010
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/02/17

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

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	***CBFB-MYH11 fusion***
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	*CBFB-MYH11 fusion* core-binding factor subunit beta - myosin heavy chain 11	cytarabine + daunorubicin cytarabine + idarubicin cytarabine + mitoxantrone gemtuzumab ozogamicin + chemotherapy	None	0
	Prognostic significance: ELN 2017: Favorable **Diagnostic significance:** Acute Myeloid Leukemia			

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
KIT p.(T417_D419delinsY) c.1249_1255delACTTACGinsT, NRAS p.(Q61K) c.181C>A

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.(Q61K)	c.181C>A	COSM580	chr1:115256530	20.01%	NM_002524.5	missense	1994
KIT	p.(T417_D419delinsY)	c.1249_1255delACTTACGinsT	.	chr4:55589767	25.35%	NM_000222.3	nonframeshift Block Substitution	1976
ETV6	p.(V66I)	c.196G>A	.	chr12:11992106	46.37%	NM_001987.5	missense	1997

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
CBFB-MYH11	CBFB-MYH11.C4M33	chr16:67100701 - chr16:15814908	40
CBFB-MYH11	CBFB-MYH11.C5M33	chr16:67116211 - chr16:15814908	9834

Biomarker Descriptions

CBFB (core-binding factor subunit beta)

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[1]. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CFB) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis[2,3,4]. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation[3,4]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[4]

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma[5]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[5]. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with bone barrow eosinophilia (M4Eo) subtype[6]. Translocations often result in CBFB-MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[6].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for CBFB aberrations. Translocations, including inv(16) and t(16;16) which result in CBFB-MYH11 fusion, are diagnostic markers for acute myeloid leukemia and are associated with favorable prognosis[7].

KIT (KIT proto-oncogene, receptor tyrosine kinase)

Background: The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR[8,9]. KIT is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells[10]. The KIT gene is flanked by the PDGFRA and KDR genes on chromosome 4q12. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, promoting cell proliferation and survival[11].

Alterations and prevalence: Recurrent somatic KIT alterations are observed in both solid and hematological cancers and include activating mutations such as single nucleotide variants, small duplications, and complex in-frame insertions or deletions (indels). Mutations in KIT exons 8, 9, 11, and 17 disrupt auto-inhibitory mechanisms and lead to constitutive activity[12]. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma[13]. Somatic mutations in exon 11 occur in 60-70% of all gastrointestinal stromal tumor (GIST), whereas alterations in exons 8 and 17 are more common in myeloid cancers[12,13,14]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis[15,16].

Potential relevance: Imatinib[17] (2001) is approved for KIT positive unresectable or metastatic GIST and adult patients with aggressive systemic mastocytosis (SM) who do not have the D816V c-Kit mutation or whose c-Kit mutational status is unknown. Imatinib is also recommended for activating mutations, including KIT P577_W582delinsPYD and KIT V560D, in melanoma and exon 9 and 11 mutations in GIST[18,19,20,21]. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib[22]. Additionally, detection of activating mutations in KIT is useful as an ancillary technique in the diagnosis of GIST[23]. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse[7]. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease[24,25].

MYH11 (myosin heavy chain 11)

Background: MYH11 encodes myosin heavy-chain 11 which is a key contractile protein involved in smooth muscle movement, protein transport, and cell-cell interaction[26]. MYH11 belongs to the myosin family of motor proteins that functions to convert chemical energy into mechanical energy through ATP hydrolysis[27,28]. MYH11 consists of two pairs of light chains and two heavy chains produced from the MYH11 gene[1]. MYH11 is frequently translocated in acute myeloid leukemia (AML) where the C-terminal of MYH11 protein that contains a coiled-coil smooth muscle myosin heavy chain (SMMHC) fuses with the core binding factor ß (CBFß) gene[29,30]. The CBFB-MYH11 fusion dimerizes with RUNX1, a key transcription factor in myelodysplastic malignancies, and inhibits RUNX1's function in hematopoiesis[31].

Alterations and prevalence: Somatic missense, nonsense, and splice-site mutations of MYH11 are observed in 13% of melanoma, 10% of uterine, 6% of stomach as well as bladder cancers, and 2% of AML cases[14]. The inv(16)(p13.1;q22) or t(16;16)(p13.1;q22) translocation results in the CBFB-MYH11 fusion and is observed in over 5% of AML cases[30].

Potential relevance: The inv(16)(p13.1;q22)/t(16;16)(p13.1;q22), that results in CBFB-MYH11 fusion, is a diagnostic entity for AML, as defined by the World Health Organization (WHO)[7,32]. The CBFB-MYH11 fusion is also associated with favorable risk stratification in AML[7]

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[33,34,35].

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[5,36]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[5,37]. Mutations at A59, K117, and A146 have also been observed but are less frequent[14,38].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[39] and panitumumab[40], 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)[38]. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787[41], 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[42] as well as melanoma[43]. In a phase III clinical trial in patients with

Biomarker Descriptions (continued)

advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[44].

Relevant Therapy Summary

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

CBFB-MYH11 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	●	✖	●	✖
cytarabine + daunorubicin	✖	●	✖	✖	✖
cytarabine + idarubicin	✖	●	✖	✖	✖
cytarabine + mitoxantrone	✖	●	✖	✖	✖
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 2023-01-03. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

CBFB-MYH11 fusion

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia

Variant class: MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

CBFB-MYH11 fusion (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

CBFB-MYH11 fusion (continued)

gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gemtuzumab ozogamicin + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2B

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

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.

CBFB-MYH11 fusion

● gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

ESMO Level of Evidence/Grade of Recommendation: II / A

Population segment (Line of therapy):
- Core Bindig Factor (Induction 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 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.

CBFB-MYH11 fusion

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

NCCN Recommendation category: 2A

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Current ESMO Information

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

CBFB-MYH11 fusion

Prognostic significance: ELN 2017: Favorable

Cancer type: Acute Myeloid Leukemia **Variant class:** MYH11-CBFB fusion [t(16;16)(p13;q22)]

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

Diagnostic Details

Current NCCN Information

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.

CBFB-MYH11 fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: inv(16) or t(16;16)

NCCN Recommendation category: 2A

Diagnostic notes:
- WHO 2016 classification defined as ≥20% blasts in blood or bone marrow, or in appropriate clinical setting with <20% blasts and recurrent cytogenetic abnormalities.

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Diagnostic significance: Acute Myeloid Leukemia

Variant class: inv(16)

NCCN Recommendation category: 2A

Diagnostic notes:
- Karyotypes t(8;21), inv16, and t(15;17) are considered to be Acute Myeloid Leukemia even if the marrow blast count is less than 20%

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

Current ESMO Information

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

CBFB-MYH11 fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: MYH11-CBFB fusion [t(16;16)(p13;q22)]

Diagnostic notes:
- Core Binding Factor-Acute Myeloid Leukemia

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

Signatures

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