Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 游美華
Gender: Female
ID No.: G220102273
History No.: 20189393
Age: 56

Ordering Doctor: DOC6266E 徐千富
Ordering REQ.: 0CTVSQH
Signing in Date: 2023/11/24

Path No.: M112-00303
MP No.: MY23077
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/11/23

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	*RUNX1::RUNX1T1 fusion* RUNX family transcription factor 1 - RUNX1 partner transcriptional co-repressor 1 **Diagnostic significance:** Acute Myeloid Leukemia	gemtuzumab ozogamicin + chemotherapy	None	0

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

NRAS p.(G13D) c.38G>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.(G13D)	c.38G>A	COSM573	chr1:115258744	5.66%	NM_002524.5	missense	1998
FLT3	p.(E573_L576delinsAAG)	c.1718_1728delAAAGCCAGCTAinsCTGCGGGG	.	chr13:28608328	9.74%	NM_004119.3	nonframeshift Block Substitution	1972
CEBPA	p.(H195_P196dup)	c.589_590insACCCGC	.	chr19:33792731	31.61%	NM_004364.4	nonframeshift Insertion	174
CEBPA	p.(P189_S190delinsSHP)	c.564_568delGCCCTinsCTCGCACC	.	chr19:33792753	2.61%	NM_004364.4	nonframeshift Block Substitution	153

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
RUNX1-RUNX1T1	RUNX1-RUNX1T1.R3R3	chr21:36231771 - chr8:93029591	14360

Biomarker Descriptions

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[1,2,3].

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[4,5]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[4,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[9] and panitumumab[10], 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)[8]. The FDA has granted fast track designation to the pan-RAF inhibitor, KIN-2787[11], 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[12] as well as melanoma[13]. 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[14].

RUNX1 (RUNX family transcription factor 1)

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors which also includes RUNX2 and RUNX3[15]. All RUNX proteins share several conserved regions with similar functionality including a highly conserved N-terminal ‘runt’ domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein interacting motifs, and a nuclear matrix targeting signal[16]. Each of these proteins are capable of interacting with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF. Specifically, CBFβ binds to the 'runt' domain of RUNX1 leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[17,18]. RUNX1 is frequently mutated in various hematological malignancies[18]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[19,20]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[18].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[21]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6-RUNX1 fusion and is observed in 20-25% of

Biomarker Descriptions (continued)

childhood ALL[22,23,24]. This translocation is also observed in adult ALL at a lower frequency (2%)[23,24]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1-RUNX1T1 fusion and is observed in 5-10% of AML[25]. The RUNX1-RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[18,25]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[18]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[4,12,18,26].

Potential relevance: AML with RUNX1-RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[26,27]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1-RUNX1T1 in AML and t(12;21)(q34;q11)/ETV6-RUNX1 in ALL, are associated with favorable risk[28,29]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[12,28,30].

RUNX1T1 (RUNX1 partner transcriptional co-repressor 1)

Background: RUNX1T1 encodes RUNX1 partner transcriptional co-repressor 1 and is member of the ETO homologues family, which also includes RUNX1T2 and RUNX1T3[31,32]. RUNX1T1 functions as a transcriptional co-repressor by interacting with transcription factors and recruiting nuclear co-repressors[32]. The RUNX1-RUNX1T1 fusion is a frequent chromosomal alteration in acute myeloid leukemia (AML), resulting in a fusion protein with the DNA-binding domain of RUNX1 fused to the RUNX1T1 co-repressor protein[33,34].

Alterations and prevalence: Recurrent translocation, t(8;21)(q22;q22), results in RUNX1-RUNX1T1 fusion and is observed in 5-10% of AML[25]. The RUNX1-RUNX1T1 fusion consists of the fusion of the RHD domain of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[18,25]. Somatic mutations in RUNX1T1 are observed in 13% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 8% of lung squamous cell carcinoma, 5% of lung adenocarcinoma and colorectal adenocarcinoma, 4% of head and neck squamous cell carcinoma and stomach adenocarcinoma, 3% of esophageal adenocarcinoma and cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, liver hepatocellular carcinoma, bladder urothelial carcinoma, and acute myeloid leukemia[4,7].

Potential relevance: AML with RUNX1-RUNX1T1 fusion is considered a distinct molecular subtype by the World Health Organization (WHO)[26,27]. Translocation t(8;21)(q22;q22)/RUNX1-RUNX1T1 in AML is associated with favorable risk[26,28].

Relevant Therapy Summary

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

RUNX1::RUNX1T1 fusion

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

Relevant Therapy Details

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 2023-09-01. For the most up-to-date information, search www.esmo.org.

RUNX1::RUNX1T1 fusion

● gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1-RUNX1T1 fusion [t(8;21)(q22;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.]

Diagnostic Details

Current NCCN Information

NCCN information is current as of 2023-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search 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.

RUNX1::RUNX1T1 fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: t(8;21)

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 2023-09-01. For the most up-to-date information, search www.esmo.org.

RUNX1::RUNX1T1 fusion

Diagnostic significance: Acute Myeloid Leukemia

Variant class: RUNX1-RUNX1T1 fusion [t(8;21)(q22;q22)]

Diagnostic notes:
- 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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