Taipei Veterans General Hospital

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Sample Information

Patient Name: 宋慶棋
Gender: Male
ID No.: T100642596
History No.: 46627003
Age: 70

Ordering Doctor: DOC5636D 吳紋綺
Ordering REQ.: 0BDEVBB
Signing in Date: 2021/03/11

Path No.: S110-98360
MP No.: MY21002
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2021/03/05
Note:

Sample Cancer Type: Acute Myeloid Leukemia

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Relevant Acute Myeloid Leukemia Variants

Gene	Finding	Gene	Finding
ABL1	Not detected	MECOM	Not detected
ASXL1	Not detected	MLLT3	Not detected
CEBPA	Not detected	MYH11	Not detected
CREBBP	Not detected	NPM1	Not detected
FLT3	Not detected	NUP214	Not detected
IDH1	Not detected	RARA	Not detected
IDH2	Not detected	RUNX1	***RUNX1 p.(P278fs) c.833_843delCGTGGTCCTAC***
KMT2A	Not detected	TP53	Not detected

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
RUNX1 p.(P278fs) c.833_843delCGTGGTCCTAC runt related transcription factor 1 Allele Frequency: 38.81% **Prognostic significance:** ELN 2017: Adverse **Diagnostic significance:** None	None	None	2

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

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
RUNX1	p.(P278fs)	c.833_843delCGTGGTCCTAC	.	chr21:36171721	38.81%	NM_001754.4	frameshift Deletion	
TET2	p.(P29R)	c.86C>G	.	chr4:106155185	52.35%	NM_001127208.2	missense	2000
TET2	p.(A1196F)	c.3586_3587delGCinsTT	.	chr4:106164076	40.65%	NM_001127208.2	missense	1995
TET2	p.(Y1345S)	c.4034A>C	.	chr4:106182995	41.57%	NM_001127208.2	missense	1999
TET2	p.(I1762V)	c.5284A>G	.	chr4:106196951	47.22%	NM_001127208.2	missense	1999
BRAF	p.(=)	c.2235A>G	.	chr7:140434463	14.45%	NM_004333.4	synonymous	2000
HRAS	p.(=)	c.81T>C	.	chr11:534242	52.25%	NM_001130442.2	synonymous	1998
WT1	p.(=)	c.1107A>G	.	chr11:32417945	99.95%	NM_024426.4	synonymous	2000
KRAS	p.(=)	c.483G>A	.	chr12:25368462	99.40%	NM_033360.3	synonymous	1997
SH2B3	p.(W262R)	c.784T>C	.	chr12:111884608	99.85%	NM_005475.2	missense	1999
NF1	p.(=)	c.2034G>A	.	chr17:29553485	99.95%	NM_001042492.2	synonymous	1999
SRSF2	p.(=)	c.144C>T	.	chr17:74733099	99.80%	NM_003016.4	synonymous	1999
ASXL1	p.(G652S)	c.1954G>A	.	chr20:31022469	54.50%	NM_015338.5	missense	2000
ASXL1	p.(L815P)	c.2444T>C	.	chr20:31022959	100.00%	NM_015338.5	missense	1997
ASXL1	p.(=)	c.3759T>C	.	chr20:31024274	50.98%	NM_015338.5	synonymous	1999
ZRSR2	p.(=)	c.864C>T	.	chrX:15838366	99.75%	NM_005089.3	synonymous	1997
BCOR	p.(=)	c.1692A>G	.	chrX:39932907	100.00%	NM_001123385.1	synonymous	1967
BCOR	p.(=)	c.1260T>C	.	chrX:39933339	100.00%	NM_001123385.1	synonymous	1992

Biomarker Descriptions

RUNX1 (runt related 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[1]. All RUNX proteins share several conserved regions with similar functionality including

Biomarker Descriptions (continued)

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[2]. 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[3,4]. RUNX1 is frequently mutated in various hematological malignancies[4]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder, with predisposition to acute myeloid leukemia (FPD/AML)[5,6]. 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)[4].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[7]. The most recurrent translocation, t(12;21)(q34;q11), results in ETV6-RUNX1 fusion and is observed in 20-25% of childhood ALL[8,9,10]. This translocation is also observed in adult ALL at a lower frequency (2%)[9,10]. Another recurrent translocation, t(8;21)(q22;q22), results in RUNX1-RUNX1T1 fusion and is observed in 5-10% of AML[11]. The RUNX1-RUNX1T1 fusion, consists of the RHD domain of RUNX1 and the majority of RUNXT1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[4,11]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[4]. RUNX1 mutations are reported in approximately 10% of de novo AML as well as 10-15% of MDS[4,12,13,14].

Potential relevance: The t(8;21)(q22;q22.1)/RUNX1-RUNX1T1 translocation is recognized as a distinct AML disease category by the World Health Organization (WHO)[15]. Additionally, AML with RUNX1 mutations is a provisional entity in the WHO[15]. 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[12,16]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[12,13,17]

Relevant Therapy Summary

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

RUNX1 p.(P278fs) c.833_843delCGTGGTCCTAC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ONC-201	✖	✖	✖	✖	● (I)
venetoclax, chemotherapy	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Prognostic Details

Current NCCN Information

NCCN information is current as of 2020-12-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

RUNX1 p.(P278fs) c.833_843delCGTGGTCCTAC

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

NCCN Recommendation category: 2A

Summary:
- Do not use as an adverse prognostic marker if it co-occurs with favorable-risk AML subtypes.

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2021]

Current ESMO Information

ESMO information is current as of 2020-12-01. For the most up-to-date information, search www.esmo.org.

RUNX1 p.(P278fs) c.833_843delCGTGGTCCTAC

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** RUNX1 mutation

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

Signatures

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Laboratory Supervisor: 2021.03.12 16:36:17 +08'00'

Pathologist: 2021.03.12 16:36:43 +08'00'

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