Taipei Veterans General Hospital

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Sample Information

Patient Name: 林麗香
Gender: Female
ID No.: P201459262
History No.: 35799532
Age: 66

Ordering Doctor: DOC1901H 高志平
Ordering REQ.: 0BSQJAT
Signing in Date: 2022/03/04

Path No.: S111-98575
MP No.: MY22009
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/03/01

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Myelodysplastic Syndrome Variants

Gene	Finding	Gene	Finding
ASXL1	***ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACT GCCAT***	NPM1	None detected
BCOR	None detected	NRAS	None detected
CBL	***CBL p.(Y371H) c.1111T>C***	NUP214	None detected
CREBBP	None detected	RUNX1	None detected
ETV6	None detected	SF3B1	None detected
EZH2	None detected	SRSF2	None detected
FLT3	None detected	STAG2	None detected
GATA2	None detected	TP53	None detected
IDH2	None detected	U2AF1	***U2AF1 p.(Q157P) c.470A>C***
KIT	None detected	WT1	None detected

Relevant Myelodysplastic Syndrome Variants (continued)

Gene	Finding	Gene	Finding
KMT2A	None detected	ZRSR2	None detected
MECOM	None detected		

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
*ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGC CACCACTGCCAT* ASXL transcriptional regulator 1 Allele Frequency: 48.48% **Prognostic significance:** NCCN: Poor **Diagnostic significance:** None	None	allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine gemtuzumab ozogamicin + chemotherapy venetoclax + chemotherapy	0
U2AF1 p.(Q157P) c.470A>C U2 small nuclear RNA auxiliary factor 1 Allele Frequency: 37.17% **Prognostic significance:** NCCN: Poor **Diagnostic significance:** None	None	None	0

Public data sources included in relevant therapies: FDA1, 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

CBL p.(Y371H) c.1111T>C

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
CBL	p.(Y371H)	c.1111T>C	COSM34052	chr11:119148891	59.20%	NM_005188.4	missense	2000
ASXL1	p.(E635Rfs*15)	c.1900_1922delAGAGAGGCGGCCACCACTGCCAT	.	chr20:31022403	48.48%	NM_015338.6	frameshift Deletion	1842
U2AF1	p.(Q157P)	c.470A>C	COSM211534	chr21:44514777	37.17%	NM_006758.2	missense	1999
TP53	p.(P177H)	c.530C>A	.	chr17:7578400	38.03%	NM_000546.5	missense	1959

Biomarker Descriptions

ASXL1 (ASXL transcriptional regulator 1)

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,2]. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3[2]. ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and histones[2,3]. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors[2,4]. In cancer, ASXL1 is the target of somatic mutations which often result in a truncated ASXL1 protein and loss of its PHD[5,6,7]. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1[8].

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)[4,9,10,11,12,13,14,15,16]. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies[6,11,17]. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence[18]. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing[19]. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation[9,18,20].

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic[21]. Mutations in ASXL1 confer poor/adverse risk in AML and are associated with poor outcomes and adverse risk[16]. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML[22]. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM[23,24].

CBL (Cbl proto-oncogene)

Background: The CBL gene encodes the casitas B-lineage lymphoma (CBL) ubiquitin ligase, a member of the ubiquitin ligase (E3) protein family that also includes CBL-b and CBL-c[25]. CBL proteins are characterized by their highly conserved N-terminal tyrosine kinase binding (TKB) domain and RING finger (RF) catalytic domain which are directly involved in the regulation of receptor tyrosine kinase (RTK) signaling[25,26]. Upon recognition of an activated RTK via its TKB domain, CBL mediates the transfer of ubiquitin from the ubiquitin-conjugating enzyme (E2) via its RF domain, consequently targeting the RTK for proteasome degradation. CBL can also function as an adaptor protein via recruitment of signaling molecules to active RTKs[26]. CBL is the target of genetic aberrations, including missense mutations and translocations, which can lead to oncogenic transformation in hematological malignancies as well as solid tumors[26,27,28,29]. Mutations in CBL often result in a loss of E3 ligase activity, thereby preventing proteasome-mediated RTK degradation, which supports the role of CBL as a tumor suppressor gene[27]. However, CBL mutants often maintain their adapter function, contributing to their transforming potential and suggesting a simultaneous oncogenic role for CBL in cancer[26]. Hereditary mutations in CBL lead to constitutive activation of RAS and MAPK pathways resulting in genetic disorders known as RASopathies which can lead to increased cancer risk[22].

Alterations and prevalence: Genetic alterations in CBL were first recognized in acute myeloid leukemia (AML) as a result of an interstitial deletion leading to MLL-CBL fusion[30,31]. However, fusions involving CBL are relatively rare. Aberrations in CBL most often involve missense mutations which commonly cluster in the linker region or RF domain corresponding to exons 8 and 9[26,27]. Such mutations lead to disruption of E3 ligase activity and have been reported in systemic mastocytosis (SM), 1-3% of de novo AML, 10% of secondary AML, 8% of atypical AML, and 10-15% of juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML)[12,26,32,33,34,35,36]. Mutations in CBL have also been reported in 1-6% of melanomas, lung, stomach, colorectal, esophageal, and uterine cancers[12,29].

Potential relevance: Mutations in CBL confer adverse prognosis in SM and have been shown to be independently predictive of inferior survival[24,33].

U2AF1 (U2 small nuclear RNA auxiliary factor 1)

Background: The U2AF1 gene encodes the U2 small nuclear RNA auxiliary factor 1 protein that belongs to the splicing factor SR family of genes involved in RNA splicing[1,37]. U2AF1, also known as U2AF35, mediates the recruitment of the U2AF complex to the 3' end of that pre-mRNA that is being spliced[38]. U2AF1 is the smaller subunit of the U2 auxiliary factor and along with the larger subunit, U2AF65 regulates the removal of introns from pre-mRNAs to produce mature mRNAs for translation during protein synthesis[39]. Mutations in U2AF1 alter the differential splicing of genes that are involved in various biological pathways, including DNMT3B in DNA methylation, ATR along with FANCA in DNA damage response, and H2AFY in X-chromosome inactivation[40]. Spliceosomal genes such as U2AF1 are

Biomarker Descriptions (continued)

common targets of somatic mutations in myelodysplastic syndrome (MDS) and are associated with the progression of MDS to acute myeloid leukemia (AML)[40,41,42].

Alterations and prevalence: Recurrent mutations in U2AF1 occur at S34 and Q157 and are observed in 8-12% of MDS[22]. Somatic mutations in U2AF1 are also observed in 10% of uterine carcinoma, 4% of AML, as well as 2% of lung adenocarcinoma and stomach adenocarcinoma[43].

Potential relevance: U2AF1 mutations including S34 and Q157 are associated with poor prognosis in MDS[22]. U2AF1 mutations are associated with inferior overall survival in primary myelofibrosis (PMF)[23]. Specifically, the Q157 mutation is associated with a significantly shorter overall survival than U2AF1 S34 mutated and U2AF1 unmutated MPN[23].

Relevant Therapy Summary

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

ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACTGCCAT

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✖	○	✖	✖	✖
azacitidine	✖	○	✖	✖	✖
cytarabine	✖	○	✖	✖	✖
cytarabine + daunorubicin	✖	○	✖	✖	✖
cytarabine + daunorubicin + etoposide	✖	○	✖	✖	✖
cytarabine + etoposide + idarubicin	✖	○	✖	✖	✖
cytarabine + fludarabine + idarubicin + filgrastim	✖	○	✖	✖	✖
cytarabine + idarubicin	✖	○	✖	✖	✖
cytarabine + mitoxantrone	✖	○	✖	✖	✖
decitabine	✖	○	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	○	✖	✖	✖
venetoclax + azacitidine	✖	○	✖	✖	✖
venetoclax + cytarabine	✖	○	✖	✖	✖
venetoclax + decitabine	✖	○	✖	✖	✖

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 2022-01-04. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACTGCCAT

○ cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

○ cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

○ cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

○ cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACTGCCAT (continued)

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACTGCCAT (continued)

cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACTGCCAT (continued)

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

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cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2022-01-04. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ASXL1 p.(E635Rfs*15) c.1900_1922delAGAGAGGCGGCCACCACTGCCAT

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** ASXL1 truncating mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® independently associate the biomarker with poor prognosis in MDS and CMML

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2022]

U2AF1 p.(Q157P) c.470A>C

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** U2AF1 Q157 mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® associate the biomarker with poor prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2022]

Signatures

Testing Personnel:

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Laboratory Supervisor:

2022.03.07 10:06:29 +08'00'

Pathologist:

Yi-Chu Yeh 2022.03.07 10:06:42 +08'00'

References

1. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
2. Katoh. Functional and cancer genomics of ASXL family members. Br. J. Cancer. 2013 Jul 23;109(2):299-306. PMID: 23736028
3. Gelsi-Boyer et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. Br. J. Haematol. 2009 Jun;145(6):788-800. PMID: 19388938
4. Gelsi-Boyer et al. Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. J Hematol Oncol. 2012 Mar 21;5:12. doi: 10.1186/1756-8722-5-12. PMID: 22436456
5. Larsson et al. The changing mutational landscape of acute myeloid leukemia and myelodysplastic syndrome. Mol. Cancer Res. 2013 Aug;11(8):815-27. PMID: 23645565
6. Alvarez et al. ASXL1 mutations in myeloid neoplasms: pathogenetic considerations, impact on clinical outcomes and survival. Curr Med Res Opin. 2018 May;34(5):757-763. PMID: 28027687
7. Yang et al. Gain of function of ASXL1 truncating protein in the pathogenesis of myeloid malignancies. Blood. 2018 Jan 18;131(3):328-341. PMID: 29113963
8. Abdel-Wahab et al. ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. Cancer Cell. 2012 Aug 14;22(2):180-93. PMID: 22897849
9. Alberti et al. Discriminating a common somatic ASXL1 mutation (c.1934dup; p.G646Wfs*12) from artifact in myeloid malignancies using NGS. Leukemia. 2018 Aug;32(8):1874-1878. PMID: 29959414
10. Kakosaiou et al. ASXL1 mutations in AML are associated with specific clinical and cytogenetic characteristics. Leuk. Lymphoma. 2018 Oct;59(10):2439-2446. PMID: 29411666
11. Paschka et al. ASXL1 mutations in younger adult patients with acute myeloid leukemia: a study by the German-Austrian Acute Myeloid Leukemia Study Group. Haematologica. 2015 Mar;100(3):324-30. PMID: 25596267
12. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
13. Jawhar et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica. 2017 Jun;102(6):1035-1043. PMID: 28255023
14. Jawhar et al. KIT D816 mutated/CBF-negative acute myeloid leukemia: a poor-risk subtype associated with systemic mastocytosis. Leukemia. 2019 May;33(5):1124-1134. PMID: 30635631
15. Damaj et al. ASXL1 but not TET2 mutations adversely impact overall survival of patients suffering systemic mastocytosis with associated clonal hematologic non-mast-cell diseases. PLoS ONE. 2014;9(1):e85362. PMID: 24465546
16. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 1.2022]
17. Boultwood et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. Leukemia. 2010 May;24(5):1062-5. doi: 10.1038/leu.2010.20. Epub 2010 Feb 25. PMID: 20182461
18. Yannakou et al. ASXL1 c.1934dup;p.Gly646Trpfs*12-a true somatic alteration requiring a new approach. Blood Cancer J. 2017 Dec 15;7(12):656. doi: 10.1038/s41408-017-0025-8. PMID: 29242575
19. Abdel-Wahab et al. The most commonly reported variant in ASXL1 (c.1934dupG;p.Gly646TrpfsX12) is not a somatic alteration. Leukemia. 2010 Sep;24(9):1656-7. doi: 10.1038/leu.2010.144. Epub 2010 Jul 1. PMID: 20596031
20. Montes-Moreno et al. Clinical molecular testing for ASXL1 c.1934dupG p.Gly646fs mutation in hematologic neoplasms in the NGS era. PLoS ONE. 2018;13(9):e0204218. PMID: 30222780
21. Landrum et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan 4;46(D1):D1062-D1067. PMID: 29165669
22. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 2.2022]
23. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2021]
24. NCCN Guidelines® - NCCN-Systemic Mastocytosis [Version 1.2020]
25. Ryan et al. The N terminus of Cbl-c regulates ubiquitin ligase activity by modulating affinity for the ubiquitin-conjugating enzyme. J. Biol. Chem. 2010 Jul 30;285(31):23687-98. PMID: 20525694
26. Liyasova et al. Molecular pathways: cbl proteins in tumorigenesis and antitumor immunity-opportunities for cancer treatment. Clin. Cancer Res. 2015 Apr 15;21(8):1789-94. PMID: 25477533
27. Katzav et al. Mutations of c-Cbl in myeloid malignancies. Oncotarget. 2015 May 10;6(13):10689-96. PMID: 26028666
28. Kales et al. Cbl and human myeloid neoplasms: the Cbl oncogene comes of age. Cancer Res. 2010 Jun 15;70(12):4789-94. PMID: 20501843

References (continued)

29. Tan et al. CBL is frequently altered in lung cancers: its relationship to mutations in MET and EGFR tyrosine kinases. PLoS ONE. 2010 Jan 29;5(1):e8972. PMID: 20126411
30. Tefferi. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia. 2010 Jun;24(6):1128-38. PMID: 20428194
31. Fu et al. Identification of CBL, a proto-oncogene at 11q23.3, as a novel MLL fusion partner in a patient with de novo acute myeloid leukemia. Genes Chromosomes Cancer. 2003 Jun;37(2):214-9. PMID: 12696071
32. Traina et al. Single nucleotide polymorphism array lesions, TET2, DNMT3A, ASXL1 and CBL mutations are present in systemic mastocytosis. PLoS ONE. 2012;7(8):e43090. PMID: 22905207
33. Pardanani et al. ASXL1 and CBL mutations are independently predictive of inferior survival in advanced systemic mastocytosis. Br. J. Haematol. 2016 Nov;175(3):534-536. PMID: 26628266
34. Loh et al. Mutations in CBL occur frequently in juvenile myelomonocytic leukemia. Blood. 2009 Aug 27;114(9):1859-63. PMID: 19571318
35. Jankowska et al. Mutational spectrum analysis of chronic myelomonocytic leukemia includes genes associated with epigenetic regulation: UTX, EZH2, and DNMT3A. Blood. 2011 Oct 6;118(14):3932-41. PMID: 21828135
36. Itzykson et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J. Clin. Oncol. 2013 Jul 1;31(19):2428-36. PMID: 23690417
37. Long et al. The SR protein family of splicing factors: master regulators of gene expression. Biochem. J. 2009 Jan 1;417(1):15-27. PMID: 19061484
38. Zuo et al. The splicing factor U2AF35 mediates critical protein-protein interactions in constitutive and enhancer-dependent splicing. Genes Dev. 1996 Jun 1;10(11):1356-68. PMID: 8647433
39. Ruskin et al. A factor, U2AF, is required for U2 snRNP binding and splicing complex assembly. Cell. 1988 Jan 29;52(2):207-19. PMID: 2963698
40. Ilagan et al. U2AF1 mutations alter splice site recognition in hematological malignancies. Genome Res. 2015 Jan;25(1):14-26. PMID: 25267526
41. Graubert et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. Nat. Genet. 2011 Dec 11;44(1):53-7. PMID: 22158538
42. Papaemmanuil et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013 Nov 21;122(22):3616-27; quiz 3699. PMID: 24030381
43. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877