

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

Date: 31 Aug 2023 1 of 16

Sample Information

Patient Name: 王俊彦 Gender: Male ID No.: P122512673 History No.: 49752934

Age: 44

Ordering Doctor: DOC4205A 柯博伸

Ordering REQ.: H47J1G3 Signing in Date: 2023/08/31

Path No.: M112-00241 **MP No.:** MY23065

Assay: Oncomine Myeloid Assay **Sample Type:** Bone Marrow

Bone Marrow Aspirating Date: 2023/08/24

Reporting Doctor: DOC5444B 楊靜芬 (Phone: 8#5444)

Note:

Sample Cancer Type: Myelodysplastic Syndrome

| Table of Contents Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) | Page 2 |
|---|-----------|
| Biomarker Descriptions Relevant Therapy Summary | 2 |
| Relevant Therapy Details | 5 |

Report Highlights

2 Relevant Biomarkers12 Therapies Available0 Clinical Trials

Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|------|---|---|--|-----------------|
| IIC | ASXL1 p.(W796Gfs*22) c.2385delC ASXL transcriptional regulator 1 Allele Frequency: 28.87% | None | allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine liposomal cytarabine-daunorubicin CPX-351 venetoclax + chemotherapy | 0 |

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Date: 31 Aug 2023

Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|------|--|--|--|-----------------|
| IIC | U2AF1 p.(S34Y) c.101C>A U2 small nuclear RNA auxiliary factor 1 Allele Frequency: 30.60% | None | allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine liposomal cytarabine-daunorubicin CPX-351 venetoclax + chemotherapy | 0 |

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

| DNA | DNA Sequence Variants | | | | | | | | |
|-------|-----------------------|------------|------------|----------------|---------------------|-------------|------------------------|----------|--|
| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect | Coverage | |
| ASXL1 | p.(W796Gfs*22) | c.2385delC | COSM34212 | chr20:31022898 | 28.87% | NM_015338.6 | frameshift Deletion | 1985 | |
| U2AF1 | p.(S34Y) | c.101C>A | COSM146287 | chr21:44524456 | 30.60% | NM_006758.2 | missense | 2000 | |

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 ASXL3². 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 ASXL1⁸.

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 sequence¹⁸. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing¹⁹. 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 pathogenic²¹. Mutations in ASXL1 confer poor/adverse risk in AML^{16,22}. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML²³. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM^{24,25}.

Biomarker Descriptions (continued)

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^{1,26}. U2AF1, also known as U2AF35, mediates the recruitment of the U2AF complex to the 3' end of that pre-mRNA that is being spliced²⁷. 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 synthesis²⁸. 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 inactivation²⁹. Spliceosomal genes such as U2AF1 are common targets of somatic mutations in myelodysplastic syndrome (MDS) and are associated with the progression of MDS to acute myeloid leukemia (AML)^{29,30,31}.

Alterations and prevalence: Recurrent mutations in U2AF1 occur at S34 and Q157 and are observed in 8-12% of MDS²³. Somatic mutations in U2AF1 are also observed in 10% of uterine carcinoma, 4% of AML, as well as 2% of lung adenocarcinoma and stomach adenocarcinoma³².

Potential relevance: U2AF1 mutations including S34 and Q157 are associated with poor prognosis in MDS²³. U2AF1 mutations are associated with inferior overall survival and adverse risk in primary myelofibrosis (PMF) and AML^{16,22,24}. Specifically, the Q157 mutation is associated with a significantly shorter overall survival than U2AF1 S34 mutated and U2AF1 unmutated myeloproliferative neoplasms (MPN)²⁴.

Relevant Therapy Summary

| In this cancer type In other cancer type | in this cancer | type and other car | icer types | X No eviden | ce |
|---|----------------|--------------------|------------|-------------|------------------|
| ASXL1 p.(W796Gfs*22) c.2385delC | | | | | |
| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
| Allogeneic hematopoietic stem cell transplantation | × | 0 | × | × | × |
| azacitidine | × | 0 | × | × | × |
| cytarabine | × | 0 | × | × | × |
| cytarabine + daunorubicin | × | 0 | × | × | × |
| cytarabine + daunorubicin + etoposide | × | 0 | × | × | × |
| cytarabine + etoposide + idarubicin | × | 0 | × | × | × |
| cytarabine + fludarabine + idarubicin + filgrastim | × | 0 | × | × | × |
| cytarabine + idarubicin | × | 0 | × | × | × |
| cytarabine + mitoxantrone | × | 0 | × | × | × |
| decitabine | × | 0 | × | × | × |
| liposomal cytarabine-daunorubicin CPX-351 | × | 0 | × | × | × |
| venetoclax + azacitidine | × | 0 | × | × | × |
| venetoclax + cytarabine | × | 0 | × | × | × |
| venetoclax + cytarabine + fludarabine + idarubicin + filgrastim | × | 0 | × | × | × |
| venetoclax + decitabine | × | 0 | × | × | × |

4 of 16

Date: 31 Aug 2023

Relevant Therapy Summary (continued)

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|-----|------|-----|------|------------------|
| Allogeneic hematopoietic stem cell transplantation | × | 0 | × | × | × |
| azacitidine | × | 0 | × | × | × |
| cytarabine | × | 0 | × | × | × |
| cytarabine + daunorubicin | × | 0 | × | × | × |
| cytarabine + daunorubicin + etoposide | × | 0 | × | × | × |
| cytarabine + etoposide + idarubicin | × | 0 | × | × | × |
| cytarabine + fludarabine + idarubicin + filgrastim | × | 0 | × | × | × |
| cytarabine + idarubicin | × | 0 | × | × | × |
| cytarabine + mitoxantrone | × | 0 | × | × | × |
| decitabine | × | 0 | × | × | × |
| liposomal cytarabine-daunorubicin CPX-351 | × | 0 | × | × | × |
| venetoclax + azacitidine | × | 0 | × | × | × |
| venetoclax + cytarabine | × | 0 | × | × | × |
| venetoclax + cytarabine + fludarabine + idarubicin + filgrastim | × | 0 | × | × | × |
| venetoclax + decitabine | × | 0 | × | × | × |

Date: 31 Aug 2023 5 of 16

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 2023-07-03. 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.

ASXL1 p.(W796Gfs*22) c.2385delC

| _ | | | _ | | | | |
|---|-----|----|----|----|---|----|--|
| | 1 2 | 7a | ci | ti | Ы | in | |
| | | | | | | | |

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Date: 31 Aug 2023 6 of 16

ASXL1 p.(W796Gfs*22) c.2385delC (continued)

O cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia

Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

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 3.2023]

O azacitidine

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O 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 3.2023]

O cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

■ (Induction therapy)

Date: 31 Aug 2023 7 of 16

ASXL1 p.(W796Gfs*22) c.2385delC (continued)

O 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 3.2023]

O liposomal cytarabine-daunorubicin CPX-351

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 3.2023]

venetoclax + azacitidine

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 3.2023]

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 3.2023]

venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

■ (Induction therapy)

Date: 31 Aug 2023 8 of 16

ASXL1 p.(W796Gfs*22) c.2385delC (continued)

O venetoclax + decitabine

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 3.2023]

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 3.2023]

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 3.2023]

O cytarabine + daunorubicin + etoposide

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 3.2023]

O cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia

Variant class: ASXL1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

■ (Induction therapy)

Date: 31 Aug 2023 9 of 16

ASXL1 p.(W796Gfs*22) c.2385delC (continued)

O cytarabine + fludarabine + idarubicin + filgrastim

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 3.2023]

O decitabine

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia Variant class: ASXL1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

(Induction therapy)

Date: 31 Aug 2023 10 of 16

U2AF1 p.(S34Y) c.101C>A

O azacitidine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

■ (Induction therapy)

Date: 31 Aug 2023 11 of 16

U2AF1 p.(S34Y) c.101C>A (continued)

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O azacitidine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O decitabine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

■ (Induction therapy)

Date: 31 Aug 2023 12 of 16

U2AF1 p.(S34Y) c.101C>A (continued)

O liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

■ (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

Date: 31 Aug 2023 13 of 16

U2AF1 p.(S34Y) c.101C>A (continued)

O venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia

Variant class: U2AF1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: U2AF1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia

Variant class: U2AF1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia

Variant class: U2AF1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia

Variant class: U2AF1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

■ (Induction therapy)

Date: 31 Aug 2023 14 of 16

U2AF1 p.(S34Y) c.101C>A (continued)

O decitabine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

■ (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2023]

O venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia Variant class: U2AF1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

(Induction therapy)

Date: 31 Aug 2023

References

- 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
- 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
- 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
- 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 3.2023]
- 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. Döhner et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377. PMID: 35797463
- 23. NCCN Guidelines® NCCN-Myelodysplastic Syndromes [Version 1.2023]
- 24. NCCN Guidelines® NCCN-Myeloproliferative Neoplasms [Version 1.2023]
- 25. NCCN Guidelines® NCCN-Systemic Mastocytosis [Version 1.2020]
- 26. 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
- 27. 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
- 28. 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

Date: 31 Aug 2023 16 of 16

References (continued)

29. Ilagan et al. U2AF1 mutations alter splice site recognition in hematological malignancies. Genome Res. 2015 Jan;25(1):14-26. PMID: 25267526

- 30. Graubert et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. Nat. Genet. 2011 Dec 11;44(1):53-7. PMID: 22158538
- 31. 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
- 32. 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