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Sample Information

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History No.: 38059937
Age: 76

Ordering Doctor: DOC1654E 林庭安
Ordering REQ.: 0CYEEQF
Signing in Date: 2024/03/14

Path No.: M113-00076
MP No.: MY24010
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2024/03/11

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*U2AF1 p.(Q157P) c.470A>C* U2 small nuclear RNA auxiliary factor 1 Allele Frequency: 16.72%	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: FDA[1], NCCN, **EMA**[2], ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
JAK2 p.(V617F) c.1849G>T

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
JAK2	p.(V617F)	c.1849G>T	COSM12600	chr9:5073770	4.13%	NM_004972.4	missense	1963
U2AF1	p.(Q157P)	c.470A>C	COSM211534	chr21:44514777	16.72%	NM_006758.2	missense	1998
MPL	p.(H108Y)	c.322C>T	.	chr1:43804322	3.35%	NM_005373.3	missense	2000
EZH2	p.(C468Vfs*15)	c.1402delT	.	chr7:148514321	15.95%	NM_004456.5	frameshift Deletion	2000
PRPF8	p.(F339=)	c.1017C>T	.	chr17:1584101	50.28%	NM_006445.4	synonymous	1999
CEBPA	p.(H195_P196dup)	c.589_590insACCCGC	.	chr19:33792731	44.43%	NM_004364.4	nonframeshift Insertion	682
CEBPA	p.(P186=)	c.558G>A	.	chr19:33792763	53.53%	NM_004364.4	synonymous	680
U2AF1L5	p.(Q84P)	c.251A>C	COSM211534	chr21:44514777	16.72%	NM_001320651.1	missense	1998

Biomarker Descriptions

JAK2 p.(V617F) c.1849G>T

Janus kinase 2

Background: The JAK2 gene encodes a non-receptor, membrane associated protein tyrosine kinase (PTK). JAK2 is a member of the Janus kinase (JAK) family that includes JAK1, JAK2, JAK3, and TYK2. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[1]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[1,2,3]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit presentation of tumor antigens and contribute to immune evasion[4,5].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) has been associated with loss of heterozygosity on chromosome 9p and subsequently to the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[6,7]. The JAK2 V617F mutation has been observed rarely in acute myeloid leukemia (AML)[8,9]. Mutations in the pseudokinase domain of JAK2 including R683G have been detected in 8% of ALL[10,11]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR genes[12,13,14,15]. JAK2 fusions are infrequently observed in solid tumors[16]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[16].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of PV[17,18]. Ruxolitinib[19] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[20]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[21]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[12,13,14,15].

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

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[22,23]. U2AF1, also known as U2AF35, mediates the recruitment of the U2AF complex to the 3' end of

Biomarker Descriptions (continued)

that pre-mRNA that is being spliced[24]. 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[25]. 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[26]. 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)[26,27,28].

Alterations and prevalence: Recurrent mutations in U2AF1 occur at S34 and Q157 and are observed in 8-12% of MDS[29]. 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[30].

Potential relevance: U2AF1 mutations including S34 and Q157 are associated with poor prognosis in MDS[29]. U2AF1 mutations are associated with inferior overall survival and adverse risk in primary myelofibrosis (PMF) and AML[17,31,32]. Specifically, the Q157 mutation is associated with a significantly shorter overall survival than U2AF1 S34 mutated and U2AF1 unmutated myeloproliferative neoplasms (MPN)[17].

Relevant Therapy Summary

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

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

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	✖	○	✖	✖	✖
liposomal cytarabine-daunorubicin CPX-351	✖	○	✖	✖	✖
venetoclax + azacitidine	✖	○	✖	✖	✖
venetoclax + cytarabine	✖	○	✖	✖	✖
venetoclax + cytarabine + fludarabine + idarubicin + filgrastim	✖	○	✖	✖	✖
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 2024-01-02. To view the most recent and complete version of the guideline, go online to 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.

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

○ 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 6.2023]

○ 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 6.2023]

○ 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 6.2023]

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

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 6.2023]

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cytarabine + 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 6.2023]

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 6.2023]

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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 6.2023]

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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 6.2023]

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

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 6.2023]

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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 6.2023]

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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 6.2023]

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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 6.2023]

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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 6.2023]

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

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 6.2023]

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venetoclax + decitabine

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 6.2023]

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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 6.2023]

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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 6.2023]

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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 6.2023]

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

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 6.2023]

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cytarabine + fludarabine + idarubicin + filgrastim

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 6.2023]

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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 6.2023]

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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 6.2023]

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venetoclax + decitabine

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 6.2023]

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