Taipei Veterans General Hospital

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Sample Information

Patient Name: 董雍晉
Gender: Male
ID No.: A101072958
History No.: 49537475
Age: 72

Ordering Doctor: DOC6258D 林益庭
Ordering REQ.: 0CLMFTX
Signing in Date: 2023/06/07

Path No.: M112-00130
MP No.: MY23030
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2023/05/29

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

Note:

Sample Cancer Type: Acute Myeloid Leukemia

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Relevant Acute Myeloid Leukemia Variants

Gene	Finding	Gene	Finding
ABL1	None detected	MECOM	None detected
ASXL1	None detected	MLLT3	None detected
CEBPA	None detected	MYH11	None detected
CREBBP	None detected	NPM1	None detected
FLT3	None detected	NUP214	None detected
IDH1	None detected	RARA	None detected
IDH2	None detected	RUNX1	None detected
KMT2A	None detected	TP53	***TP53 p.(R273C) c.817C>T***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*TP53 p.(R273C) c.817C>T* tumor protein p53 Allele Frequency: 91.10%	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	**idelalisib + rituximab** [2] acalabrutinib ibrutinib obinutuzumab + venetoclax rituximab + venetoclax venetoclax	0

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

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
TP53	p.(R273C)	c.817C>T	COSM10659	chr17:7577121	91.10%	NM_000546.5	missense	1999
EZH2	p.(D677delinsGN)	c.-1_0insGTA	.	chr7:148507424	44.95%	NM_004456.5	nonframeshift Insertion	1989

Biomarker Descriptions

TP53 (tumor protein p53)

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[1]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[2,3].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[4,5,6,7,8,9]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[4,5]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[10,11,12,13].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[14]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[15] and breakthrough designation[16] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[17,18]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL)[19,20,21,22]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[23]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[24].

Relevant Therapy Summary

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

TP53 p.(R273C) c.817C>T

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 + decitabine	✖	●	✖	✖	✖
idelalisib + rituximab	✖	✖	○	○	✖
acalabrutinib	✖	✖	✖	○	✖
ibrutinib	✖	✖	✖	○	✖
obinutuzumab + venetoclax	✖	✖	✖	○	✖
rituximab + venetoclax	✖	✖	✖	○	✖
venetoclax	✖	✖	✖	○	✖

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 2023-03-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

TP53 p.(R273C) c.817C>T

● cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

● cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

● cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

● cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

TP53 p.(R273C) c.817C>T (continued)

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

TP53 p.(R273C) c.817C>T (continued)

decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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liposomal cytarabine-daunorubicin CPX-351

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

TP53 p.(R273C) c.817C>T (continued)

azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

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cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2022]

Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

EMA information is current as of 2023-03-15. For the most up-to-date information, search www.ema.europa.eu/ema.

TP53 p.(R273C) c.817C>T

○ idelalisib + rituximab

Cancer type: Chronic Lymphocytic Leukemia **Label as of:** 2021-10-06 **Variant class:** TP53 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/zydelig-epar-product-information_en.pdf

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 2023-03-01. For the most up-to-date information, search www.esmo.org.

TP53 p.(R273C) c.817C>T

○ acalabrutinib

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Relapsed (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

○ ibrutinib

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Relapsed (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

○ rituximab + venetoclax

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Relapsed (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

○ ibrutinib

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):
- Relapsed (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

TP53 p.(R273C) c.817C>T (continued)

idelalisib + rituximab

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: II / B

Population segment (Line of therapy):
- Relapsed (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

acalabrutinib

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

ibrutinib

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

idelalisib + rituximab

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

TP53 p.(R273C) c.817C>T (continued)

obinutuzumab + venetoclax

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

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venetoclax

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):
- (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

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venetoclax

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

ESMO Level of Evidence/Grade of Recommendation: III / B

Population segment (Line of therapy):
- Relapsed (Subsequent therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Chronic Lymphocytic Leukaemia [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.09.019.]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-03-15. For the most up-to-date information, search www.fda.gov.

TP53 p.(R273C) c.817C>T

eprenetapopt + azacitidine, eprenetapopt + venetoclax + azacitidine

Cancer type: Myelodysplastic Syndrome **Variant class:** TP53 mutation

Supporting Statement:

The FDA has granted Breakthrough Designation to the small molecule inhibitor, eprenetapopt, in combination with azacitidine or azacitidine and venetoclax for TP53 mutant myelodysplastic syndrome (MDS).

Reference:

http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167

eprenetapopt + azacitidine, eprenetapopt + venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** TP53 mutation

Supporting Statement:

The FDA has granted Fast Track Designation to the small molecule inhibitor, eprenetapopt, in combination with azacitidine or azacitidine and venetoclax for TP53 mutant acute myeloid leukemia (AML).

Reference:

https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2023-03-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

TP53 p.(R273C) c.817C>T

chemoimmunotherapy

Cancer type: Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma **Variant class:** TP53 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):

- "Chemoimmunotherapy is not recommended since del(17p)/TP53 mutation is associated with low response rates."

Reference: NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 2.2023]

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2023-03-01. For the most up-to-date information, search www.esmo.org.

TP53 p.(R273C) c.817C>T

lenalidomide

Cancer type: Myelodysplastic Syndrome **Variant class:** TP53 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "TP53 gene mutations, found in ~20% of lower-risk MDS with del(5q), confer resistance to LEN and a higher risk of AML progression."

Reference: ESMO Clinical Practice Guidelines - ESMO-Myelodysplastic Syndromes [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.11.002]

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