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Date: 11 Mar 2024

101.02 2070 7445

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Sample Information

Patient Name: THAN THAN WIN

Gender: Female ID No.: MH329876 History No.: 44152149

Age: 61

Ordering Doctor: DOC6496F 盧姵鈞

Ordering REQ.: 0CYBGVZ Signing in Date: 2024/03/06

Path No.: M113-00065 **MP No.:** MY24009

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

Bone Marrow Aspirating Date: 2024/03/04

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

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Report Highlights

2 Relevant Biomarkers 18 Therapies Available

0 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	TP53 p.(P151T) c.451C>A, TP53 p. (R273H) c.818G>A tumor protein p53 Allele Frequency: 48.40%, 47.02% (2 variants)	None	idelalisib + rituximab ² acalabrutinib allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone	0

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

Date: 11 Mar 2024

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
			decitabine ibrutinib liposomal cytarabine-daunorubicin CPX-351 obinutuzumab + venetoclax rituximab + venetoclax venetoclax venetoclax venetoclax + chemotherapy	
	Diagnostic significance: Myelodysp	lastic Syndrome		

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

🛕 Alerts informed by public data sources: 🧿 Contraindicated, 🏼 🛡 Resistance

TP53 p.(P151T) c.451C>A, TP53 □ lenalidomide p.(R273H) c.818G>A

Public data sources included in alerts: FDA1, NCCN, EMA2, ESMO

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

DNA Sequence Variants Variant ID Gene Amino Acid Change Coding Locus Frequency Transcript Variant Effect Coverage TP53 p.(R273H) c.818G>A COSM10660 chr17:7577120 47.02% NM_000546.5 missense 1999 TP53 p.(P151T) c.451C>A COSM43911 chr17:7578479 48.40% NM_000546.5 missense 2000 SH2B3 p.(G307V) c.920G>T chr12:111884831 48.15% NM_005475.3 missense 1998

Biomarker Descriptions

TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

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. 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 R2824.5. 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 mutation¹⁴. 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 and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)^{19,20,21,22,23,24}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant²⁵.

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Biomarker Descriptions (continued)

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 system²⁶.

Relevant Therapy Summary

■ In this cancer type O In other cancer type In this cancer type and other cancer types X No example 1
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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A					
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	×	×	×
idelalisib + rituximab	×	×	0	0	×
acalabrutinib	×	×	×	0	×
ibrutinib	×	×	×	0	×
obinutuzumab + venetoclax	×	×	×	0	×
rituximab + venetoclax	×	×	×	0	×
venetoclax	×	×	×	0	×

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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.

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

O azacitidine

Cancer type: Acute Myeloid Leukemia Variant class: TP53 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

O cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia Variant class: TP53 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

O cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia Variant class: TP53 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

O cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia

Variant class: TP53 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

O cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia

Variant class: TP53 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: TP53 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: TP53 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

O cytarabine

Cancer type: Acute Myeloid Leukemia

Variant class: TP53 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

(Consolidation therapy)

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

O cytarabine + mitoxantrone

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 6.2023]

O 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 6.2023]

O 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 6.2023]

venetoclax + azacitidine

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 6.2023]

O venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia

Variant class: TP53 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

■ (Induction therapy)

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

O 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 6.2023]

venetoclax + decitabine

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 6.2023]

O 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 6.2023]

O 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 6.2023]

O cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia

Variant class: TP53 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

■ (Induction therapy)

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

O cytarabine + etoposide + idarubicin

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 6.2023]

O cytarabine + fludarabine + idarubicin + filgrastim

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 6.2023]

O decitabine

Cancer type: Acute Myeloid Leukemia Variant class: TP53 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

(Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

venetoclax + cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia Variant class: TP53 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

(Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 6.2023]

O venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia Variant class: TP53 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

■ (Induction therapy)

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Current EMA Information

	In this cancer type	O In other cancer t	ype ①	In this cance	er type and other	cancer types
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EMA information is current as of 2024-01-17. For the most up-to-date information, search www.ema.europa.eu/ema.

TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

O idelalisib + rituximab

Cancer type: Chronic Lymphocytic Leukemia Label as of: 2023-06-23 Variant class: TP53 mutation

Reference:

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

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Current ESMO Information

In this cancer type

O In other cancer type

In this cancer type and other cancer types

ESMO information is current as of 2024-01-02. For the most up-to-date information, search www.esmo.org.

TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

acalabrutinib

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

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

Population segment (Line of therapy):

■ Symptomatic, 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.(published)]

O ibrutinib

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

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

Population segment (Line of therapy):

Symptomatic, 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.(published)]

O rituximab + venetoclax

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

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

Population segment (Line of therapy):

Symptomatic, 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.(published)]

O idelalisib + rituximab

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

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

Population segment (Line of therapy):

■ Symptomatic, 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.(published)]

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

acalabrutinib

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

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

Population segment (Line of therapy):

- Early-stage; Symptomatic (First-line therapy)
- Advanced-stage (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.(published)]

O ibrutinib

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

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

Population segment (Line of therapy):

- Early-stage; Symptomatic (First-line therapy)
- Advanced-stage (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.(published)]

O idelalisib + rituximab

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

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

Population segment (Line of therapy):

- Early-stage; Symptomatic (First-line therapy)
- Advanced-stage (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.(published)]

obinutuzumab + venetoclax

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

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

Population segment (Line of therapy):

- Early-stage; Symptomatic (First-line therapy)
- Advanced-stage (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.(published)]

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

O venetoclax

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

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

Population segment (Line of therapy):

- Early-stage; Symptomatic (First-line therapy)
- Advanced-stage (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.(published)]

O venetoclax

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

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

Population segment (Line of therapy):

Symptomatic, 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.(published)]

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Diagnostic Details

Current NCCN Information

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For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

Diagnostic significance: Myelodysplastic Syndrome

Variant class: TP53 mutation

NCCN Recommendation category: 2A

Diagnostic notes:

■ 2022 WHO Classification of Myelodysplastic Neoplasms (MDS); MDS-Biallelic (or multi-hit) TP53 mutation: ≥2 TP53 mutations or 1 mutation with TP53 copy number loss or cnLOH at the 17p TP53 locus, usually with complex karyotype, or a VAF >23%.

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2023]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

FDA information is current as of 2024-01-17. For the most up-to-date information, search www.fda.gov.

TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

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-fdabreakthrough-therapy-designation-1769167

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A (continued)

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

A Fast Track

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.

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TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

chemoimmunotherapy

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

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 1.2024]

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Current ESMO Information

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

ESMO information is current as of 2024-01-02. For the most up-to-date information, search www.esmo.org.

TP53 p.(P151T) c.451C>A, TP53 p.(R273H) c.818G>A

Ienalidomide

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 [Ann of Oncol (2020), https://doi.org/10.1016/j.annonc.2020.11.002]

References

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