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Sample Information

Patient Name: 莊國榮
Gender: Male
ID No.: Y120475692
History No.: 3527820
Age: 64

Ordering Doctor: DOC8721H 李瑋宸
Ordering REQ.: 0BRNEBL
Signing in Date: 2022/01/28

Path No.: S111-98300
MP No.: MY22004
Assay: Oncomine Myeloid Assay
Sample Type: Bone Marrow
Bone Marrow Aspirating Date: 2022/01/24

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

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.(Y220C) c.659A>G***

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
TP53 p.(Y220C) c.659A>G tumor protein p53 Allele Frequency: 93.19% **Prognostic significance:** ELN 2017: Adverse **Diagnostic significance:** None	None	**idelalisib + rituximab** [2] acalabrutinib ibrutinib obinutuzumab + venetoclax rituximab + venetoclax venetoclax	0

Public data sources included in relevant therapies: FDA[1], 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
SETBP1 p.(I871T) c.2612T>C, ETV6-ACSL6 fusion

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.(Y220C)	c.659A>G	COSM10758	chr17:7578190	93.19%	NM_000546.5	missense	1998
SETBP1	p.(I871T)	c.2612T>C	COSM1685364	chr18:42531917	44.87%	NM_015559.3	missense	1999
CEBPA	p.(F33=)	c.99T>C	.	chr19:33793222	12.45%	NM_004364.4	synonymous	2000

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
ETV6-ACSL6	ETV6-ACSL6.E1A2	chr12:11803094 - chr5:131329944	224
ETV6-ACSL6	ETV6-ACSL6.E2A2.Non-Targeted	chr12:11905513 - chr5:131329944	1410

Biomarker Descriptions

ETV6 (ETS variant transcription factor 6)

Background: The ETV6 gene encodes the E twenty-six (ETS) variant 1 transcription factor. ETV6 contains an N-terminal pointed (PNT) domain responsible for protein-protein interactions and a C-terminal ETS domain involved in DNA binding[1]. ETV6 plays a critical role in embryonic development as well as hematopoiesis and is the target of chromosomal rearrangement and missense mutations in hematological malignancies as well as solid tumors[2,3]. Hereditary mutations in ETV6 are associated with a predisposition to hematological cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS)[4,5,6].

Alterations and prevalence: ETV6 translocations are prevalent in hematological malignancies and have been observed with numerous fusion partners[7]. The most recurrent translocation is t(12;21)(q34;q11) which results in ETV6-RUNX1 fusion and is observed in 20-25% childhood acute lymphoblastic leukemia (ALL)[7,8,9]. ETV6-RUNX1 fusions are also observed in adult ALL (2%)[8,9]. The t(5;12)(q33;p13) translocation which results in the ETV6-PDGFRB fusion is recurrent in chronic myelomonocytic leukemia (CMML)[7,10]. Other ETV6 fusions including ETV6-PDGFRA, ETV6-NTRK2, ETV6-NTRK3, and ETV6-ABL1 are reported in hematological malignancies as well as solid tumors[3,7,11]. ETV6 fusions involving a receptor tyrosine kinase (RTK) fusion partner retains the ETV6 PNT domain and the tyrosine kinase domain of the RTK, leading to constitutive kinase activation[7,11]. Mutations in ETV6 are primarily missense, nonsense, or frameshift and are observed in about 1-5% of select myeloid malignancies and solid tumors, including chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), MDS, AML, ALL, melanoma, lung, bladder, stomach,

Biomarker Descriptions (continued)

colorectal, and uterine cancers[1,12,13]. ETV6 mutations occur in the PNT and ETS domain of ETV6 and may impair ETV6 oligomerization or DNA-binding, respectively[1].

Potential relevance: ETV6-NTRK3 fusions are used as an ancillary diagnostic marker in congenital/infantile fibrosarcoma[14]. Nonsense or frameshift mutations in ETV6 are independently associated with poor prognosis in MDS[6]. However, ETV6-RUNX1 fusions are associated with favorable outcomes in ALL and good risk in B-cell ALL (B-ALL)[9]. ETV6 fusions that partner with a RTKs demonstrate response to various tyrosine kinase inhibitors such as imatinib, nilotinib, and entrectinib. Specifically, individual case reports of an ETV6-PDGFRA fusion chronic eosinophilic leukemia patient and an ETV6-PDGFRB fusion CMML patient treated with imatinib demonstrated complete cytogenetic response (CCyR) and complete hematological responses, respectively[15,16]. Additionally, an ETV6-ABL1 fusion Ph-negative CML patient treated with nilotinib demonstrated CCyR and major molecular response (MMR) at 22 months from diagnosis[17]. In another case report, an ETV6-NTRK3 fusion mammary analogue secretory carcinoma (MASC) patient demonstrated partial response to entrectinib with 89% reduction in tumor burden[18].

SETBP1 (SET binding protein 1)

Background: The SETBP1 gene encodes the SET binding protein 1, a multi-functional protein which contributes to several cellular processes including transcriptional regulation, proliferation, differentiation, and transformation[19]. SETBP1 contains a SET binding domain, which enables SETBP1 to form complexes with SET domain containing proteins, including the nuclear SET oncoprotein, a potent inhibitor of protein phosphatase 2A (PP2A)[19,20,21]. SETBP1 binding stabilizes SET, leading to elevated SET expression and increased inhibition of PP2A[19,22,23]. SETBP1 mediated inhibition of PP2A facilitates leukemic transformation in hematological malignancies including acute myeloid leukemia (AML)[23]. SETBP1 also contains three AT-hook domains, three nuclear localization motifs, and a SKI-homologous region which can influence transcriptional regulation[19]. SETBP1 is the target of somatic mutations in both hematological malignancies as well as solid tumors[13,24]. SETBP1 mutations often result in a gain of function and can lead to HOX gene upregulation, suggesting an oncogenic role for SETBP1 in cancer[24,25]. Additionally, germline gain of function mutations in SETBP1 are found to be causal of Schinzel-Giedion syndrome (SGS), a rare developmental disorder characterized by multiple malformations, severe neurological alterations and increased risk of cancer[26].

Alterations and prevalence: SETBP1 mutations are observed in up to 32% of atypical chronic myeloid leukemia (aCML), 24% of juvenile myelomonocytic leukemia (JMML), 18% of chronic myelomonocytic leukemia (CMML), 10% of myelodysplastic/myeloproliferative neoplasms (MDS/MPN), 1-3% of primary AML and up to 17% of secondary AML (sAML)[13,24,27,28,29]. Additionally, mutations in SETBP1 are reported in solid tumors including up to 12% of melanoma, 11% of lung adenocarcinoma, 9% of stomach and uterine cancer, as well as, 6% of esophageal and colorectal carcinoma[13]. SETB1 mutations are predominantly missense, the most recurrent involving amino acid substitutions at D868, G870, and I871[24,28,29]. SETBP1 fusions have also been described in hematological malignancies. The t(11;18)(p15;q12)/NUP98-SETBP1 and t(12;18)(p13;q12)/ETV6-SETBP1 fusions have been reported in individual cases of T-cell acute lymphoblastic leukemia (T-ALL) and AML, respectively[3,30].

Potential relevance: The presence of SETBP1 mutations is one of the diagnostic criteria for CMML as defined by the World Health Organization(WHO)[31]. Overexpression of SETBP1 is associated with accelerated leukemic transformation and poor prognosis in AML[23,27]. Additionally, mutations in SETBP1 are associated with poor prognosis in MDS/MPN, CMML, JMML, and aCML[27,29,32,33].

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[34]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[35,36].

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%)[13,37,38,39,40,41]. 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[13,37]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[42,43,44,45].

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[46]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[47] and breakthrough designation[48] (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[49,50]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic

Biomarker Descriptions (continued)

lymphocytic leukemia (CLL),[6,51,52,53]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[54]. 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[55].

Relevant Therapy Summary

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

TP53 p.(Y220C) c.659A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
idelalisib + rituximab	✖	✖	○	○	✖
acalabrutinib	✖	✖	✖	○	✖
ibrutinib	✖	✖	✖	○	✖
obinutuzumab + venetoclax	✖	✖	✖	○	✖
rituximab + venetoclax	✖	✖	✖	○	✖
venetoclax	✖	✖	✖	○	✖

Relevant Therapy Details

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 2021-11-17. For the most up-to-date information, search www.ema.europa.eu/ema.

TP53 p.(Y220C) c.659A>G

○ 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 2021-11-01. For the most up-to-date information, search www.esmo.org.

TP53 p.(Y220C) c.659A>G

○ 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.(Y220C) c.659A>G (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.]

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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.]

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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.]

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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.(Y220C) c.659A>G (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.]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2021-11-01. 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.(Y220C) c.659A>G

Prognostic significance: ELN 2017: Adverse

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

NCCN Recommendation category: 2A

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2021]

Current ESMO Information

ESMO information is current as of 2021-11-01. For the most up-to-date information, search www.esmo.org.

TP53 p.(Y220C) c.659A>G

Prognostic significance: ELN 2017: Adverse

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Acute Myeloblastic Leukaemia in Adult Patients [Ann Oncol (2020); 31(6): 697-712.]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-11-17. For the most up-to-date information, search www.fda.gov.

TP53 p.(Y220C) c.659A>G

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

TP53 p.(Y220C) c.659A>G (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 Fast Track

NCCN information is current as of 2021-11-01. 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.(Y220C) c.659A>G

chemoimmunotherapy

Cancer type: Chronic Lymphocytic Leukemia **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 1.2022]

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-11-01. For the most up-to-date information, search www.esmo.org.

TP53 p.(Y220C) c.659A>G

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]

Signatures

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