Taipei Veterans General Hospital

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Sample Information

Patient Name: 林惟祥
Gender: Male
ID No.: A103982662
History No.: 46816302
Age: 71

Ordering Doctor: DOC6368C 黃睿慈
Ordering REQ.: 0BQHALR
Signing in Date: 2021/12/29

Path No.: S110-97820
MP No.: MY21009
Assay: Oncomine Myeloid Assay
Sample Type: Blood
Date of blood drawing: 2021/12/23

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	***KMT2A-MLLT10 fusion***	TP53	***TP53 p.(G245D) c.734G>A***

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
TP53 p.(G245D) c.734G>A tumor protein p53 Allele Frequency: 44.25% **Prognostic significance:** ELN 2017: Adverse **Diagnostic significance:** None	None	**idelalisib + rituximab** [2] acalabrutinib ibrutinib obinutuzumab + venetoclax rituximab + venetoclax venetoclax	0
KMT2A-MLLT10 fusion lysine methyltransferase 2A - MLLT10 histone lysine methyltransferase DOT1L cofactor **Prognostic significance:** ELN 2017: Adverse **Diagnostic significance:** None	None	None	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
NRAS p.(Q61K) c.181C>A

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
NRAS	p.(Q61K)	c.181C>A	COSM580	chr1:115256530	43.52%	NM_002524.5	missense	1990
TP53	p.(G245D)	c.734G>A	COSM43606	chr17:7577547	44.25%	NM_000546.5	missense	2000

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
KMT2A-MLLT10	KMT2A-MLLT10.K8M10	chr11:118353210 - chr10:21959378	22
KMT2A-MLLT10	KMT2A-MLLT10.K8M9	chr11:118353210 - chr10:21940602	3916
KMT2A-MLLT10	KMT2A-MLLT10.K7M9.Non-Targeted	chr11:118352807 - chr10:21940602	2180

Biomarker Descriptions

KMT2A (lysine methyltransferase 2A)

Background: The KMT2A gene encodes the lysine methyltransferase 2A protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily. KMT2A influences epigenetic regulation by means of its methyltransferase activity which regulates a variety of cellular functions including neurogenesis, hematopoiesis, and osteogenesis[1]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[2]. Such translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[2]. Loss of methyltransferase activity along with partner gene gain of function contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[2,3,4,5].

Biomarker Descriptions (continued)

Alterations and prevalence: KMT2A fusions are observed in 3-10% of AML cases with highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[2,6,7]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1-KMT2A, t(9;11)(p22;q23)/MLLT3-KMT2A, t(11;19)(q23;p13.3)/KMT2A-MLLT1, t(10;11)(p12;q23)/MLLT10-KMT2A, and t(6;11)(q27;q23)/AFDN-KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[2]. In infant acute leukemic cases, KMT2A rearrangement is reported in up to 70% of those diagnosed with either AML or ALL[2,8,9]. Mutations in KMT2A are also reported in diverse solid tumors including 10-20% of melanoma, stomach, bladder, and uterine cancers and around 5% of lung and head and neck cancers[10]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations which result in KMT2A truncation and loss of methyltransferase activity[10,11].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[7]. For example, t(6;11)(q27;q23)/AFDN-KMT2A fusions are associated with poor prognosis whereas, t(9;11)(p22;q23)/MLLT3-KMT2A fusions confer more favorable or intermediate prognosis in AML[12,13,14]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[15].

MLLT10 (MLLT10 histone lysine methyltransferase DOT1L cofactor)

Background: The MLLT10 gene encodes the AF10 protein, a histone lysine methyltransferase cofactor. MLLT10 functions as part of the super elongation complex (SEC) responsible for rapid transcriptional induction of immediate response and developmental genes[16,17,18]. MLLT10 possesses a plant homeodomain (PHD) which can interact with the histone methyltransferase, DOT1L, and promote DOT1L activity[19]. MLLT10 interaction with DOT1L also influences HOXA gene expression, whose dysregulation plays a critical role in leukemic oncogenesis[19,20,21]. MLLT10 is the target of recurrent chromosomal translocation in myeloid malignancies including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[22,23].

Alterations and prevalence: Chromosomal rearrangements involving MLLT10 have been observed with various fusion partners[24,25]. Specifically, the t(10;11)(p12;q23) rearrangement is recurrent in hematological malignancies, including ALL and AML[22,26]. This translocation results in MLLT10-KMT2A fusion, which likely promotes mis-targeting of DOT1L, leading to subsequent activation of oncogenes such as HOX9A[27]. Another recurrent MLLT10 translocation, observed in ALL and AML, includes t(10;11)(p13;q14-21), which results in the MLLT10-PICALM fusion[24,28].

Potential relevance: The MLLT10-KMT2A fusion confers poor prognosis in AML, while the MLLT10-PICALM fusion confers poor prognosis in AML as well as ALL[7,23,24].

NRAS (NRAS proto-oncogene, GTPase)

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[29,30,31].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[10,32]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[10,33]. Mutations at A59, K117, and A146 have also been observed but are less frequent[34,35].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[36] and panitumumab[37], are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[35]. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[38] as well as melanoma[39]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[40].

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[41]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[42,43].

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%)[10,34,44,45,46,47]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense

Biomarker Descriptions (continued)

mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[10,34]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[48,49,50,51].

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[52]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[53] and breakthrough designation[54] (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[55,56]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[7,15,38,57]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[58]. 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[59].

Relevant Therapy Summary

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

TP53 p.(G245D) c.734G>A

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.(G245D) c.734G>A

○ 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.(G245D) c.734G>A

○ 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.(G245D) c.734G>A (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.(G245D) c.734G>A (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.(G245D) c.734G>A

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]

KMT2A-MLLT10 fusion

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

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.(G245D) c.734G>A

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.]

KMT2A-MLLT10 fusion

Prognostic significance: ELN 2017: Adverse

Cancer type: Acute Myeloid Leukemia **Variant class:** KMT2A fusion

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.(G245D) c.734G>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-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 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.(G245D) c.734G>A

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.(G245D) c.734G>A

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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References

1. Huang et al. Epigenetic regulation of NOTCH1 and NOTCH3 by KMT2A inhibits glioma proliferation. Oncotarget. 2017 Sep 8;8(38):63110-63120. PMID: 28968975
2. Krivtsov et al. MLL translocations, histone modifications and leukaemia stem-cell development. Nat. Rev. Cancer. 2007 Nov;7(11):823-33. PMID: 17957188
3. Ayton et al. Molecular mechanisms of leukemogenesis mediated by MLL fusion proteins. Oncogene. 2001 Sep 10;20(40):5695-707. PMID: 11607819
4. DiMartino et al. The AF10 leucine zipper is required for leukemic transformation of myeloid progenitors by MLL-AF10. Blood. 2002 May 15;99(10):3780-5. PMID: 11986236
5. Biswas et al. Function of leukemogenic mixed lineage leukemia 1 (MLL) fusion proteins through distinct partner protein complexes. Proc. Natl. Acad. Sci. U.S.A. 2011 Sep 20;108(38):15751-6. PMID: 21896721
6. Schoch et al. AML with 11q23/MLL abnormalities as defined by the WHO classification: incidence, partner chromosomes, FAB subtype, age distribution, and prognostic impact in an unselected series of 1897 cytogenetically analyzed AML cases. Blood. 2003 Oct 1;102(7):2395-402. PMID: 12805060
7. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 3.2021]
8. Biondi et al. Biological and therapeutic aspects of infant leukemia. Blood. 2000 Jul 1;96(1):24-33. PMID: 10891426
9. Pui et al. Biology and treatment of infant leukemias. Leukemia. 1995 May;9(5):762-9. PMID: 7769837
10. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
11. Rao et al. Hijacked in cancer: the KMT2 (MLL) family of methyltransferases. Nat. Rev. Cancer. 2015 Jun;15(6):334-46. PMID: 25998713
12. Krauter et al. Prognostic factors in adult patients up to 60 years old with acute myeloid leukemia and translocations of chromosome band 11q23: individual patient data-based meta-analysis of the German Acute Myeloid Leukemia Intergroup. J. Clin. Oncol. 2009 Jun 20;27(18):3000-6. PMID: 19380453
13. Balgobind et al. The heterogeneity of pediatric MLL-rearranged acute myeloid leukemia. Leukemia. 2011 Aug;25(8):1239-48. PMID: 21566656
14. Tamai et al. 11q23/MLL acute leukemia : update of clinical aspects. J Clin Exp Hematop. 2010;50(2):91-8. PMID: 21123966
15. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2021]
16. Bernt et al. A role for DOT1L in MLL-rearranged leukemias. Epigenomics. 2011 Dec;3(6):667-70. doi: 10.2217/epi.11.98. PMID: 22126283
17. Luo et al. The super elongation complex (SEC) family in transcriptional control. Nat. Rev. Mol. Cell Biol. 2012 Sep;13(9):543-7. PMID: 22895430
18. Scholz et al. AF4 and AF4N protein complexes: recruitment of P-TEFb kinase, their interactome and potential functions. Am J Blood Res. 2015;5(1):10-24. PMID: 26171280
19. Deshpande et al. AF10 regulates progressive H3K79 methylation and HOX gene expression in diverse AML subtypes. Cancer Cell. 2014 Dec 8;26(6):896-908. PMID: 25464900
20. Okada et al. hDOT1L links histone methylation to leukemogenesis. Cell. 2005 Apr 22;121(2):167-78. PMID: 15851025
21. Zhang et al. Structural and functional analysis of the DOT1L-AF10 complex reveals mechanistic insights into MLL-AF10-associated leukemogenesis. Genes Dev. 2018 Mar 1;32(5-6):341-346. PMID: 29563185
22. Peterson et al. Acute leukemias harboring KMT2A/MLLT10 fusion: a 10-year experience from a single genomics laboratory. Genes Chromosomes Cancer. 2019 Aug;58(8):567-577. PMID: 30707474
23. Savage et al. Acute leukemia with PICALM-MLLT10 fusion gene: diagnostic and treatment struggle. Cancer Genet. Cytogenet. 2010 Oct 15;202(2):129-32. PMID: 20875875
24. Huret et al. Atlas of genetics and cytogenetics in oncology and haematology in 2013. Nucleic Acids Res. 2013 Jan;41(Database issue):D920-4. PMID: 23161685
25. Brandimarte et al. New MLLT10 gene recombinations in pediatric T-acute lymphoblastic leukemia. Blood. 2013 Jun 20;121(25):5064-7. PMID: 23673860
26. Chaplin et al. The t(10;11) translocation in acute myeloid leukemia (M5) consistently fuses the leucine zipper motif of AF10 onto the HRX gene. Blood. 1995 Sep 15;86(6):2073-6. PMID: 7662954
27. Nguyen et al. The diverse functions of Dot1 and H3K79 methylation. Genes Dev. 2011 Jul 1;25(13):1345-58. PMID: 21724828
28. Dreyling et al. MLL and CALM are fused to AF10 in morphologically distinct subsets of acute leukemia with translocation t(10;11): both rearrangements are associated with a poor prognosis. Blood. 1998 Jun 15;91(12):4662-7. PMID: 9616163

References (continued)

29. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
30. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
31. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
32. Janku et al. PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS ONE. 2011;6(7):e22769. PMID: 21829508
33. Ohashi et al. Characteristics of lung cancers harboring NRAS mutations. Clin. Cancer Res. 2013 May 1;19(9):2584-91. PMID: 23515407
34. 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
35. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
36. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
37. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf
38. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2022]
39. Johnson et al. Treatment of NRAS-Mutant Melanoma. Curr Treat Options Oncol. 2015 Apr;16(4):15. doi: 10.1007/s11864-015-0330-z. PMID: 25796376
40. Dummer et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017 Apr;18(4):435-445. PMID: 28284557
41. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
42. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1):a001008. PMID: 20182602
43. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
44. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
45. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
46. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780
47. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061
48. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum. Mutat. 2002 Jun;19(6):607-14. PMID: 12007217
49. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. Genes Cancer. 2011 Apr;2(4):466-74. PMID: 21779514
50. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007 Apr 2;26(15):2157-65. PMID: 17401424
51. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. Hum. Mutat. 2014 Jun;35(6):766-78. PMID: 24729566
52. https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html
53. https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation
54. http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167
55. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534

References (continued)

56. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
57. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 1.2022]
58. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 5.2021]
59. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829