Laboratorio Inov | www.inovlabs.es
Calle Goana 48 Granada España 18004
Tel: 34 958 65 43 21

Case ID **XB-1065-SP**	Patient sex **Male**	Diagnosis **Acute myeloid leukemia**	Tumor purity not specified	Ordering physician **Arturo López, MD**
Patient MRN not specified	Patient DOB **15/09/1959**	Sample type **Blood**	Sample collection date **29/09/2020**	Ordering institution **Hospital Privado San José**
Patient name not specified	Patient ethnicity not specified	Sample site **Blood**	Sample receipt date **02/10/2020**	Ordering institution ID **HPSJ**

Report summary

4 clinically significant variants & combinations
0 other biomarkers
1 relevant therapy
2 clinical trials

present in combination **IDH2** p.R140W
present in combination **NRAS** p.G12D
variant **EZH2** p.E745fs

variant present in combination

IDH2 p.R140W VAF **25%** RD **409** Tier I-B

One IDH2 inhibitor is approved and recommended for certain patients with acute myeloid leukemia harboring IDH2 hotspot mutations (IDH2 R140Q/L/G/W or R172K/M/G/S/W) (FDA, Health Canada, TGA, NCCN, and ESMO, pending EMA approval), based on phase I/II clinical trial results. Additional clinical trials reported sensitivity to a BCL2 inhibitor in IDH-mutant AML. IDH2 mutations are associated with neutral or conflicting prognosis in AML (WHO, NCCN).

Therapies associated with: **Acute myeloid leukemia**

- **enasidenib**

2

combination

NRAS p.G12D, **IDH2** p.R140W Tier II-C

In a phase I/II clinical trial, NRAS hotspot mutations correlated with decreased response rate with an IDH2 inhibitor in IDH2-mutant AML.

no approved therapies

variant present in combination

NRAS p.G12D VAF **31%** RD **426** Tier II-C

No therapies are approved or recommended for hematologic cancer based on NRAS mutation status (FDA, EMA, Swissmedic, Health Canada, TGA, NCCN, ESMO, NICE, eviQ). A phase I/II trial suggests RAS-mutant leukemia patients may be sensitive to a MEK inhibitor. Patients with NRAS-mutant AML match inclusion criteria for clinical trials, such as trials with MEK inhibitors and a combination of MEK and AKT inhibitors. Preclinical studies suggest NRAS G12D AML, CMML, and MM cell lines are more sensitive to MEK inhibitors in combination with PI3K, JAK2, or BRD4 inhibitors. NRAS mutations are not regarded as appropriate single markers of minimal residual disease in AML (ELN). Mutations in this gene can be of germline origin and may have implications for clinical management for patients and family members; thus, germline testing may be considered in the appropriate clinical context (NCCN Guidelines for Myelodysplastic Syndromes). For patients with colorectal cancer harboring NRAS hotspot mutations, two anti-EGFR monoclonal antibodies are contraindicated and not recommended (FDA, EMA, Swissmedic, Health Canada, TGA, NCCN, ESMO, NICE, eviQ).

Therapies approved/guidelines-recommended in: **other indications**

× cetuximab
resistance

× panitumumab
resistance

variant

EZH2 p.E745fs VAF **23%** RD **116** Tier II-C

EZH2 inactivating mutations are associated with worse prognosis in MDS (WHO, NCCN), including after HSCT (ELN), MDS/MPN (NCCN), and PMF (NCCN). The presence of at least one mutation in either SH2B3, IDH2, U2AF1, SF3B1, EZH2, or TP53 is associated with worse prognosis in ET (NCCN). Testing for EZH2 mutations is recommended for patients with CMML, since some studies associate these mutations with poor prognosis (ELN, EHA). In one retrospective analysis, patients with EZH2-mutant myelodysplasia related neoplasms, including AML-MRC, had worse outcomes, and in another, EZH2 mutations were not associated with prognosis in CMML. EZH2 or other accompanying mutations may aid in determining clonality in JAK2/CALR/MPL wild-type PMF and MPN-U (WHO, NCCN, ELN, EHA). These mutations may be present in CHIP (WHO).

no approved therapies

Clinical trials from MolecularMatch

Selected trials recruiting: **Male, age ≥ 18** within **Spain**

EUDRACT2015-000344-42 Phase **3**

IDH2, IDH2 R140W

A Phase 3, Multicenter, Open-label, Randomized Study Comparing the Efficacy and Safety of AG-221 (CC-90007) Versus Conventional Care Regimens in Older Subjects with Late Stage Acute Myeloid Leukemia Harboring an Isocitrate Dehydrogenase 2 Mutation.

NCT04090736 Phase **3**

IDH2

Study to Compare Azacitidine Plus Pevonedistat Versus Azacitidine in Patients With Acute Myeloid Leukemia Not Eligible for Standard Chemotherapy

End of findings section

IDH2 p.R140W missense variant

Tier I-B

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
IDH2 codon 140 mutation IDH2 hotspot mutation	Gain of function	Chr:15 Pos:90088703 Change:G>A	c.418C>T p.Arg140Trp	ENST00000330062.7

Gene clinical summary
Alterations in IDH2 are founder in cancers, including colon, brain and blood cancer. Missense mutations in the active site result in neomorphic enzymatic activity, converting α-KG to R-2-hydroxyglutarate (2-HG). 2-HG is an oncogenic metabolite that inhibits α-KG-dependent enzymes. An IDH2 inhibitor (enasidenib) is approved for IDH2 positive AML (FDA)(PMID: 28879540). Additional IDH2 inhibitors are under clinical and preclinical investigation (PMID: 27292784).

Variant clinical summary
Enasidenib is approved and recommended for certain patients with acute myeloid leukemia (AML) harboring IDH2 hotspot mutations (IDH2 R140Q/L/G/W or R172K/M/G/S/W) (FDA, Health Canada, TGA, NCCN, and ESMO, pending EMA approval), based on results from a phase I/II clinical trial in which treatment with enasidenib resulted in overall response in 53.3% and complete response in 24.4% of AML patients harboring IDH2 R172 mutations (n=45) and overall response in 35.4% and complete response in 17.7% of AML patients harboring IDH2 R140 mutations (n=130). Reduction in 2-HG production did not correlate with clinical response (PMID: 28588020).

In additional clinical trials, 33% (4/12) of AML patients harboring IDH1 or IDH2 mutations responded to venetoclax monotherapy (PMID: 27520294) and 72% (13/18) of patients with IDH-mutant AML who were ineligible for intensive chemotherapy responded to venetoclax in combination with low-dose chemotherapy (ASH Annual Meeting, Dec 2018, Abstract 284).

IDH2 mutations are associated with neutral or conflicting prognosis in AML (WHO, NCCN). In normal karyotype AML, some studies did not associate IDH2 mutations with prognosis and others associated IDH2 codon 172 mutations or IDH1/2 mutations with worse prognosis (WHO). In AML with various abnormal and normal karyotypes combined, IDH1/2 mutations were not associated with prognosis (WHO).

Variant group clinical summary
Enasidenib is approved and recommended for certain patients with acute myeloid leukemia (AML) harboring IDH2 hotspot mutations (IDH2 R140Q/L/G/W or R172K/M/G/S/W) (FDA, Health Canada, TGA, NCCN, and ESMO, pending EMA approval), based on results from a phase I/II clinical trial in which treatment with enasidenib resulted in overall response in 53.3% and complete response in 24.4% of AML patients harboring IDH2 R172 mutations (n=45) and overall response in 35.4% and complete response in 17.7% of AML patients harboring IDH2 R140 mutations (n=130). Reduction in 2-HG production did not correlate with clinical response (PMID: 28588020).

In additional clinical trials, 33% (4/12) of AML patients harboring IDH1 or IDH2 mutations responded to venetoclax monotherapy (PMID: 27520294) and 72% (13/18) of patients with IDH-mutant AML who were ineligible for intensive chemotherapy responded to venetoclax in combination with low-dose chemotherapy (ASH Annual Meeting, Dec 2018, Abstract 284).

IDH2 mutations are associated with neutral or conflicting prognosis in AML (WHO, NCCN). In normal karyotype AML, some studies did not associate IDH2 mutations with prognosis and others associated IDH2 codon 172 mutations or IDH1/2 mutations with worse prognosis (WHO). In AML with various abnormal and normal karyotypes combined, IDH1/2 mutations were not associated with prognosis (WHO).

Gene biological summary
IDH2, a mitochondrial isocitrate dehydrogenase, catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) in metabolic pathways (PMID: 23999441). Important domains in IDH2 include a mitochondrial signal peptide (residues 1-39), two NADP binding domains (residues 115-117 and 349-354), and the substrate binding site (residues 117, 149 and 172) (UniProt.org).

Variant functional summary
IDH2 R140W lies within the substrate binding of the IDH2 protein (UniProt.org). This mutation confers a gain of function to the IDH2 protein, as demonstrated by the conversion of alpha-ketoglutarate to 2-HG (2-hydroxyglutarate) in an in vitro assay (PMID: 21647154).

Variant group functional summary
IDH2 codon 140 mutation indicates any change in the IDH2 protein at codon 140. These hotspot mutations may be activating, confering a gain of novel function to IDH2 by enabling conversion of alpha-ketoglutarate to the onco-metabolite 2HG (R(-)-2-hydroxyglutarate). This results in increased 2HG levels in patient samples and is transforming in cell culture (PMID: 20171147)(PMID: 21647154)(PMID: 23558173).

IDH2 hotspot mutation refers to a mutation in codon 140 or 172. Many of these mutations are known to be activating, confering a gain of novel function to IDH2 by enabling conversion of alpha-ketoglutarate to the onco-metabolite 2HG (R(-)-2-hydroxyglutarate). This results in increased 2HG levels in patient samples and is transforming in cell culture (PMID: 20171147)(PMID: 23071358)(PMID: 23558173)(PMID: 25495392)(PMID: 27621679).

NRAS p.G12D, **IDH2** p.R140W

Tier II-C

Variant combination clinical summary
In a phase I/II clinical trial, samples taken before and after treatment with enasidenib from acute myeloid leukemia (AML) patients harboring IDH2 R140Q or R172K were assayed ex vivo. Patients also harboring NRAS hotspot mutations had a lower than average clinical response rate (PMID: 28588019).

Variant combination functional summary
IDH2 hotspot mutation refers to a mutation in codon 140 or 172. Many of these mutations are known to be activating, confering a gain of novel function to IDH2 by enabling conversion of alpha-ketoglutarate to the onco-metabolite 2HG (R(-)-2-hydroxyglutarate). This results in increased 2HG levels in patient samples and is transforming in cell culture (PMID: 20171147)(PMID: 23071358)(PMID: 23558173)(PMID: 25495392)(PMID: 27621679).

NRAS hotspot mutation refers to a mutation in codons 12, 13, 59, 61, 117, or 146. Many of these mutations are known to be activating (PMID: 27664710)(PMID: 6092966).

NRAS p.G12D missense variant

Tier II-C

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
NRAS codon 12 mutation NRAS hotspot mutation	Gain of function	Chr:1 Pos:114716126 Change:C>T	c.35G>A p.Gly12Asp	ENST00000369535.4

Gene clinical summary
Oncogenic NRAS missense mutations are found in cancers, including melanoma, colorectal, and thyroid cancer (PMID: 28666118). Hotspot mutations result in loss of GTPase function and net downstream activation (PMID: 26815308). Germline mutations in NRAS are associated with RASopathies, which confer increased cancer risk (PMID: 28957739). Currently, no effective RAS inhibitors have been developed, however emerging drugs target codon 12 and the hypervariable domain, as well as downstream effectors of RAS and regulators of RAS membrane association and activity (PMID: 25878363). Additionally, studies have reported that NRAS activation leads to resistance to EGFR tyrosine kinase inhibitors (PMID: 27279914) and anti-EGFR antibodies (PMID: 24758538).

Variant clinical summary
No therapies are approved or recommended for hematologic cancer based on NRAS mutation status (FDA, EMA, Swissmedic, Health Canada, TGA, NCCN, ESMO, NICE, eviQ). In a phase Ib/II clinical trial, treatment with trametinib resulted in an overall response rate of 28% in RAS-mutant leukemia patients, with 12% (7/57) of patients achieving complete remission (ASH 2012 Annual Meeting, Abst 677). Patients with NRAS-mutant acute myeloid leukemia (AML) match inclusion criteria for clinical trials, such as trials with MEK inhibitors (NCT01907815)(NCT02049801)(NCT02418000) and a combination of MEK and AKT inhibitors (NCT01907815). Preclinical studies suggest NRAS G12D AML, CMML, and MM cell lines are more sensitive to MEK inhibitors in combination with PI3K, JAK2, or BRD4 inhibitors (PMID: 20331454)(PMID: 24569456)(PMID: 24812670)(PMID: 25361812)(Blood Dec 2016, 128 (22) 1654).

NRAS mutations are not regarded as appropriate single markers of minimal residual disease in AML (ELN). Mutations in this gene can be of germline origin and may have implications for clinical management for patients and family members; thus, germline testing may be considered in the appropriate clinical context (NCCN Guidelines for Myelodysplastic Syndromes).

For patients with colorectal cancer harboring NRAS hotspot mutations, cetuximab and panitumumab are contraindicated and not recommended (FDA, EMA, Swissmedic, Health Canada, TGA, NCCN, ESMO, NICE, eviQ).

Variant group clinical summary
No therapies are approved or recommended for hematologic cancer based on NRAS mutation status (FDA, EMA, Swissmedic, Health Canada, TGA, NCCN, ESMO, NICE, eviQ). In a phase Ib/II clinical trial, treatment with trametinib resulted in an overall response rate of 28% in RAS-mutant leukemia patients, with 12% (7/57) of patients achieving complete remission (ASH 2012 Annual Meeting, Abst 677). Patients with NRAS-mutant acute myeloid leukemia (AML) match inclusion criteria for clinical trials, such as trials with MEK inhibitors (NCT01907815)(NCT02049801)(NCT02418000) and a combination of MEK and AKT inhibitors (NCT01907815). In preclinical studies, NRAS-mutant AML cells were sensitive to MEK, RAF, and BRD4/BET inhibitors and resistant to multikinase, VEGF, and BRAF inhibitors (PMID: 26343583)(PMID: 27573426)(PMID: 30333627).

NRAS mutations are not regarded as appropriate single markers of minimal residual disease in AML (ELN). Mutations in this gene can be of germline origin and may have implications for clinical management for patients and family members; thus, germline testing may be considered in the appropriate clinical context (NCCN Guidelines for Myelodysplastic Syndromes).

For patients with colorectal cancer harboring NRAS hotspot mutations, cetuximab and panitumumab are contraindicated and not recommended (FDA, EMA, Swissmedic, Health Canada, TGA, NCCN, ESMO, NICE, eviQ).

Gene biological summary
NRAS is a member of the RAS GTPase superfamily and is a key regulator of the RAS/RAF/MEK/ERK pathway and the downstream PI3K/AKT/MTOR pathway, regulating cell survival, proliferation and migration. RAS proteins cycle between an inactive GDP-bound and an active GTP-bound state in response to receptor tyrosine kinase activation. Downstream effectors are recruited to the membrane and activated by RAS (PMID: 28666118). Important domains in NRAS include the catalytic domain (residues 1-166) and the hypervariable domain (residues 167-189) (PMID: 28597297).

Variant functional summary
NRAS G12D lies within a GTP-binding region of the NRAS protein (UniProt.org). This mutation results in decreased NRAS GTPase activity, leading to activation of downstream signaling and transformation of cultured cells (PMID: 19075190), (PMID: 25252692).

Variant group functional summary
NRAS codon 12 lies within a GTP-binding region of the NRAS protein (UniProt.org). Missense mutations in codon 12, with the exception of NRAS G12P, result in decreased NRAS GTPase activity, leading to activation of downstream signaling and transformation of cultured cells (PMID: 27664710)(PMID: 6092966)(PMID: 8357792).

NRAS hotspot mutation refers to a mutation in codons 12, 13, 59, 61, 117, or 146. Many of these mutations are known to be activating (PMID: 27664710)(PMID: 6092966).

EZH2 p.E745fs frameshift variant

Tier II-C

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
EZH2 inactivating mutation EZH2 truncating mutation	Loss of function	Chr:7 Pos:148807669 Change:C>CCCGG	c.2232_2233insCCGG p.Glu745fs	ENST00000320356.6

Gene clinical summary
Mutations in EZH2 are found in cancers, including hematological cancers and breast cancer. Activating mutations, including hot spot mutations at codon 641, are found in lymphomas and melanoma and result in increased silencing of tumor suppressor genes (PMID: 24362326). Mutations causing loss of EZH2 are found in myeloid neoplasms and T-cell acute lymphoblastic leukemia (PMID: 26845405). EZH2 inhibitors are under clinical investigation for patients harboring wild type EZH2 or gain of function mutations (NCT02601950)(NCT03456726).

Variant group clinical summary

EZH2 inactivating mutations are associated with worse prognosis in myelodysplastic syndrome (MDS) (WHO, NCCN), including after hematopoietic stem cell transfer (HSCT) (ELN), myelodysplastic/myeloproliferative neoplasms (MDS/MPN) (NCCN), and primary myelofibrosis (PMF) (NCCN). The presence of at least one mutation in either SH2B3, IDH2, U2AF1, SF3B1, EZH2, or TP53 is associated with worse prognosis in essential thrombocythemia (ET) (NCCN). Testing for EZH2 mutations is recommended for patients with chronic myelomonocytic leukemia (CMML), since some studies associate these mutations with poor prognosis (ELN, EHA).

In a retrospective analysis, patients with EZH2-mutant myelodysplasia related neoplasms (n=61), including acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) (n=10), had shorter median overall survival (29 months) compared to patients with wild type EZH2 (n=29, median overall survival not reached, p=0.003). These neoplasms included MDS, MDS/MPN, and acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) (PMID: 29359794). In a retrospective analysis of patients with chronic myelomonocytic leukemia (CMML) (n=173), EZH2 mutations (n=8) were not significantly associated with prognosis (median overall survival of 8.1 vs. 46.4 months for EZH2 wild type, p=0.07 and AML-free survival of 8.1 vs. 34.5 months for EZH2 wild type, p=0.12) (PMID: 23690417).

EZH2 or other accompanying mutations may aid in determining clonality in JAK2/CALR/MPL wild-type PMF and unclassified myeloproliferative neoplasms (MPN-U) (WHO, NCCN, ELN, EHA). These mutations may be present in clonal hematopoiesis of indeterminate potential (CHIP) (WHO).

Gene biological summary
EZH2 is the catalytic subunit of Polycomb Repressive Complex 2 (PRC2), a histone methyltransferase which methylates lysine 27 of histone H3, resulting in transcriptional repression of tumor suppressor genes involved in many pathways, including hematopoietic cell differentiation (PMID: 24362326). Important domains in EZH2 include the WD-40 binding domain (residues 39-68), the D1 and D2 domains (residues 94-159 and 218-334), the SANT domains (residues 159-250 and 428-476), the cysteine-rich domain (residues 503-605), and the SET catalytic domains (residues 605-725) (PMID: 26497210) (PMID: 24367611).

Variant group functional summary

EZH2 inactivating mutations result in a loss of function of the EZH2 protein, which has been verified via biochemical, in vitro, or in vivo assays. Additionally, this group includes variants that are predicted to have a loss of function due to a truncation leading to the disruption or deletion of key functional domains (PMID: 26845405).

Variants of Unknown Significance

The variants listed here are not sufficiently characterized in the current literature and variant databases, and are therefore, currently, of uncertain or unknown clinical significance. They are reported here for future reference in the event they become clinically significant in light of additional supporting evidence.

No variants of unknown significance found.

✓ Electronically Signed by Anoop Grewal | **Evan Scott, MD** Lab Director | *05/10/2020*

Appendix

Clinical Disclaimer

Interpretation of the test results is limited by the information that is currently available at the time. Treatment decisions are the responsibility of the physician. Results of this test must always be interpreted within the clinical context, such as the patient's conditions, patient and family history, physical examinations, information from other diagnostic tests and patient preferences.
The Inov Heme Panel was developed and its performance characteristics determined by Inov Labs.

Genomic Regions Tested

We sequence all coding exons for each given transcript, plus approximately 10 basepairs of flanking non-coding DNA in each intron-exon junction. Unless specifically indicated, test results contain no information about other regions of the gene, such as regulatory domains or deep intronic regions.
The genes on the panel: ABL1, ASXL1, ATM, BCL11B, BCOR, BCORL1, BRAF, BRCC3, CALR, CBL, CBLB, CD79B, VRBPS, CNOT3, CREBBP, CRLF2, CSF1R, CSF3R, CTCF, CTNNB1, CUX1, CXCR4, DNMT3A, DNMT3B, EED, EGFR, EP300, ETV6, EZH2, FANCL, FBXW7, FLT3, GATA1, GATA2, GATA3, GNAS, GNB1, IDH1, IDH2, IKZF1, IKZF2, IKZF3, IL7R, JAK1, JAK2, JAK3, KIT, KRAS, LUC7L2, MAPK2K1, MEF2B, MPL, MYD88, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NT5C2, PAX5, PDGFRA, PDS5B, PHF6, PIGA, PIM3, PRPF40B, PRPF8, PTEN, PTPN11, RAD21, RET, RIT1, RPL10, RUNX1, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, TET2, TLR2, TP53, U2AF1, U2AF2, WT1, XPO1, ZRSR2.
LIMIT OF DETECTION: 5 percent variant allele fraction for single nucleotide variants (SNVs), small to medium sized multi-nucleotide variants (MNV) (less than 50bp).

Methodology

Genomic DNA is isolated from plasma and then enriched for the targeted regions of the tested genes. The variant status of the targeted genes is determined by massively parallel sequencing (next generation sequencing). The GRCh38 reference sequence is used as a reference for identifying genetic variants.

Limitations

This test will not detect variants in areas outside the targeted genomic regions or below the assay's limit of detection. This test evaluates for variants in hematological samples only. It cannot distinguish between somatic and germline variants.
For variants of potential germline origin, germline testing may be warranted. Consider seeking genetic counseling prior to such testing. In some cases, variants may not be identified due to technical limitations, especially when in the presence of known pseudogenes, homologous regions or regions of low mappability. Larger insertions or deletions (>50 basepairs) may not be detected.

NAVIFY® Mutation Profiler disclaimer

The information available in this report is obtained from third party sources (such as biomedical literature, medical guidelines, and publicly available data such as drug labels and clinical trials) and is subject to change over time based on future findings (including scientific and medical research).

NAVIFY® Mutation Profiler is not able to differentiate between germline and somatic variants. In general, variant interpretations are provided assuming the variants are of somatic origin.

3rd party attributions

A portion of the somatic gene variant annotations and related content have been provided by The Jackson Laboratory Clinical Knowledgebase (JAX-CKB™)

Clinical trial matching based on reported biomarkers are provided by MolecularMatch.

Tier definitions

Tier I-A: Approved therapy. Included in professional guidelines.

Tier I-B: Well-powered studies with consensus from experts in the field.

Tier II-C: Approved therapies for different tumor types or investigational therapies. Multiple small published studies with some consensus. Inclusion criteria for clinical trials.

Tier II-D: Limited clinical or preclinical studies.

Tier III (VUS): Variants of Unknown Clinical Significance.

Tier IV: Benign or likely benign variants (not included in the report, except for other biomarkers).

Software and content version numbers

NAVIFY® Mutation Profiler Version 2.0.0.7b4557e, Release date: 30/09/2020

NAVIFY® Therapy Matcher Version 2.0.0.7b4557e, Release date: 30/09/2020

Roche content Version 2.29.0, Release date: 18/08/2020

CIViC Version 01-july-2020, Release date: 01/07/2020

ClinVAR Version 20200727, Release date: 27/07/2020

COSMIC Version v91.r1, Release date: 07/04/2020

dbNSFP Version 4.0, Release date: 03/05/2019

gnomAD Version 2.1.1-VnV, Release date: 16/10/2019

TCGA Version 24.0.r2, Release date: 07/05/2020

Mitelman Version 15-apr-2020, Release date: 15/04/2020

References

[PMID19075190] Tyner JW et al (2009 Feb 19) "High-throughput sequencing screen reveals novel, transforming RAS mutations in myeloid leukemia patients." Blood 113(8): 1749-55.

[PMID20171147] Ward PS et al (2010 Mar 16) "The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate." Cancer Cell 17(3): 225-34.

[PMID20331454] Kim K et al (2010 May) "Blockade of the MEK/ERK signalling cascade by AS703026, a novel selective MEK1/2 inhibitor, induces pleiotropic anti-myeloma activity in vitro and in vivo." Br J Haematol 149(4): 537-49.

[PMID21647154] Andersson AK et al (2011 Oct) "IDH1 and IDH2 mutations in pediatric acute leukemia." Leukemia 25(10): 1570-7.

[PMID23071358] Yang H et al (2012 Oct 15) "IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives." Clin Cancer Res 18(20): 5562-71.

[PMID23558173] Wang F et al (2013 May 3) "Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation." Science 340(6132): 622-6.

[PMID23690417] Itzykson R et al (2013 Jul 1) "Prognostic score including gene mutations in chronic myelomonocytic leukemia." J Clin Oncol 31(19): 2428-36.

[PMID23999441] McKenney AS et al (2013 Sep) "Isocitrate dehydrogenase mutations in leukemia." J Clin Invest 123(9): 3672-7.

[PMID24362326] Tan JZ et al (2014 Feb) "EZH2: biology, disease, and structure-based drug discovery." Acta Pharmacol Sin 35(2): 161-74.

[PMID24367611] Wu H et al (2013) "Structure of the catalytic domain of EZH2 reveals conformational plasticity in cofactor and substrate binding sites and explains oncogenic mutations." PLoS One 8(12): e83737.

[PMID24569456] Gritsman K et al (2014 Apr) "Hematopoiesis and RAS-driven myeloid leukemia differentially require PI3K isoform p110α." J Clin Invest 124(4): 1794-809.

[PMID24758538] Meriggi F et al (2014) "The Emerging Role of NRAS Mutations in Colorectal Cancer Patients Selected for Anti-EGFR Therapies." Rev Recent Clin Trials 9(1): 8-12.

[PMID24812670] Kong G et al (2014 Jun) "Combined MEK and JAK inhibition abrogates murine myeloproliferative neoplasm." J Clin Invest 124(6): 2762-73.

[PMID25252692] Burd CE et al (2014 Dec) "Mutation-specific RAS oncogenicity explains NRAS codon 61 selection in melanoma." Cancer Discov 4(12): 1418-29.

[PMID25361812] Burgess MR et al (2014 Dec 18) "Preclinical efficacy of MEK inhibition in Nras-mutant AML." Blood 124(26): 3947-55.

[PMID25495392] Koh J et al (2015 Jun) "IDH2 mutation in gliomas including novel mutation." Neuropathology 35(3): 236-44.

[PMID25878363] Cox AD et al (2015 Apr 15) "Targeting RAS Membrane Association: Back to the Future for Anti-RAS Drug Discovery?" Clin Cancer Res 21(8): 1819-27.

[PMID26343583] Peng SB et al (2015 Sep 14) "Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in RAS or BRAF Mutant Cancers." Cancer Cell 28(3): 384-98.

[PMID26497210] Herviou L et al (2016 Jan 19) "EZH2 in normal hematopoiesis and hematological malignancies." Oncotarget 7(3): 2284-96.

[PMID26815308] Lu S et al (2016 Jun 8) "Ras Conformational Ensembles, Allostery, and Signaling." Chem Rev 116(11): 6607-65.

[PMID26845405] Kim KH et al (2016 Feb) "Targeting EZH2 in cancer." Nat Med 22(2): 128-34.

[PMID27279914] Ma P et al (2016) "Adaptive and Acquired Resistance to EGFR Inhibitors Converge on the MAPK Pathway." Theranostics 6(8): 1232-43.

[PMID27292784] Chen J et al (2016) "The Evolving Landscape in the Development of Isocitrate Dehydrogenase Mutant Inhibitors." Mini Rev Med Chem 16(16): 1344-1358.

[PMID27520294] Konopleva M et al (2016 Oct) "Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia." Cancer Discov 6(10): 1106-1117.

[PMID27573426] Rhyasen GW et al (2016 Nov) "AZD5153: A Novel Bivalent BET Bromodomain Inhibitor Highly Active against Hematologic Malignancies." Mol Cancer Ther 15(11): 2563-2574.

[PMID27621679] Mondesir J et al (2016) "IDH1 and IDH2 mutations as novel therapeutic targets: current perspectives." J Blood Med 7: 171-80.

[PMID27664710] Grill C et al (2016 Oct) "NRAS, NRAS, Which Mutation Is Fairest of Them All?" J Invest Dermatol 136(10): 1936-1938.

[PMID28588019] Amatangelo MD et al (2017 Aug 10) "Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response." Blood 130(6): 732-741.

[PMID28588020] Stein EM et al (2017 Aug 10) "Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia." Blood 130(6): 722-731.

[PMID28597297] Nussinov R et al (2017 Sep) "Intrinsic protein disorder in oncogenic KRAS signaling." Cell Mol Life Sci 74(17): 3245-3261.

[PMID28666118] Simanshu DK et al (2017 Jun 29) "RAS Proteins and Their Regulators in Human Disease." Cell 170(1): 17-33.

[PMID28879540] Kim ES (2017 Oct) "Enasidenib: First Global Approval." Drugs 77(15): 1705-1711.

[PMID28957739] Tafazoli A et al (2018 Mar) "Novel mutations and their genotype-phenotype correlations in patients with Noonan syndrome, using next-generation sequencing." Adv Med Sci 63(1): 87-93.

[PMID29359794] McGraw KL et al (2019 Feb) "Association of EZH2 protein expression by immunohistochemistry in myelodysplasia related neoplasms with mutation status, cytogenetics and clinical outcomes." Br J Haematol 184(3): 450-455.

[PMID30333627] Tyner JW et al (2018 Oct) "Functional genomic landscape of acute myeloid leukaemia." Nature 562(7728): 526-531.

[PMID6092966] Seeburg PH et al (1984 Nov 1-7) "Biological properties of human c-Ha-ras1 genes mutated at codon 12." Nature 312(5989): 71-5.

[PMID8357792] Franken SM et al (1993 Aug 24) "Three-dimensional structures and properties of a transforming and a nontransforming glycine-12 mutant of p21H-ras." Biochemistry 32(33): 8411-20.