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# Menin Inhibitors: A Novel Targeted Agents in Clinical Development

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**Abstract**

Lysine methyltransferase 2A-rearranged (KMT2Ar) gene and the nucleophosmin 1-mutated (NPM1mut) gene are harbored by approximately 10-30% of acute myeloid leukemia (AML) patients. The gene expression profile of NPM1mut AML and KMT2Ar leukemias subset is similar with upregulation of HOX genes (specifically HOXA and their cofactor MEIS1). Menin is a key driver of leukemogenesis as menin is an essential oncogenic cofactor for binding to HOX gene promoters. KMT2A rearrangement and NPM1 mutations leukemia are considered a challenging problem. Current treatment regimens are often associated with limited long-term success and significant toxicity. Menin inhibitors are novel targeted agents in clinical development mainly for the treatment of acute leukemia subsets driven by KMT2A gene rearrangement, and by NPM1 gene mutation.

**Keywords:** Menin inhibitors; Acute myeloid leukemia; Lysine methyltransferase 2A; Nucleophosmin 1; HOXA gene

**Abbreviation:** AML: Acute Myeloid Leukemia; MEIS1: Myeloid Ecotropic Virus Insertion site 1 Genes; MEN1: Multiple Endocrine Neoplasia type 1; KMT2Ar: Lysine Methyltransferase 2A-rearranged; NPM1 mut: Nucleophosmin1-mutated; MLL: Mixed-Lineage Leukemia; MPAL: Mixed-Phenotype Acute Leukemia; ALL: Acute Lymphoblastic Leukemia; WHO: World Health Organization; ELN: European Leukemia Network; NUP98: Nucleoporin 98 gene; BCL-2: B-cell lymphoma 2; FLT3: FMS-like Tyrosine kinase 3; CDK4/6: cyclin-Dependent Kinase Inhibitors

## Introduction

Lysine methyltransferase 2A (KMT2A) gene, previously known as mixed-lineage leukemia (MLL), rearrangement and the nucleophosmin 1 (NPM1) gene mutation cause blood cells to regress or dedifferentiate and behave like the stem cells they arose from. This results in hematopoietic differentiation block and leukemic transformation [1]. KMT2A rearrangements are present in 5–10% of adults and in approximately 20% of children with de novo acute myeloid leukemia (AML) and are associated with a poor prognosis, chemotherapy resistance and higher relapse rates. KMT2A rearrangements are not only restricted to myeloid leukemia, but also occur in acute lymphoblastic leukemia (ALL) and in mixed-phenotype acute leukemia (MPAL). Nucleophosmin 1 (NPM1) is one of the most common gene mutations in AML. It occurs in 25-30% of adult AML patients and in 10% of pediatric AML patients. The NPM1-mutated AML is classified as a distinct entity in the 2022 World Health Organization (WHO 2022) and in European Leukemia Network (ELN 2022) classifications of myeloid neoplasms and is mostly associated with a favorable prognosis [2].

A dependence on menin, a nuclear scaffold protein encoded by multiple endocrine neoplasia type 1 (MEN1) gene located on chromosome 11q13, is known in KMT2Ar leukemias, in NPM1mut AML and in some types of neoplasms [3]. Menin is involved in many biological processes including regulation of hematopoiesis and myeloid proliferation. This protein acts as a link between transcription factors and epigenetic effectors. It is mutated in patients with multiple endocrine neoplasia type 1 (MEN1). Menin has a tumor suppressor function in endocrine glands and controls cell growth directly in endocrine organs. Menin has numerous binding partners, some of which are still unknown. Menin inactivation (lack of enzymatic or DNA binding activity) represents an oncogenic transformation. Menin has oncogenic properties in various tissues [3].

## Role of Menin in KMT2Ar and NPM1mut AML

The KMT2A proto-oncogene is located on chromosome 11q23 and encodes for a transcription factor (KMT2A) which is an important epigenetic regulator involved in hematopoiesis.

KMT2A regulates key genes such as HOXA and HOXB, MEIS1 (myeloid ecotropic virus insertion site 1 genes), PBX3, MEF2C and CDK6. In KMT2Ar leukemia, KTM2A fusion proteins interact with chromatin-associated protein complexes, including menin. Upon binding to menin, KMT2A fusion proteins translocate to the nucleus [2]. Nuclear localization leads to stimulation of aberrant genes transcription critical for hematopoietic cell proliferation and differentiation including homebox (HOX A/B) and MEIS1. Expression of HOX A/B and MEIS1 genes is high in the immature stem cell population and decreases during maturation and differentiation of hematopoiesis. KMT2A is a crucial regulator of HOX genes transcription which affects the proliferation and differentiation of myeloid progenitors and is critical for the pathogenesis of KMT2Ar AML. Menin is a key driver of leukemogenesis, as menin is an essential cofactor for binding to HOX gene promoters [2].

NPM1 is a chaperone protein that shuttles between the nucleus and the cytoplasm. It has multiple biological functions. NPM1wt prevents uncontrolled proliferation, interacts with p53 in the event of oxidative damage and plays an important role in the prevention of mutagenesis (through the regulation of apoptosis and DNA repair). The NPM1-mutated AML has a gene expression profile similar to KMT2Ar leukemia. In NPM1mut AML, KMT2A regulates the oncogenic expression of HOXA, MEIS1 and FLT3, thereby stimulates the proliferation of myeloid progenitor cells. The exact mechanism by which NPM1 induces the overexpression of HOX, MEIS1 and other genes is still less clear [2].

AML particularly the subtypes characterized by genomic instability, such as KMT2A rearrangement and NPM1 mutations are considered a challenging problem. Current treatment regimens, including chemotherapy and targeted therapies, are often associated with significant toxicity and limited long-term success [4]. Menin inhibitors are novel targeted agents in clinical development [1]. They are mainly used for the treatment of acute leukemia subsets driven by KMT2A gene rearrangement, or by NPM1 gene mutation [1]. Other leukemias overexpressing HOX and MEIS1 genes such as leukemias with rearrangement of the nucleoporin 98 gene (NUP98) might respond to menin inhibition [2].

## The Structure and Biological Mechanisms of Menin Inhibitors

Menin inhibitors work differently from other targeted therapies. Instead of blocking the activity of dysfunctional proteins, they stop the genes affected by the altered KMT2A or NPM1 from being expressed in the first place [1]. Menin inhibitors exert their therapeutic effect by preventing the binding of menin protein and KMT2A complex. Thus, menin–KMT2A complex cannot bind to chromatin, leading to switching off the pathway [1]. Menin inhibitors downregulate the key mediators of MLL–menin complex such as HOXA9, MEIS1, PBX3, or CDK6. They also reduce the anti-apoptotic signaling molecules like B-cell lymphoma 2 (BCL-2) or fms-like tyrosine kinase 3 (FLT3) and promote the differentiation of leukemic immature cells in vitro and in vivo [2]. Preclinical studies in mouse models showed that menin inhibitors lead to KMT2Ar or NPM1mut leukemia regression by reversing aberrant gene expression mediated by HOX genes and their cofactor MEIS1 [1]. The cells that had acted like haywire stem cells either turn back into normal cells or die [1].

The first generation of the small molecule inhibitors of menin-MLL1 interactions includes M-525, M-808, M-89, and M-1121 that target HOXA9 and MEIS1.They were a series of hydroxymethyl and aminomethyl piperidine compounds that were tested against various malignancies. These compounds displayed strong inhibitory activity, and poor metabolic stability which limits their use in in vivo pharmacodynamics research [1]. The second generation of menin inhibitors include compounds such as MI-2, MI-3, MI-136, MI-538, MI-463, MI-503, and MI-1481, which target HOXA9 and MEIS1, VTP-50469 which target MEIS1 and FLT3, BAY-155 which target MEIS1, KO-539 targeting MEIS1, FLT3, and PBX3, and MI- 3454 targeting HOXA9, MEIS1, and FLT3. They are a new type of small molecule inhibitor, corresponding to thiophenpyrimidine inhibitors. They have good oral bioavailability and strong target binding activity. These menin inhibitors display good biological activity with no hematopoietic function damage, or obvious tissue and organ toxicity in mice [1]. Thiophenpyrimidine inhibitors were also effective in inhibiting the proliferation of solid tumors, including prostate cancer, breast cancer, lung cancer, liver cancer, and osteosarcoma. However, the molecular mechanism of inhibiting solid tumor cells proliferation by these menin/MLL1 small molecules is not clear. It has been speculated that they have a synergistic effect with cancer chemotherapy drugs and may participate in the signaling pathway of chemotherapy drugs to inhibit tumors. This speculation needs to be further proven [5].

Macrocyclic peptide-like inhibitors were obtained via different method. They include MCP-1, which targets HOXA9 and MEIS1. Menin-KMT2A inhibitors such as SNDX-5613 (revumenib), KO-539 (ziftomenib), DSP-5336, DS-1594, BN104, BMF-219, and JNJ-75276617, developed subsequently and were introduced in the first clinical trials on acute leukemias in 2020. These inhibitors have reduced molecular weight and are based directly on the menin-KMT2A interaction. The first clinical trials with revumenib and ziftomenib demonstrated encouraging efficacy with approximately 30% response rates in patients with NPM1mut. In patients with KMT2Ar-driven leukemias, revumenib and ziftomenib showed response rates of 27% and 5.6% respectively. The safety profile of menin inhibitors appears easily manageable [1].

## Monitoring Response to Menin Inhibitors

The potential biomarker for monitoring the response to menin inhibitors is the evaluation of HOX (A and/or B) gene expression


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together with levels of its cofactor, MEIS1 [3].

### Main Adverse Events of Menin Inhibitors

The most common adverse events of menin inhibitors in phase 1 of AUGMENT-101 trial, included QT prolongation (56%, any grade), nausea (50%), vomiting (40%), and febrile neutropenia (31%). The most frequent grade 3 or higher emergent adverse events of revumenib treatment were febrile neutropenia (31%), thrombocytopenia (19%), and sepsis (18%). Asymptomatic prolongation of the QT interval was also identified [1]. Differentiation syndrome is a notable treatment-related adverse event in phase 1 trials of menin inhibitors. It occurred in 57.5% of ziftomenib recipients and in 16% of revumenib recipients with 30% of grade 3 or higher. Differentiation syndrome arose at a median time of 18 days (5-41 days). It is caused by cytokine alterations associated with hematopoietic differentiation and can include fever, arthralgias, leukocytosis, pleural or pericardial effusions, and respiratory or renal failure in severe cases. Detection of differentiation syndrome justifies the evidence of a successful reversal of the differentiation block caused by KMT2Ar through menin inhibition. In phase 1 trial with revumenib, all cases with differentiation syndrome resolved following steroids treatment. Hydroxyurea was added in presence of leukocytosis [1].

### Menin Inhibitor Resistance

Recently, acquired resistance, was observed in patient-derived blasts under revumenib treatment due to a rapid acquisition of somatic mutations within the menin gene (MEN1-mutations). A possible molecular mechanism to overcome menin inhibitor resistance is the combination of menin inhibitors with cyclin-dependent kinase inhibitors (CDK4/6). Pre-clinical data provide evidence for potential strategies to improve efficacy and avoid the early onset of resistance mutations by combining menin inhibitors with BCL-2 inhibitor venetoclax as well as with BET or CBP/p300 inhibitors [2].

## Conclusion

Still there are many questions remains to be answered on the use of menin inhibitors in acute myeloid leukemia and how to incorporate them in a global therapeutic strategy. Should they be used as single agents or in combination with other lines of therapies, or as part of large combinations or successions of treatments?.

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