# Evolving Frontiers in Targeted Therapy: Menin inhibition in AML

**Eytan M. Stein**
*Memorial Sloan Kettering Cancer Center, USA*

The pathogenesis of both lysine methyltransferase 2A–rearranged (KMT2Ar) and nucleophosmin-mutant (NPM1m) leukemias depends on upregulation of HOX genes, mediated in part by the interaction of the scaffolding protein menin with the KMT2A complex. NPM1 mutations occur in approximately 30% of patients with newly diagnosed acute myeloid leukemia (AML). KMT2Ar occurs in both acute myeloid and acute lymphoid leukemias and is overrepresented in therapy-related AML. Overall, KMT2Ar leukemias account for approximately 5%–9% of all acute leukemia diagnoses.

Menin inhibitors disrupt the interaction between menin and KMT2A, leading to downregulation of HOX gene expression. In preclinical in-vitro and in-vivo models, this restores normal myeloid differentiation. Clinically, two menin inhibitors have been approved by the U.S. Food and Drug Administration for relapsed/refractory (R/R) disease in the United States: revumenib for KMT2Ar and NPM1-mutant acute leukemia, and ziftomenib for NPM1m acute leukemias. Additional menin inhibitors, including bleximenib, enzomenib, and BN104, are also being evaluated in clinical trials for R/R acute leukemia with KMT2Ar and NPM1m.

Overall response rates (ORRs) with single-agent menin inhibitors in R/R AML range from 40% to 65%, whereas rates of complete remission/complete remission with partial hematologic recovery (CR/CRh) are more modest, at 20%–40%, depending on the agent studied. In addition, the duration of CR/CRh is relatively short, with a mean duration of 4–6 months. One explanation for this limited durability is the rapid emergence of resistance mutations in menin that impair inhibitor binding. In one study of revumenib, 38.7% of patients developed a menin resistance mutation while receiving therapy. This finding underscores both the central role of menin in the pathogenesis of these leukemias and the need to develop next-generation inhibitors that can overcome acquired resistance. Similarly, combining menin inhibitors with standard-of-care therapies, such as azacitidine/venetoclax or intensive chemotherapy, particularly in newly diagnosed KMT2Ar and NPM1m AML, may help mitigate the resistance observed with single-agent therapy.

The major toxicity associated with menin inhibitors, as with other differentiation agents used in acute leukemia, is differentiation syndrome (DS). Like other capillary leak syndromes, DS can develop rapidly and lead to respiratory failure and death if not recognized and treated promptly. A distinctive feature of menin inhibitor–associated DS is that, unlike DS induced by all-trans retinoic acid (ATRA), arsenic, or IDH inhibitors, corticosteroids are sometimes ineffective. This highlights the need to better understand the pathogenesis of menin inhibitor–associated DS, identify patients at highest risk for life-threatening complications, and develop more effective therapies to blunt the cytokine storm that drives this condition.