# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## The Development of Menin Inhibitors in AML and ALL

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**H&O** What are menin inhibitors, and how do they function in the context of acute myeloid leukemia/acute lymphoblastic leukemia?

**GI** Menin inhibitors are a new form of targeted therapy in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) that specifically targets epigenetic modifiers.[1] Menin is an important cofactor for certain transcription factors and processes that play a key role in regulating gene transcription. Menin inhibitors work to reprogram leukemia cells back to a normal state by shutting down the gene expression programs responsible for causing leukemia. In this case, the *HOXA9* and *MEIS1* genes are dependent on the interaction between menin and the protein KMT2A.

**H&O** In what ways do menin inhibitors differ from other targeted therapies and the current standard of care used in AML/ALL?

**GI** Menin inhibitors, much like other targeted therapies, are designed for specific genotypes of acute leukemia, particularly those dependent on the interaction between menin and KMT2A for leukemia development.[2] The best-studied genotypes include *KMT2A*-rearranged leukemias and *NPM1*-mutant AML, which is the most common mutation in AML. This parallels the mechanism of action seen with IDH inhibitors, which target *IDH*-mutant AML. Menin inhibitors differ from other targeted therapies in that they mostly target epigenetic modifiers. Epigenetic therapy has been studied for a long time, and the most known are hypomethylating agents in myelodysplastic syndromes, although their main mechanism of action is cell killing. IDH inhibitors are epigenetic modifiers, and menin inhibitors are the first great example of a therapeutic intervention working by affecting transcription.

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The current standard of care for AML and ALL is chemotherapy, which operates by inducing cell death in rapidly dividing cells. Menin inhibitors represent a promising new advancement in therapeutic approaches by specifically targeting and addressing underlying genetic abnormalities rather than focusing on rapidly dividing cells.

**H&O** How does genotype testing play a role, and what specific proteins do menin inhibitors target?

**GI** Menin inhibition disrupts the binding of the protein menin to the protein KMT2A. Transcription of genes that cause leukemia in these genotypes depends on this interaction, and by disrupting the menin and KMT2A interaction, menin inhibition shuts down this transcription. This has been well-studied in *KMT2A*-rearranged leukemias, previously known as *MLL1*-rearranged leukemias. These are aggressive leukemias that occur in infants, children, and adults and are resistant to therapy. They can also occur in *NPM1*-mutant leukemia, which is the most common acute leukemia.

However, we are also learning that various other genetic alterations in acute leukemia could also depend on menin. For example, good preclinical data have shown that patients with NUP98 rearrangements, another fusion frequently associated with resistance, can respond to menin inhibition.[1] We are about to study a variety of other rare fusions soon to determine whether they could also respond to menin inhibition.

**H&O** Could you please highlight the data from trials on menin inhibitors?

**GI** There are multiple oral menin inhibitors at various stages of clinical development. Some are still in phase 1 as monotherapy, whereas others have already entered combination studies. The published results we have are from the menin inhibitor revumenib, previously called SNDX5613.

Findings from the phase 1 study, which were published in *Nature* last year, showed an overall response rate (ORR) of approximately 60% and complete remission with partial hematologic recovery (CRh) of 30% in patients with *NPM1*- or *KMT2A*-rearranged leukemias.[3]

Since then, the phase 2 study of revumenib, which is a pivotal study intended for regulatory approval in *KMT2A*-rearranged leukemia, has been completed and successfully met its primary endpoint of efficacy.[4] These results, presented at the 2023 American Society of Hematology (ASH) Annual Meeting & Exposition by my colleague, Dr Ibrahim Aldoss, led to a similar response rate as what we saw in the phase 1 trial: an overall response rate of 63.2%, and a CR/CRh rate of 22.8%. Those results were submitted to the US Food and Drug Administration (FDA) last December for regulatory approval.

The other menin inhibitor that is further along in development is ziftomenib, previously known as KO539. Phase 1 study results with this agent, which were presented at the European Hematology Association (EHA) and ASH annual meetings, show a response as a single agent mostly in *NPM1*-mutant acute leukemias with a CR/CRh rate of 35%, with a lower response rate in *KMT2A*-rearranged leukemias.[5]

Research on the Johnson & Johnson menin inhibitor JNJ-75276617 monotherapy that was presented at the 2023 ASH annual meeting showed an ORR of 50% in the patients who met the recommended phase 2 dose definition and were evaluable for that analysis, and a CR/CRh rate of 25%.[6]

Results with combination therapy have not yet been published. I am leading the SAVE study (NCT05360160), which is looking at the combination of the SNDX-5613 menin inhibitor plus decitabine/cedazuridine (ASTX727) and venetoclax. In results were presented at the 2023 ASH annual meeting on 9 patients in this study, all patients responded to treatment, with a CR/CRh rate of roughly 50%.[7]

**H&O** What were the side effects, and how were they managed?

**GI** Common side effects are shared across various menin inhibitors, with a notable one being differentiation syndrome. The frequency of that side effect ranges from 1% to 20%, depending on the specific menin inhibitor. Differentiation syndrome is an adverse event (AE) associated with targeted therapy that leads to differentiation, akin to what is observed with all-trans retinoic acid or arsenic for acute promyelocytic leukemia, or IDH inhibitors for *IDH*-mutant leukemia. In severe cases, it can lead to a cytokine storm that affects the lungs and kidneys and causes an increase in the white cell count; this can be managed with corticosteroids. In the case of revumenib, differentiation syndrome in the phase 1 study was effectively managed by all patients through the administration of corticosteroids. Regarding ziftomenib and the JNJ-75276617 menin inhibitor, results have not been published yet, but based on available data from the phase 1 studies, differentiation syndrome appears manageable after adjusting the dose.

Another side effect related to revumenib is QT prolongation, which was asymptomatic. Other possible side effects of menin inhibitors can be low blood counts, such as neutropenia or thrombocytopenia, but the frequency and degree of these events has not been fully characterized. Otherwise, these treatments seem to be well tolerated.

**H&O** What observations suggest that menin inhibitors might be an effective treatment?

**GI** Menin inhibitors have demonstrated effectiveness based on standard response assessments of acute leukemia.

Patients participating in the study were examined by morphology, including a bone marrow biopsy before and after treatment, revealing remission with count recovery. This is evidence of an effective therapy. Moreover, in-depth analyses, such as measurable residual disease (MRD) testing by flow cytometry, indicate that a good number of patients treated on revumenib achieved MRD-negative remission.

More importantly, these responses have allowed patients to get a stem cell transplant despite being highly refractory, and a good number of patients are in remission after treatment. Although resistance may occur in some patients treated with monotherapy, ongoing efforts are focused on developing strategies to overcome this resistance. It is anticipated that the likelihood of resistance will be diminished when patients receive treatment in earlier rounds, underscoring the potential effectiveness of menin inhibitors in acute leukemia therapy.

**H&O** Is there any distinction in outcomes based on whether a patient has AML or ALL?

**GI** The current dataset is too small, making it challenging to draw definitive conclusions. So far, the response rate seems to be similar, irrespective of whether the patient has AML or ALL. Specifically, when considering *KMT2A*-rearranged leukemia in either AML or ALL treated with menin inhibition, the most robust data available are on revumenib. Thus far, there is no discernible difference in treatment responses between the 2 leukemia types.

**H&O** What is next for menin inhibitors?

**GI** There are several exciting developments on the horizon. I expect menin inhibitors to be established as standard therapies, in large part based on the promising revumenib data. Other menin inhibitors are in the pipeline, such as ziftomenib and the J&J menin inhibitors, and are either seeking approval or expected to apply for approval in the near future.

The next phase involves exploring combinations, particularly with rational targeted therapies. We have already started on some of these combinations, such as the one with venetoclax in the SAVE study. There could also be future combinations with FLT3 inhibitors, IDH inhibitors, or even standard chemotherapy. The ultimate goal is to progress toward incorporating menin inhibitors into frontline therapies or as part of maintenance strategies to increase the chances of cure.

***Disclosures***

*Dr Issa no disclosures.*

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