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Menin Inhibitors: Biologic and Clinical Rationale

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Dr. Fathi:
This is CME on ReachMD, and I'm Dr. Amir Fathi. Today I'll provide a brief overview of the rationale for targeting menin and menin inhibitors in clinical development.

KMT2A, formerly known as MLL, is a histone methyl transferase and contributes to promoter activation by catalyzing H3K4, thereby supporting transcriptional activation. Menin, an adaptor protein, binds to the N-terminal portion of KMT2A, and in this fashion, interacts with it and modulates its chromatin interactions. KMT2A is affected by chromosomal translocations, leading to the formation of oncogenic fusion proteins in the KMT2A-rearranged leukemias, including AML and ALL.

Much of this work has been developed by Drs. Scott Armstrong and Florian Perner, showing that chromosomal translocations involving 11q23 locus produce oncogenes with various partners. The consequences are oncogenic proteins that have lost H3K4 methyltransferase activity but are able to associate with KMT2A target genes and recruit multiple chromatin-associated protein complexes that drive aberrant gene expression. And there are over 100 KMT2A fusion partners, which have been identified. The average activation of KMT2A target genes, part of a stem cell program, is driven by KMT2A fusion oncogenes are activated by wild-type KMT2A complexes, as demonstrated specifically in NPM1-mutated leukemias. NPM1 acts as a cofactor of the transcriptional activation of leukemogenic genes in these settings. KMT2A rearrangements occur in about 10% of AMLs and all acute leukemias, including AMLs and ALL, while NPM1 mutations occur in about 1/3 of patients with AML.

Menin inhibitors have been developed to disrupt the complex nononcogenic KMT2A complex by interfering with the interaction of KMT2A and menin, particularly as a complex on chromatin, including in AMLs that are driven by NPM1 mutations and KMT2A rearrangements. NPM1 mutations and KMT2A rearrangements drive overexpression of HOXA9 and MEIS1 genes, which is critical for transformation to AML. KMT2A-dependent genes also contribute to therapeutic resistance and relapse to cytotoxic therapies. Menin inhibition downregulates HOXA9 and MEIS1, leading to differentiation of leukemic blasts and, ultimately, a therapeutic.

Soon after the conduct of the clinical trial studying menin inhibitors, there was increasing understanding of menin resistance mutations that we have explained some of the critical resistance that was being seen in clinical trials and in patients who are developing progression or disease relapse. In the revumenib study, for example, mutations in MEN1 were seen in 38.7% of patients who had experienced disease progression or relapse. So it's a sizable minority of patients.

These MEN1 resistance alterations were looked at among samples treated with various menin inhibitors. And it's interesting, there are several different types of MEN1 resistance alterations, and each of them confer different degrees of resistance to the various menin inhibitors that have been studied in clinical trials. For example, as can be seen in this slide, ziftomenib shows a decreased efficacy in patients who have M327I alterations, but it seems to have preserved efficacy in patients, for example, with another MEN1 resistance mutation, T349M. Whereas revumenib seems to have decreased efficacy across the mutations that are seen here. Of note, the most common form of MEN1 resistance that has been seen seems to confer resistance across these menin inhibitors.

In the ziftomenib study, among the several patients that developed resistance, 29 subjects, this was presented at EHA in 2023, only one was identified with a specific MEN1 resistance, M327I, alteration. So that would suggest that there are probably other mechanisms of resistance that need to be developed and studied that may not be dependent on MEN1 resistance mutation.

Well, my time is up. I hope you found this overview useful, and I thank you so much for your attention.

Announcer:
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