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https://reachmd.com/programs/cme/emerging-directions-in-menin-directed-aml-therapy/36184/

Released: 07/25/2025
Valid until: 07/25/2026
Time needed to complete: 1h 00m

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Emerging Directions in Menin-Directed AML Therapy

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Dr. Fathi:
This is CME on ReachMD, and I'm Dr. Amir Fathi.

Dr. Issa:
And I'm Dr. Ghayas Issa.

Dr. Fathi:
Dr. Issa, can you discuss some of the combination strategies involving menin inhibitors in relapsed or refractory AML?

Dr. Issa:
Yes. So there's emerging data showing excellent synergy combining the menin inhibitors with BCL2 inhibition, or the BCL2 inhibitor, venetoclax, and a hypomethylating agent. And these are multiple trials that have been presented either this past meeting at EHA, or the last ASH meeting. These include either the all-oral combination that we call SAVE. This would be oral decitabine plus venetoclax plus the menin inhibitor, revumenib. Or in the case of ziftomenib, the combination of azacitidine and venetoclax, or the menin-inhibitor bleximenib, that also is combining the azacitidine and venetoclax.

And what we are seeing across these studies is high rates of response, especially in NPM1-mutant acute myeloid leukemia, and an improvement of the response rate over single agent menin inhibitors.We hope this will translate to deeper remissions and less grade of resistance, so longer duration of response. But the data is not mature yet to tell if we're headed in that way. Certainly, it looks very encouraging.

Dr. Fathi, can you discuss the clinical studies investigating menin inhibitors in newly diagnosed AML?

Dr. Fathi:
Sure. As Dr. Issa mentioned, there are efforts across the spectrum of the number of menin inhibitors to combine them with standard therapies, whether it is with hypomethylating agents and venetoclax in the relapsed/refractory setting, or even in the upfront setting in older patients, or combining them with intensive chemotherapy in induction-eligible patients. At recent meetings, the presentations have also focused on upfront patients. The BEAT AML trial that included the menin inhibitor, revumenib, in combination with the venetoclax and azacitidine was reported. The combination was promising with an impressive response rate. I think it is oftentimes challenging to

combine drugs with venetoclax and azacitidine, especially in older patients, because the combination can be marrow suppressive. So I think over time, we will have to determine how to more effectively do these combinations, whether they are with menin inhibitors, with FLT3 inhibitors, with other targeted agents to maximize or optimize tolerability.

The KOMET-007 trial, which incorporates both the combination of the menin inhibitor, ziftomenib, with venetoclax and HMA, but also intensive chemotherapy, was also presented in part at the recent EHA meeting. And particularly, with the focus of the combination of ziftomenib with induction chemotherapy. The composite remission rates in both NPM1 and KMT2A were remarkably high.

Of course, these are single-arm studies. Ultimately, larger randomized studies that are planned will need to let us know if this is better than the current standard of care.

Other menin inhibitors are also being combined, including the menin inhibitor, bleximenib, with venetoclax and azacitidine. And I think many of these are now moving on to upfront combination. So it's a very exciting time for frontline trials.

Dr. Issa, I do not know if you have any additional thoughts or commentary on these combination studies.

Dr. Issa:
So what I would add is that the next wave of combinations will include probably FLT3 inhibitors. There are multiple trials that have launched, and we haven't seen the results yet, but this would be a very promising, at least preclinically, combination with their synergy between FLT3 inhibition and menin inhibition. And because of how encouraging those results are looking in combination with azacitidine and venetoclax, or high-intensity chemotherapy, there are multiple randomized phase 3 studies that are about to launch, and testing the addition of a menin inhibitor. And hopefully, that would lead to changing the standard of care where menin inhibitors become part of the frontline treatment of acute myeloid leukemia.

Dr. Fathi:
I agree. I think it's a very exciting time for AML. We have a lot of trials coming up that are going to be engaging and accrual across the globe: United States, Europe, Asia. And hopefully, in time, we'll help a lot of our patients who have these targeted alterations.

Well, that's all the time we have today. Thank you for our great discussion, Dr. Issa, and thanks to the audience for listening.

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