

Menin Inhibitors in Acute Myeloid Leukemia: An Overview of “Encouraging” Early Data



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Following a panel discussion of menin inhibitors and other topics at a recent *Around the Practice*® program, moderator Naval G. Daver, MD, spoke with CancerNetwork® about how these new agents may affect the standard of care and improve outcomes for patients with acute myeloid leukemia (AML).

Daver, an associate professor in the Department of Leukemia, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston, also highlighted other standard and emerging treatment options for AML, including CD47-targeting antibodies and CD123-targeting antibody-drug conjugates (ADCs). He also emphasized the critical importance of multidisciplinary care in the AML space.

Q: Are there any therapy options on the horizon that might affect the standard of care in newly diagnosed AML?

DAVER: There are [some promising] emerging treatment options and ongoing clinical trials [in this disease space], including menin inhibitors, which seem to have a very good chance of being approved and used initially in the relapsed/refractory setting and then combined up front with either hypomethylating agents [HMAs] plus venetoclax [Venclexta] or intensive chemotherapy, or in the salvage [setting] with FLT3 inhibitors. The second group of drugs we’re hoping to see [emerge soon], and for which there are multiple ongoing phase 3 trials, are

CD47-targeting antibodies. These are showing efficacy, especially in the frontline setting, including TP53-mutated AML and other high-risk subsets of both myelodysplastic syndromes [MDS] and AML. Based on a lot of work we’ve done at [The University of Texas] MD Anderson Cancer Center, leading these efforts in both MDS and AML, we believe these could be very important additions to the treatment armamentarium for newly diagnosed, high-risk MDS and newly diagnosed AML—potentially both TP53-mutant and wild-type disease.

Thirdly, there’s a group of CD123-targeting [ADCs] led by IMG632, also called pivekimab sunirine, that are quite exciting, both in the blastic plasmacytoid dendritic cell neoplasm space and in the frontline AML space combined with HMAs. These are the 3 agents that, in the next 1 to 2 years, may have a direct treatment impact.

Q: Which unmet need in this disease space is most pressing? Which do you hope to see overcome soon?

DAVER: The biggest unmet need right now is frontline, TP53-mutated AML. When we say TP53-mutant, that includes patients with chromosome 17 abnormalities and complex cytogenetics, [in addition to those with] a TP53 mutation itself. These patients tend to experience very poor responses to available therapies, including HMAs alone,

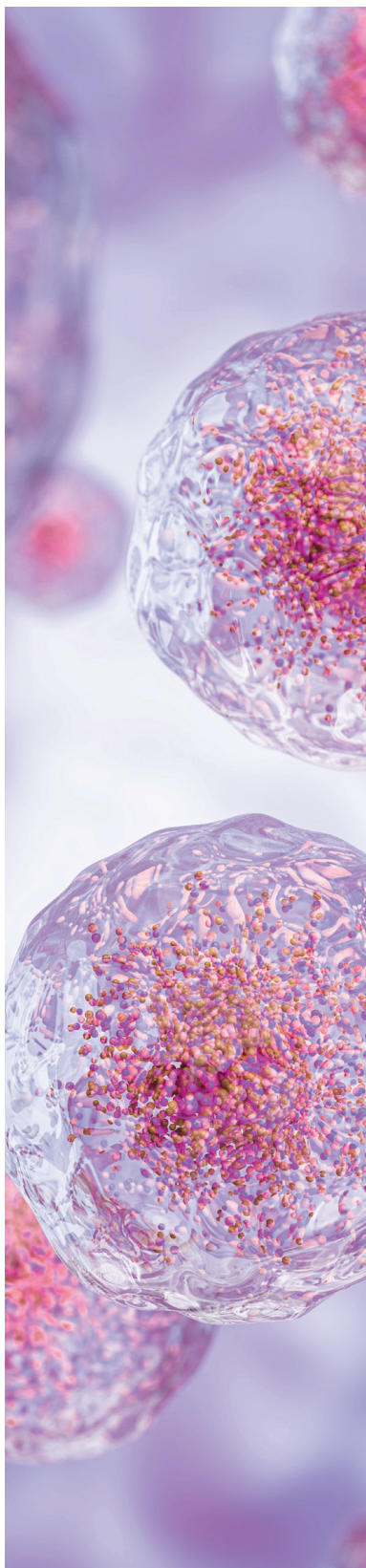
HMA plus venetoclax, and intensive chemotherapy. Even an approach that works well for almost every group—fludarabine, high-dose cytosine arabinoside, idarubicin, and granulocyte colony-stimulating factor [FLAG-Ida] plus venetoclax—[does not work well in] these *TP53*-mutant cases with chromosome 17 alterations. There's a lot of ongoing effort with CD47-targeting antibodies, such as magrolimab and others, as well as other immunotherapies, to improve outcomes in these patients.

The other big unmet need [involves] the other adverse cytogenetic molecular groups, including *MLL*-rearranged disease in the relapsed and frontline settings. This is where the menin inhibitors show encouraging activity. We could maybe use them up front in combination to improve survival in this group of patients with traditionally high-risk, *MLL*-rearranged disease. These are the 2 biggest unmet needs, and we may see at least some progress [on these challenges soon], which we're looking forward to.

Q: Can you speak to the importance of multidisciplinary care?

DAVER: In the management of AML, it's critical to have a team effort. We work very closely with our hematopathologist, our molecular and phylogenetic labs, our clinical case manager, and our social worker. When we see a new patient with AML, we often need to provide them assistance not only with treatment of the disease but also with housing, logistics, and finances. We also need support from our molecular team to get the molecular information very quickly, which helps us identify the optimal frontline targeted or immune therapy.

More than most other diseases and most other malignancies, in AML, it's critical to have a multidisciplinary support team integrating molecular [testing], hematopathology, cytogenetics, leukemia-treating teams, stem cell transplant [teams], social workers, case managers, nurses, pharmaceutical doctors, and advanced



practice providers.

It really does take a village to deliver the most optimal, effective, and curative treatment for patients with newly diagnosed, acute AML.

Q: What were the major takeaways from your discussion with your colleagues?

DAVER: The biggest takeaway is that we now have a new targeted therapy to add to [our armamentarium] in AML, beyond the established FLT3, IDH1, and IDH2 inhibitors. [The armamentarium] now includes the menin inhibitors that target *NPM1*-mutant, *MLL*-rearranged disease. The data [regarding the use of these inhibitors as] single agents in multiple-relapsed/refractory disease are very encouraging. Patients in the third and fourth salvage [setting]—patients whom we would historically send to transplant because we had no good options—are showing response rates of 35% to 40%, which is great.¹ To add to that, we now believe using these drugs up front in combination with standard intensive chemotherapy, such as FLAG-Ida, [anthracycline plus cytarabine] therapy, or lower-intensity therapies like HMA plus venetoclax, could improve curative outcomes and survival among patients with this high-risk disease, especially *MLL*-altered disease.

We're also hoping to see, with the CD47-targeting antibodies in *TP53*-mutant disease and other immunotherapies like natural killer cell therapy and chimeric antigen receptor [CAR] T-cell therapy, further additions to the immunotherapy armamentarium for the treatment of AML.

There are many exciting things to come over the next 1 to 2 years in this treatment landscape. ■

Reference

1. Fathi A, Wang E, Issa G, et al. Activity, tolerability, and resistance profile of the menin inhibitor ziftomenib in adults with relapsed/refractory *NPM1*-mutated AML. Presented at: European Hematology Association 2023 Hybrid Congress; June 8-11, 2023; Frankfurt, Germany. Abstract LB2713.