When considering venetoclax plus azacitidine or decitabine, does a patient's mutational status matter?

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Hi, welcome to *Managing AML*. I'm Dr. Brian Jonas. I'm frequently asked, "When considering venetoclax plus azacitidine or decitabine as a treatment option, does a patient's mutational status matter?" I think this is another great question and I think you end up with different opinions depending perhaps on who you ask.

What I would point out for now is that right now the mutation status doesn't matter. Azacitidine-venetoclax or decitabine-venetoclax based on the Phase Ib trial that looked at both combinations, as well as the VIALE-A trial which looked at the AZA-venetoclax combination, these were active across the board. Whether patients had intermediate- or poor-risk cytogenetics, whether there was de novo or secondary AML, or whether the patients had IDH1, IDH2 mutations, NPM1 mutations, FLT3 mutations, TP53 mutations, there was a considerable activity of these combinations across the board. These combinations are approved by the FDA for the patients 75 or older or those less than 75 who have significant comorbidities that prevent their eligibility for induction in chemotherapy. Encountering one of those patients, the mutation status right now would not matter to me, and I would recommend using one of these combinations for them.

Now that being said, there are some interesting new HMA combinations that are being explored, including with IDH inhibitors, with FLT3 inhibitors. There's a number of other new molecules like CD-47 antibody, TIM3 antibody, NEDD8-activating enzyme inhibitors, and p53-stabilizing drugs. There's a number of other combinations that are being explored in clinical trials that are evaluating some of the mutational and/or disease subsets of AML and I think they're showing promise in combination. Now, whether or not they would be able to be superior head-to-head with AZA-venetoclax, of course, would require randomized clinical trials comparing these combinations. It's difficult for me to say right now whether one of those combinations might be more likely to work or be better used in these patients.

There is some possibility of decreased toxicity with some of the combinations. AZA-venetoclax, decitabine-venetoclax is difficult on the blood counts and does take some practice to manage those appropriately. Whether or not these combinations might be easier to tolerate, certainly could be seen with some of these new trials.

Then the other thing I would like to point out is the evaluation of so-called triplet therapies, which are these venetoclax-AZA or venetoclax-decitabine combinations with the addition of another drug. I think these are going to be explored on many of these mutational subsets like p53, FLT3, or IDH1/2. That will be, I think, the next generation of clinical trials that then, I think you might have more relevance of the individual mutation pattern of the patient because it might have you lean towards one triplet or a different triplet.

Again, overall, I think right now, regardless of mutation status, I typically recommend AZA-venetoclax or decitabine-venetoclax for my patients who are 75 or older or less than 75 who have significant comorbidities that prevent them being eligible for standard induction.