Molecular Mechanisms Mediating Relapse Following Ivosidenib Monotherapy in Patients with IDH1 Mutant Relapsed and Refractory Acute Myeloid Leukemia

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Welcome to *Managing AML*. I'm Dr. Eytan Stein, and I'm live at the 61st ASH conference in Orlando, Florida. Today I will be reviewing Abstract 545 which is the data recently reported on *Molecular Mechanisms Mediating Relapse Following Ivosidenib Monotherapy in Patients with IDH1 Mutant Relapsed and Refractory Acute Myeloid Leukemia*. The background for this important study is that we know that in patients with relapsed and refractory IDH1-mutant acute myeloid leukemia, the IDH1 inhibitor, ivosidenib, leads to a rate of complete remission and complete remission with partial hematologic recovery of just about 30%. Of those 30% of patients, the vast majority of them will end up relapsing at some point during their treatment course, usually after six months or more of being in remission. And it's very important for us to understand, well why do these patients relapse? Because if we understand why these patients relapse, we can then go and try to come up with therapies, either to prevent the relapse or to treat them when they do relapse. What the investigators and Agios Pharmaceuticals did on this study was look at all of the patients at the time of diagnosis, look at the molecular mutations they had at the time of diagnosis, and then look at those same mutations and any new mutations which might have emerged at the time of the patients' relapse. And the upshot of the study is that there are really three mechanisms of relapse that predominate in patients who achieved the remission, and then subsequently went on to lose that remission, and these are what they are. The first is that there are patients who develop a second mutation in IDH1 at the binding site of ivosidenib, which is the drug that causes the disease to go away, and by having that second site mutation, what happens is that the drug is unable to bind into its binding site, and therefore the drug doesn't work anymore. So that's one mechanism of relapse. Second mechanism of relapse is that patients will develop new mutations or the expansion of pre-existing mutations and what are called receptor tyrosine kinase genes. These are mutations in genes such as FLT3 and RAS where those mutant clones grow out and cause the relapse of the disease. And what's interesting about this is that the emergence of RAS mutations has not only been seen in patients who relapse while on IDH inhibitors, but we've also seen it in patients who relapse while on FLT3 inhibitors. And finally, the third mechanism of relapse is that patients who have IDH1 mutations will actually relapse with an IDH2 mutation. So, for some reason, this cell that is IDH1 mutant loves mutant IDH and when it can't get enough mutant IDH1, it develops mutations in IDH2, and this has important implications for therapy. If you think about the three mechanisms which I've just told you about, second-site mutations, IDH2 mutations, and receptor tyrosine kinase mutations, you can start to

think about ways to target this. For example, in a patient who has relapsed and refractory IDH1-mutant AML who has received ivosidenib, went into remission then relapsed, if they relapse with the FLT3 mutation, there are clinical trials that are starting which are combining FLT3 inhibitors with IDH1 inhibitors. If a patient relapses with an IDH2 mutation, you can think about giving them now the IDH2 mutation inhibitor or one could even think about doing a clinical trial of combining an IDH1 and IDH2 inhibitor, although, of course, that's not ready yet for a standard clinical practice outside of a clinical trial. I think the hardest thing to deal with is going to be the second-site mutations because when you have a mutation in the binding pocket of the IDH1 protein, that's going to take some development of a new drug that can overcome that inability for ivosidenib to bind. I think this is, as I said before, an extremely important abstract. I think it's important for community practitioners to know that if you have a patient on ivosidenib and you see that patient is relapsing, at the time the patient relapses, it's crucial to send that bone marrow sample that is showing the relapse for next-generation sequencing again, for getting a panel to show you what is the mechanism of relapse because that will influence further therapy.

Reference: Choe S, et al. Molecular Mechanisms Mediating Relapse Following Ivosidenib Monotherapy in Patients with IDH1-Mutant Relapsed or Refractory Acute Myeloid Leukemia. Abstract 545. ASH 2019.
https://ash.confex.com/ash/2019/webprogram/Paper122671.html

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Rates Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia with an IDH2 Mutation

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Rates Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia with an IDH2 Mutation. These are interim phase 2 results from an ongoing randomized study. The background to this study is we know that enasidenib in patients with IDH2 mutations and relapsed/refractory AML leads to a rate of complete remission of just about 20% and a duration of remission that approaches six months. The question has always been what happens if you combine enasidenib with the hypomethylating agent azacitidine, which in older patients with acute myeloid leukemia might be a standard of care. What this trial aimed to do was really answer the question or try to answer the question, if you combine enasidenib with azacitidine in patients with an IDH2 mutation with newly diagnosed acute myeloid leukemia, is that better than getting azacitidine alone? This was an open-label phase 2 randomized study where patients were randomized in a 2:1 fashion to receive enasidenib plus azacitidine or to receive azacitidine alone. Patients were followed to look at their complete remission rates, to look at the overall response rates, and also to look at event-free survival and look at overall

survival. What's very interesting is that the overall response rates. and the complete remission rates were significantly higher in patients who received the combination of enasidenib and azacitidine over azacitidine alone. So, the overall response rate in the combination arm was 68% versus 42% in those patients who just received azacitidine, while the complete remission rates were 50% in patients who received the combination, and only 12% in the patients who received azacitidine alone. The median duration of response was not reached with enasidenib and azacitidine, and was 10.2 months in the azacitidine only arm. An important point to be made is that the event-free survival in those patients who received azacitidine and enasidenib was longer than the event-free survival in those patients who received azacitidine alone; however, the overall survival was statistically equivalent. And we think the reason that the overall survival might be statistically equivalent, while the event-free survival favored the enasidenib and the azacitidine arm, is that the patients who got azacitidine alone and didn't respond, when they came off study because it was open label, their doctors had the ability to then go and prescribe enasidenib for them. Essentially what happens is that those patients then get salvaged with single-agent enasidenib or if enasidenib gets added on to azacitidine, and that leads to an equivalence in overall survival, but an improvement in event-free survival. Another important thing to note is that the maximal suppression of mutant IDH2 from baseline was significantly greater with enasidenib and azacitidine versus azacitidine alone. Something we always worry about in patients who get differentiation agents like enasidenib is whether differentiation syndrome will occur. There were a few cases of differentiation syndrome seen in the patients who received enasidenib with azacitidine, but those were easily managed with the standard management for differentiation syndrome, which is dexamethasone 10 mg twice a day. I think the conclusions from this study which are important for a community oncologist to know is that number one, the combination of azacitidine and enasidenib is safe. So, there don't seem to be any new safety concerns. In addition, it seems to be quite effective. It definitely leads to an event-free survival benefit, but it may have led to an overall survival benefit had crossover not occurred, and I think that the question is going to be going forward that now that we have essentially adopted azacitidine and venetoclax as the standard of care regimen for newly diagnosed patients with acute myeloid leukemia who can't receive induction chemotherapy, whether this data is sufficient to start giving enasidenib with azacitidine in combination. I typically like waiting for final results of a study to be published before I change my practice. But I think that it's very possible that if the final results hold up that I will change my practice in IDH2 mutation patients. I will be giving them the combination of enasidenib and azacitidine over venetoclax and azacitidine. Thank you very much for your attention.

Reference: DiNardo C, et al. Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (IDH2) Mutations: Interim Phase II Results from an Ongoing, Randomized Study. Abstract 643. ASH 2019. https://ash.confex.com/ash/2019/webprogram/Paper130362.html