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## Enasidenib Is Highly Active in Previously Untreated IDH2 Mutant AML: Early Results from the Beat AML Master Trial

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Live from ASH. I am going to be discussing Abstract 287: Enasidenib is Highly Active in Previously Untreated IDH2 Mutant AML: Early Results from the Beat AML Master Study.

The Beat AML Master Study is a large, precision medicine study where patients are assigned a specific genomic subgroup based on whether they have a targetable mutation that is available. The way this works is the patient signed up for what is called the Master Protocol, they have their bone marrow samples sent to a central lab where we get genomic results back within seven days of sample receipt. Once that genomic data is available, the patient can then get assigned to a treatment subgroup based on what their genomic mutations are. What I am going to be talking about right now is that the S3 subgroup, this is the subgroup of patients with IDH2 mutant AML. In patients with IDH2 mutant AML, overall this occurs in approximately 15% to 20% of the patients with acute myeloid leukemia and IDH2 mutations lead to the production of the cancer-associated oncometabolite beta hydroxyglutarate. There is a very potent inhibitor of mutant IDH2 out there, a drug called enasidenib, and that enasidenib, at least in the relapse and refractory setting, led to an overall response rate of about 40% in patients with IDH2 mutant relapsed and refractory acutely myeloid leukemia. What we wanted to do in this S3 subprotocol of the Beat AML trial was see if there were patients who were newly diagnosed older than the age of 60 who could get enasidenib and see what their outcomes would be; and that is what we did. There were 28 patients enrolled on this trial, that is 28 patients who were assigned to start therapy with enasidenib. One of those patients for a variety of reasons dropped out of the study before they got their first dose of treatment. For those 27 patients who got enasidenib monotherapy, the response rates were really quite remarkable. The response rate including complete remission and complete remission with incomplete count recovery was 44.4%, that is over 40% of patients achieved a complete remission or complete remission with partial hematologic recovery. That is really a remarkable result, a result that we do not typically see in this older patient population with standard chemotherapy.

Finally, this drug seemed remarkably safe. The adverse event that was highest and the severe adverse event that was highest was what is called differentiation syndrome, that occurred in 21.4% of patients. Differentiation syndrome is a noncardiogenic edematous state that occurs when cytokines get released from the differentiating cells and when these cytokines get released, they cause this capillary leak syndrome. The treatment for this is giving

dexamethasone steroids 10 mg twice a day. The important point for the practicing clinician is that if there is a patient on enasidenib and that patient starts complaining of anything that sounds like pulmonary edema – dyspnea, dyspnea on exertion, leg swelling, anything like that – that’s a patient who should be seen in the clinic immediately to decide whether you think they do have differentiation syndrome, and if there is any hint of differentiation syndrome, they should get on dexamethasone 10 mg twice a day immediately. One other point I want to make is that of the patients who did not respond, 5 out of 6 patients with a RAS pathway mutation did not respond to enasidenib monotherapy. What we think now based on the analyses that have been done is that we need a better strategy for those patients. A better strategy for patients who are RAS mutated and IDH mutated because they do not seem to respond well to IDH inhibitors alone. Thank you very much.

## **Reference**

Stein E, Shoben A, Borate U, et al. Enasidenib Is Highly Active in Previously Untreated IDH2 Mutant AML: Early Results from the Beat AML Master Trial. ASH 2018. Abstract 287.