Enasidenib in mutant-IDH2 relapsed or refractory acute myeloid leukemia: Results of a phase 1 dose-escalation and expansion study

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This is Eytan Stein. I am going to be discussing an abstract from ASCO 2017 entitled, "**Enasidenib in mutant-IDH2 relapsed or refractory acute myeloid leukemia: Results of a phase 1 dose-escalation and expansion study**." Approximately 10% to 15% of patients with acute myeloid leukemia have a mutation in a gene called IDH2. When this gene is not mutated, the normal function of the gene is to help produce energy for the cell and convert isocitrate to alpha-ketoglutarate. The enzymatic product of this gene, the enzyme isocitrate dehydrogenase, converts isocitrate to alpha-ketoglutarate. When there is a mutation in IDH2, in this case, that mutant enzyme instead of converting isocitrate to alpha-ketoglutarate converts alpha-ketoglutarate to beta-hydroxyglutarate. Such that intracellularly, there are increased levels of beta-hydroxyglutarate and those elevated levels of beta-hydroxyglutarate lead to epigenetic changes in the cell, including histone hypermethylation which blocks cellular differentiation. That block in cellular differentiation is the phenotypic effect. What you see phenotypically when the patient has acute myeloid leukemia such that their bone marrow cells are frozen in an immature state at the myeloblast stage of development. Preclinical studies have shown quite nicely that by blocking mutant-IDH2, you get lower levels of beta-hydroxyglutarate intracellularly that will allow these immature cells to be unfrozen and to mature into normal healthy neutrophils. Based on that preclinical work, a phase 1 and 2 clinical study was developed. That clinical study came in three pieces. The first piece was a phase 1 dose-escalation component where the oral drug enasidenib is given in 28-day cycles. At the beginning, either once or twice day, and now it is just once day. That dose-escalation competent of the study was deemed to be successful because the drug was safe and tolerable and there was some preliminary evidence of activity. There were four dose expansion arms that were opened in that phase 1 study. The first two dose expansion arms were in patients with relapsed and refractory AML. The third dose expansion arm was in patients with untreated AML, and the fourth dose expansion arm was for patients with IDH2 mutations that did not fit into the first three dose expansion arms.

The subject of this abstract is all of those patients in the phase 1 dose-escalation and the phase 1 dose-expansion arms who had relapsed and refractory acute myeloid leukemia. There is a separate phase 2 expansion of the study only for patients with relapsed and refractory acute myeloid leukemia, that is not the topic of this abstract. The patients that were treated in this dose-escalation and dose-expansion arm with relapsed and refractory AML had a median age of 67 years old. Most of the patients had the predominant isoform of IDH2 mutation called the R140 mutation, while about 25% of patients had the less predominant R172 isoform of the

mutation. Many of these patients were older and could not receive induction chemotherapy, so they had been on and failed a low-intensity regimen like a hypomethylating agent or low-dose cytarabine. The proportion of patients who had either not responded to induction chemotherapy or had relapsed after a bone marrow transplant or relapsed quickly after initial induction therapy was quite high. The point of all this is to say that this is a very poor-risk patient population. Even though all patients with AML are a poor-risk patient population, I would argue that this is the poorest of the poor-risk patient population. This drug was given. When you look at the safety of the drug, the drug was considered very, very safe in the sense that there were few grade 3 or 4 adverse events that were attributable to the study drug. The most frequent was an indirect hyperbilirubinemia which has no clinical sequelae, which is an off-target effect of the drug in that it inhibits an enzyme called UGT1A1. That enzyme is important for conjugating bilirubin, but when you have inhibition of that enzyme, you can get a small increase in the indirect bilirubin. When we looked at the efficacy of the drug, we were really quite excited. In this poor-risk patient population, the overall response rate was about 40% with 20% of those patients achieving a true complete remission with blast clearance and hematologic recovery. The other 20% of patients achieving either a complete remission with incomplete count recovery or partial remission or morphologic leukemia-free state. What that all translated into in terms of overall survival was an overall survival rate, is a median overall survival of 9.3 months in the entire patient population that was treated. If you then broke that down by patients who were in complete remission, had a response but not a complete remission response, or patients with no response, the median overall survival in patients with the complete remission was over a year and a half, 19.3 months. The median overall survival of the patients with a complete remission with incomplete count recovery or partial remission was a little bit less at about 11 months. Obviously, the patients who did not respond had a lower median overall survival.

There are a couple of translational aspects that I found interesting. Number 1, it did not depend what the baseline beta- hydroxyglutarate level was at diagnosis in terms of response, so whether you had a low beta-hydroxyglutarate level or high beta-hydroxyglutarate level at diagnosis, it did not influence if you responded to the drug. Secondly, there was no influence on response to the drug based on variant allele fraction of the drug; that is, you could have low levels of an IDH2 mutation or high levels of an IDH2 mutation, and you have an equally as great chance of responding to enasidenib. Overall, I think this is a real advance forward for patients with relapsed and refractory acute myeloid leukemia with an IDH2 mutation. The drug is actually now being evaluated by the Food and Drug Administration for approval and we are excited and hopeful that the drug will be approved. The next step, when it comes to treating patients with this drug, is moving this drug into earlier lines of therapy. Right now, there are clinical trials that are combining this with standard-of-care induction chemotherapy and with standard-of-care hypomethylating agents for patients who are a little bit older who cannot tolerate induction chemotherapy. That is what we are excited about and that is where this drug is moving forward.