Ivosidenib and Enasidenib: Do These IDH Inhibitors Impact Survival in Newly Diagnosed AML Patients?

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560. Ivosidenib or Enasidenib Combined with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed AML with an IDH1 or IDH2 Mutation Is Safe, Effective, and Leads to MRD-Negative Complete Remissions

Live from ASH. We are going to be talking about Abstract 560 *Ivosidenib or Enasidenib Combined with Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed AML With an IDH1 or IDH2 Mutation Is Safe, Effective, and Leads to MRD-Negative Complete Remissions.*

Let us talk a little bit about IDH mutations in acute myeloid leukemia. Mutations in IDH1 and IDH2 are found in approximately 20% of patients with acute myeloid leukemia. In general, they are set to portend a prognosis which is not great. For example, in a large study that was reported at this ASH in abstract form, patients with IDH1 or IDH2 mutations who got standard induction chemotherapy, their complete remission rates were in the range of 38% to 40%. That gives you a baseline of how these patients do without any targeted inhibitors. What we were attempting to do in this clinical study was to combine the targeted IDH1 inhibitor ivosidenib or the targeted IDH2 inhibitor enasidenib with induction and consolidation chemotherapy, and those patients who made it that far went on to get maintenance therapy. The way that trial was conducted was as follows: This is a single arm phase 1 study with an expansion cohort where the patients are allocated if they have an IDH1 mutation to receive idarubicin and cytarabine or daunorubicin and cytarabine with the IDH1 inhibitor ivosidenib. On the flipside, if you have an IDH1 mutation, you go on to get enasidenib with idarubicin and cytarabine, or enasidenib with daunorubicin and cytarabine. For those patients who achieved a complete remission, a complete remission with incomplete blood count recovery, or a complete remission with incomplete platelet count recovery, they go on to get consolidation chemotherapy and then those patients want to continue on go on to get maintenance therapy. Now it is important to note that these patients are, anytime when their doctor thinks it is appropriate, allowed to come off the study and get an allogeneic bone marrow transplant. When that is the case, the patients are removed from study and they no longer get the mutant IDH inhibitors.

What about safety for these combinations? The safety of the combination is actually quite good. I am not going to go through all the different things that we saw, but I think the more important thing to note is that all of the side effects we would have expected to see with

chemotherapy alone. When you think about differentiation syndrome, we have talked about this a lot in other contexts with single-agent IDH inhibitors, when you combine that IDH inhibitors with chemotherapy, it seems the differentiation syndrome does not really occur very much. It only occurred in two patients who had ivosidenib plus chemotherapy, the IDH1 inhibitor, and only in one patient who had enasidenib, the IDH2 inhibitor, with chemotherapy, so that is an important thing to know. The 30-day mortality rate in both arms of the study was 5%. The 60-day mortality rate was 8% in the ivosidenib treated arm, 9% in the enasidenib treated arm. One of things people worry about is, well if you are combining new drugs with induction chemotherapy, is that going to cause the bone marrow to take a longer time to recover than it would if you did not give these new drugs? The answer to this question is, in this case at least, it does not seem to be the case. With the median time to both platelet and neutrophil recovery in the ivosidenib-treated patients was in the range of 28 days, and the enasidenib treatment patients the median time to neutrophil recovery was 34 days, well within what we think is an appropriate timeframe for account recovery, while the median time to platelet count recovery was in the range of 30 days.

What is the effectiveness of these drugs together? Well in the ivosidenib treated patients who got that with induction chemotherapy, this combination appears to induce a CR, Cri, or CRP in about 75% of patients. In the enasidenib treated patients, this drug seems to induce the CR, Cri, or CRP in about 70% of patients. Those numbers are lower though in those patients who have secondary acute myeloid leukemia.

Finally, we did present some overall survivor curves which I think are very interesting. In the ivosidenib treated patients, the median overall survival has not yet been reached. The one-year overall survival is about 75%. Similarly, in the enasidenib treated patients, the median overall survival has not yet been reached. The one-year overall survival is also about 75%. We are very, very excited about this combination. We are so excited about the combination that this is now moving into a randomized phase 3 study. Randomized phase 3 multinational international study being led by the HOVON group where patients are being randomized to get either induction chemotherapy with ivosidenib, or induction chemotherapy with placebo, induction chemotherapy with enasidenib, or induction chemotherapy with placebo. Same thing, they can go on to get consolidation either with ivosidenib or placebo or enasidenib or placebo, and there is a maintenance phase to that study as well. I think we are really eagerly awaiting the results of that study to see whether the combination of IDH inhibitors with induction chemotherapy and consolidation and given as maintenance leads to a survival benefit for this high-risk patient population.

Reference: Stein E, DiNardo C, Fathi A, et al. Ivosidenib or Enasidenib Combined with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed AML with an IDH1 or IDH2 Mutation Is Safe, Effective, and Leads to MRD-Negative Complete Remissions. ASH 2018. Abstract 560.

561. Ivosidenib (AG-120) Induced Durable Remissions and Transfusion Independence in Patients with IDH1-Mutant Untreated AML: Results from a Phase 1 Dose Escalation and Expansion Study

We are going to be discussing Abstract 561 *Ivosidenib (AG-120) Induced Durable Remissions and Transfusion Independence in Patients with Mutant IDH1 Untreated AML: Results from a Phase 1 Dose Escalation and Expansion Study*.

As you all know, ivosidenib is an inhibitor of mutant IDH1, and what does mutant IDH1 do? Well, it occurs in approximately 10% to 15% of patients with acute myeloid leukemia and when you have a mutation IDH1, you get the production of an oncometabolite called beta hydroxyglutarate. That oncometabolite accumulates, causes a block and myeloid blast differentiation and gives you the phenotype of acute myeloid leukemia. What ivosidenib does is that it drugs this mutation, lowers the intracellular levels of beta hydroxyglutarate allowing those cells to mature normally. There was a large phase 1/2 study that had a variety of different arms. One arm of which had patients with untreated IDH1 mutant acute myeloid leukemia. The total number of patients in that arm I believe was 34 patients, and when you look at those 34 patients and you ask yourself, "How did they do just with single-agent IDH1 inhibitor, what were the big things that happen to them?" One thing to note is that the drug was very, very well tolerated. The patients typically did not have any adverse or serious adverse events with the exception of something that is really unique to this drug called differentiation syndrome.

Differentiation syndrome is a noncardiogenic edematous state where the patients can get weight gain, they can get peripheral edema, they can get pulmonary edema that occurs when these immature myeloid blasts start maturing. Once these blasts start maturing, they release cytokines which cause this episode of pleural or pericardial or pulmonary edema. The treatment for this is dexamethasone 10 mg b.i.d. It is important to recognize this entity right away because once you recognize it right away, it is reversible with this dexamethasone. If you do not recognize it, patients can get very ill, go to an ICU and end up being intubated which is certainly none of us want to see happen. In terms of the responses these patients had, they were really quite robust. The complete remission rate was 26.5%. The complete remission plus partial hematologic remission rate was 41.2%, and the overall response rate was 58.8%. That is really remarkable on a group of older patients unwilling or unfit to get induction chemotherapy or standard of care chemotherapy to see an overall response rate in the 60% range. Although this drug is not yet approved for patients with newly diagnosed IDH1 mutant acute myeloid leukemia, we are very hopeful that it will be approved in this setting very, very soon. Thank you very much.

Reference: Roboz G, DiNardo C, Stein E, et al. Ivosidenib (AG-120) Induced Durable Remissions and Transfusion Independence in Patients with IDH1-Mutant Untreated AML: Results from a Phase 1 Dose Escalation and Expansion Study. ASH 2018. Abstract 561.