New Data from the Ongoing Phase 1 Study Evaluating Single-Agent IDH1 Inhibitor AG-120 in Relapsed/Refractory AML

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Hi, this is Dr. Eunice Wang. I am reporting live from the ASCO 2018 meeting in Chicago, Illinois. I am here to talk to you about two abstracts which are representative of new advances in the therapy of acute myeloid leukemia (AML) and myeloid dysplastic syndrome. Now, the first abstract I'll be talking about is a phase 1 study result from a potent oral IDH1 inhibitor, ivosidenib, in refractory/relapsed AML patients with IDH1 mutations. This inhibitor is sort of like a cousin inhibitor to enasidenib. Enasidenib is an oral IDH2 inhibitor which was approved by the FDA for treatment of relapsed and refractory AML patients with IDH2 mutations. As you know, IDH1 and IDH2 mutations occur in about 20% of AML patients. Their prognostic significance is a little uncertain, but we know that biologically, these mutations change the metabolism of the cell. They allow for accumulation of an interim metabolite 2HG. Accumulation of 2HG alters the epigenetics of the leukemic cell, leading to inhibition of DNA methylases, and eventually a cellular impairment in differentiation. Ivosidenib (AG-120) is a potent oral inhibitor which has been shown in biochemical in vitro assays to have a very high ability to inhibit IDH1 mutations at about five to thirteen nanomoles. This study was a phase 1 study led by Dan Pollyea from the University of Colorado and his colleagues, which examines the doses of ivosidenib in a dose escalation study. The results being presented here are with 179 AML patients who received ivosidenib at 500 mg and above. The major endpoint they were looking for was complete response with hematologic insufficiency and as I mentioned, the median age of these patients was about 70 years old.

What were the results of the study? They actually were very promising, in fact, they were very similar when you compare the results with this IDH1 inhibitor with the IDH2 inhibitor that was approved in 2017. Ivosidenib led to an overall response rate of about 40% with a complete remission rate of 24%, and stable disease in almost 40% of patients who received treatment. Time to response was a median of 1.9 months. Overall disease-free survival was a little over 6 months, and the overall response rate for these patients was approximately the same as we saw as enasidenib (about 40%). Toxicities were relatively mild: 20% or 25% of the patients have QTC prolongation. About 10% of the patients had clinical differentiation syndrome.

What does this mean for our patients with AML? Given the similarity in the outcome and tolerability of this agent with its cousin agent, I would anticipate that ivosidenib is going to be approved as standard of care therapy for relapsed/refractory AML patients with an IDH1 mutation in the very near future.* There are still some questions that remain with this drug.

Why are the response rates so low? Can we enhance those response rates in some way? At this meeting, there are some abstracts being presented that are reporting the preliminary results of ivosidenib with azacitidine as a combination approach. There are also results of a phase 1 dose escalation study looking at a novel IDH1 inhibitor FT-2102 which is also being presented. We are looking forward to further improving these outcomes as we move forward in this field.

The second abstract that I'd like to talk about is an abstract involving the treatment of lower-risk MDS patients. The standard of care for higher-risk MDS patients is really azacitidine or decitabine. Azacitidine at least has been shown to result in overall survival benefit in these individuals, and it is really considered the agent that most of us would start with in those higher-risk patients with poor cytogenetics and prolonged cytopenia.

What Dr. Swaminathan and colleagues demonstrated in this study from MD Anderson is that there may be a role for hypomethylating agents in lower-risk MDS. Lower-risk MDS patients (typically untreated) have an overall survival of anywhere between three-and-a-half to six years. Generally, per NCCN national guidelines, we do not treat these individuals until they develop transfusion dependence, or if they start to look like they are going to transform to AML with increased marrow blasts. This was a retrospective study that looked at 80 patients treated at MD Anderson with very short courses of hypomethylating agents: decitabine for three days or azacytidine for three to five days. These patients were not transfusion-dependent and received multiple cycles of therapy without significant hematologic toxicity. There were actually no deaths on the study, it was very well-tolerated. Overall response rates were also pretty impressive: 74% in this patient population. The authors here and in another publication have stated that there is a potential for this attenuated hypomethylating course to really alter the natural history of this lower-risk disease. That would be a big change because for now, we do not really treat these individuals until they get sicker. To start these agents earlier would be a little bit of paradigm shift. There are some limitations with the study. This was a retrospective analysis of data that they collected on 80 patients in a single institution. They used a couple of different chemotherapy regimens and they used a heterogeneous population; about three-quarters of the patients had intermediate-risk disease.

There is currently a phase 3 trial looking at the same patient population with the same regimens. We are going to have to wait for that data before we can truly say that this is an advance. The thing that I am worried about is the median overall survival for these patients has not been reached. Is this really going to be an advance? Maybe these patients would have just done fine with even no treatment, or any kind of treatment. I think it is really hard to know and given the prolonged survival, I think we are going to need to wait a little bit longer to see if that is going to change the standard of care.

**On July 20, 2018 the FDA granted approval to ivosidenib for the treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved companion diagnostic.*

Abstracts:

Pollyea D, DiNardo C, de Botton S, et al. Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study. ASCO 2018. Abstract 7000.
https://meetinglibrary.asco.org/record/161682/abstract

Swaminathan M, Jabbour E, Ravandi F, et al. Association of early intervention in transfusion independent (TI) patients (Pts) with lower-risk myelodysplastic syndromes (MDS) treated with attenuated doses of hypomethylating agents (HMAs) with high response rates and long duration of response. ASC0 2018. Abstract 7001.
https://meetinglibrary.asco.org/record/161754/abstract