IDH1 and IDH2 Inhibitors in Combination with Aza in the Upfront Setting

Richard Stone, MD
Professor of Medicine
Harvard Medical School
Chief of Staff
Director, Adult Acute Leukemia Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Hello, my name is Richard Stone. I am Chief of Staff and Director of the Adult Leukemia Program at Dana-Farber Cancer Institute in Boston, Massachusetts. I am live at ASCO to talk about some important abstracts having to do with targeted therapy in acute myeloid leukemia (AML). Over the past 10 or 20 years, we are aware that AML is a very heterogeneous disease. Its heterogeneity has to do with the host factors like the patient's age, comorbidities, and even philosophy of life; but mainly it has to do with disease-related characteristics. These could be subsumed into the different cytogenetic abnormalities and, perhaps even more importantly, to the different molecular abnormalities that patients have at diagnosis. We can generally subset patients into those with certain dominant mutations, such as FLT3 mutations, p53 mutations, or what we will be talking about today, IDH1 and IDH2 mutations. IDH1 and IDH2 mutations represent about 9% and 12%, respectively, of all AML patients. It is not a huge subset, but it is an important one. The finding of IDH mutations is interesting because both IDH1 and IDH2 mutations represent changes in the normal isocitrate dehydrogenase enzyme that normally functions in the Krebs or oxidative decarboxylation cycle, so it is important in cell energy metabolism. As it turns out, if the patients' blasts have an IDH1 or IDH2 mutation, there is a novel reaction product called 2-hydroxyglutarate from this reaction (which normally yields alpha-ketoglutarate), and 2-hydroxyglutarate or 2-HG as it's known is capable of changing the epigenetic milieu of the cell to a more leukemogenic state. It actually phenocopies another common mutation in AML called TET2. So IDH1 and IDH2 are leukemogenic. The prognostic impact of having the mutation is a bit controversial, but nonetheless, there is a gain-of-function mutation and represents a target of therapy. Agios and Celgene Corporation in partnership have developed two drugs, one called enasidenib which hits IDH2 mutation enzyme, and another one called ivosidenib which hits IDH1 mutation enzyme. The IDH2 inhibitor enasidenib is already approved as a single agent for the treatment of relapsed/refractory IDH2 mutant AML, and ivosidenib, the IDH1 inhibitor, will probably be approved for the treatment of relapsed and refractory IDH1 mutant AML.*

Interestingly, just today, right after the presentation by Dr. Dan Pollyea of the updated data of the IDH1 single-agent inhibition study, there is a publication in the *New England Journal of Medicine* that describes the reason for the approval, the results of giving ivosidenib to patients with IDH1 mutant AML who are relapsed/refractory, so I encourage everyone to look at that paper. The first author is Dr. Courtney DiNardo of MD Anderson Cancer Center in Houston.

There are some follow-up abstracts presented at this meeting to understand how we might be able to use these two drugs in other ways, other than single agents in relapsed/refractory AML. Specifically, we are going to talk about use of ivosidenib and enasidenib in upfront AML in older adults who are not deemed fit for intensive chemotherapy, but are actually deemed fit for non-intensive chemotherapy in the form of azacitidine, which is commonly used as a single agent to treat unfit AML older adults. One trial, which was a phase 1B trial, assigned patients who had IDH1 mutant AML to azacitidine plus ivosidenib, and assigned patients who had IDH2 mutant AML to azacitidine plus enasidenib. The data that Dr. DiNardo will present on Monday describes the preliminary results of this phase 1B trial and shows that combining either enasidenib or ivosidenib with azacitidine for unfit AML patients with the appropriate mutation is safe, and at least from preliminary results, suggests a response rate higher than one would expect with azacitidine alone in these patients. Again, it is not a randomized trial, it is a safety trial, but an important one. Dr. Stein will provide a trials-in-progress presentation discussing the AGILE trial in which we will figure out whether the addition of ivosidenib (IDH1 inhibitor) to azacitidine leads to a better overall survival than azacitidine alone in the IDH1 mutant older adult unfit patient, and it will be very interesting to see how that trial comes out. It is a very hopeful trial but tough logistically because you are going to have to find just patients with IDH1 mutations (again, only about 9% of all AML) and you are going to randomize those patients to azacitidine plus or minus ivosidenib, but it would be great to see an improvement over azacitidine alone in this difficult-to-treat population. I am happy to say that we have some new targeted agents in AML that are approved or will be approved as single agents, and then we will find out how to use these in combination with non-intensive chemotherapy and in other cases how to use them in combination with intensive chemotherapy in more fit patients with AML.

**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:

Stein E, DiNardo C, Jang JH, et al. AGILE: A phase 3, multicenter, randomized, placebo-controlled study of ivosidenib in combination with azacitidine in adult patients with previously untreated acute myeloid leukemia with an IDH1 mutation. ASCO 2018. Abstract TPS7074. *https://meetinglibrary.asco.org/record/165530/abstract*

DiNardo C, Stein A, Stein E, et al. Mutant IDH (mIDH) inhibitors, ivosidenib or enasidenib, with azacitidine (AZA) in patients with acute myeloid leukemia (AML). ASCO 2018. Abstract 7042. *https://meetinglibrary.asco.org/record/162432/abstract*