Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory AML

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This is a study that we designed with the AbbVie and Astellas teams as well as lead investigators at other sites in the United States. The study combines two very active drugs in AML, one being a BCL-2 inhibitor, venetoclax, that is approved in the frontline setting as a combination of azacitidine or low-dose cytarabine with venetoclax for older AML, not suitable for induction; the other is a highly potent selective FLT3 inhibitor that targets both FLT3 ITD and TKD as well as dual mutation and has been approved in the relapsed/refractory setting as a single agent, the drug is called gilteritinib. The approval of gilteritinib was based on a randomized phase 3 study that showed that single-agent gilteritinib was able to produce higher response rates, bone marrow responses, CR/CRh, as well as significantly improved overall survival as compared to standard-of-care high-dose chemotherapy or epigenetic therapy. One of the big questions is, why did we do this combination? Well, one reason is that there is actually very potent preclinical synergy for the FLT3 inhibitors, gilteritinib, but also for quizartinib with venetoclax, and our group has done studies in the lab, as have AbbVie, Astellas, and Genentech teams that support a very high degree of synthetic lethality when you combine next-generation FLT3 inhibitors with the BCL-2 inhibitors such as venetoclax. Also, important to note that one of the major mechanisms of resistance or relapse post-venetoclax is MCL1 upregulation, and the FLT3 inhibitors block MCL1, thereby blocking the escape or relapsed potential by using single-agent venetoclax. And on the converse, we also know that people who had FLT3 mutations had very low or no responses to venetoclax single-agent therapy in the phase 1 study, and for those who had responses when they relapsed, a number of those had a newly detectable FLT3 clone. All of these suggested that venetoclax alone or even HMA-venetoclax may not be enough in the FLT3-mutated but a combination with a highly potent FLT3 inhibitor could induce high synergy.

In this study, this is an early report. We have a total of 22 patients that have been reported, of which 18 were FLT3-ITD mutated. In the initial dose escalation period, we allowed both FLT3-mutated as well as FLT3-unmutated patients. However, after we completed the initial 12-patient dose escalation, we then only are focusing on relapsed FLT3-mutated patients, they could have had either ITD or D835 or both. We looked at dose level of 80 mg gilteritinib with venetoclax 400 mg continuously, day 1-28 as well as 120 mg gilteritinib with venetoclax 400 mg day 1-28. We did continue to apply a three-day ramp up going up on the venetoclax from 100, 200, to 400. Azoles were not allowed during the first cycles so we used caspofungin and did escalate the venetoclax to the full 400. And we did do a bone marrow at the end of cycle 1 to assess whether there was marrow myelosuppression with no active disease, presence of active disease, and that would then help us be guided towards the next step.

Overall, what we see is that the response rates are very, very promising in the FLT3 group, especially where we have 18 evaluable patients at the time of the ASH meeting and the data that we will be presenting. We see 16 out of 18 patients have achieved some form of marrow remission, so CR/CRi/MLFS; this is about 87%. Now, one would say well how does this compare to single-agent gilteritinib which is what has been approved and is used in the United States? So, in this patient population where I have to say, a majority of these patients had received a prior TKI like midostaurin with induction, because now that is the standard based on the midostaurin phase 3 study, we would expect, and our group has actually presented this data last year at ASH, the response rate the second-generation FLT3 inhibitor, quizartinib-gilteritinib, would be 30%. We are seeing 85% plus where we would expect to see 30% with a single agent. This is obviously very, very encouraging early signal. Also looks like the responses may be happening a little bit earlier, 1.5 versus 2.5 months, and what's very, very nice is that the early mortality, even in the relapsed/refractory population, which is a very difficult one, remains zero and it is an oral-oral regimen. So we really think that this could be the next step to combine venetoclax with FLT3 inhibitors and, of course, the next logical step is also can we move upfront and do Aza/Ven but add gilteritinib in a modified dose schedule and really potentially cure a lot of these patients? And those kinds of studies are being designed. In the relapsed setting, I think this study is open now at 8 or 10 sites, additional sites may be added; and the goal is to see if with 70 to 80 patients we continue to see good safety, low early mortality, high CR/CRi/MLFS rates and, of course, eventually the duration of response and overall survival, which can be compared to real-world outcomes with single-agent gilteritinib in patients who receive prior 3+7 midostaurin. And I think this could be a combination that even in the next 8 to 10 months or a year could be going for potential NCCN review and see if we could publish the data and allow physicians in the community to use it.

One word of caution we did see two patients who had very prolonged myelosuppression, even though gilteritinib as a single agent does not cause that much myelosuppression, the combination we did have two or three patients who had more than 45 days count recovery. So we usually are doing a bone marrow at the end of cycle 1 and if the bone marrow is hypocellular, ablated, with low neutrophil-platelet counts, we interrupt the venetoclax to allow for count recovery but we keep the gilteritinib going. And with this approach of interruption of venetoclax, we are seeing the counts recover in the majority of patients and not seeing as much prolonged myelosuppression. So stay tuned for updates on this data later next year and hopefully this will be another good breakthrough for FLT3-mutated relapsed AML building on single-agent gilteritinib activity. Thank you.

Reference:

Perl AE, Daver NG, Pratz KW, et al. Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory Acute Myeloid Leukemia: A Phase 1B Study. *Blood.* 2019;134 (Supplement_1):3910.
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