Transcription - ASH 2016: Matthew Davids Discusses the Combination of a BTK and PI3K Inhibitor in CLL

Dr. Brian Koffman- Hi. Dr. Brian Koffman, a family doctor, and a CLL patient and here in the last hours of the American Society of Hematology, ASH 2016, learning a lot.

Dr. Matthew Davids- I'm Dr. Matthew Davids. I'm the associate director for the CLL center at the Dana-Farber Cancer Institute in Harvard Medical School in Boston.

BK- Dr. Davids, at ASH, even though it's an enormous conference, there's a lot of competition among physicians and institutions to get their research heard. To get a poster accepted is competitive, but to get an oral presentation, what you have to say has to be very clinically relevant. Has to really make a difference. And you had one of the very few oral presentations at ASH. Can you tell us about your research and why it might be important to patients with CLL?

MD- Sure. Well thank you very much for allowing me to highlight my research. I'm very excited about it and I think they choose the oral presentations that, I think, may have an impact directly on the patients in the relatively near future. And I think that's the case with our study. Our study looks to combine two new types of drugs: The BTK inhibitors, like Ibrutinib, and then PI 3-kinase inhibitors. And some of the audience may be familiar with Idelalisib, which an FDA approved agent in this space.

BK- Zydelig

MD- Zydelig is the other name for it. And while that may be an effective drug, there are some significant side effects to it. So as we think about combination strategies, we want to use drugs that have the best side effect profile possible. And so for our study, we wanted to combine with Ibrutinib, but we decided to use a different drug called TGR-1202. So it works in a similar way to Idelalisib by targeting this PI 3-kinase, but it seems to have less side effects, at least when we give it as a mono-therapy, meaning one drug at a time. And so our study was a combination of Ibrutinib with TGR-1202 for patients with relapse refractory CLL, meaning they had already had progression of their disease after other therapies.

BK- So, let me stop you there. Could those other therapies been a tyrosine kinase inhibitor such as Idelalisib or Ibrutinib?

MD- Yes, they could have. In fact, we've had a few patients on the study like that. These were not patients who were refractory to these therapies. They came off for various reasons. Whether it was side effects or other reasons.

BK- But most of them would have been chemoimmunotherapy before?

MD- That's right. Most of the prior therapies were that.

BK- And is this, am I right, this is the first study of combining a PI3-kinase inhibitor and a BTK inhibitor.

MD- That's right, this is the first study.

BK- So there's a lot of safety issues that you needed to address.

MD- Exactly. And in fact, in an earlier study, they tried to target a different protein in this pathway and ended up having significant side effects. And so we were a bit nervous and we decided to do a Phase 1 study to be very cautious and look at the dosing of the drug and make sure we have a safe regimen before we expanded it out to other patients.

BK- Alright. And what did you find?

MD- So, we found that we were able to feasibly combine these two drugs with a very relatively benign safety profile. We did see some side effects, but nothing out of proportion to what we'd expect from either drug on its own. We were able to figure out the correct dose of the TGR-1202 to use moving forward which looks to be 800 milligrams daily. And I think most excitingly, we saw very high response rates in our CLL patients. 88% of these CLL patients responded and some of the patients have very high-risk disease. We've seen a complete remission already in one of our patients, which we don't often see in the relapse refractory setting with Ibrutinib alone. And we have several patients approaching what we call a radiographic complete remission, meaning their lymph nodes have shrunk all the way down, almost back to normal. So I think time will tell whether this is going to be a regimen that is better than Ibrutinib on its own. I think if we start to see a significant number of complete remissions evolve over time then I think that would be the case. However, if we don't, then we can make the argument that maybe you just need the Ibrutinib by itself. But that's something we'll learn from the study.

BK- And how long have you looked at this? What's the length of this data? Because often with Ibrutinib and with the PI 3-kinase inhibitors, a lot of patients get better further and further down the line.

MD- That's right. The average patient on this study has been on for a little over a year.

BD- Not long then.

MD- So, not too long. We do have some patients getting out to two-year mark. So I think, again, time will tell to see how deep these responses get and whether that compares favorably to Ibrutinib on its own. But we know that Ibrutinib on its own for patients with the high-risk forms of the disease can have limited efficacy in certain cases.

BK- And did you have a significant cohort of these high-risk patients, the deletion of the short arm of 17p, the complex karyotype?

MD- Yeah, about a quarter of the patients on our study had deletion 17p and then another 40% had deletion 11q, which is a more intermediate marker but certainly can suggest more aggressive disease.

BK- And have you done any sub-group analysis to look at if the outcomes were as good for those patients as they were for a majority of patients?

MD- So, the numbers get small. But they certainly seem comparable. The one more formal sub-group analysis we did was looking at the mutated vs the un-mutated IGHV patients and there the response rates and the durability seemed comparable so far.

BK- And you said there was no new safety signals, if I'm hearing you correct.

MD- That's right.

BK- So, some of the hits against the Idelalisib, some of the concerns from a patient's perspective were the infections, were the liver inflammation, and was the colitis. Did you see any evidence of that in your study?

MD- So we did not see any colitis in our study. And we did not see any severe liver inflammation. We had a few patients who had some very mild liver inflammation, but not even enough to have to stop the drug. And we did not see any classical sort of severe pneumonitis like we might have expected from the other combinations so it's actually surprisingly very well tolerated, this particular combination.

BK- Any final thoughts or anything that you'd want to share with patients about this novel combination?

MD- I mean, I think this is just another example of it's great for patients to know about what other options are and to at least have a consultation with a CLL center so they can learn about clinical trial options. And I think the patients who've gone on this study have been very happy that they have been able to have this novel combination.

BK- I think you and I agree on that. That patients often get the best care in a clinical trial and often have access to the best medications and the best combinations.

MD- I agree.

BK- Thank you very much, Dr. Davids, for what you're doing. Thank you.

MD- My pleasure.