ASH 2017 Dr. John Byrd on Acalabrutinib in CLL - Transcript

Dr. Brian Koffman – Hi, Dr. Brian Koffman. I'm a family doctor and a CLL patient myself, and I'm here as the founder and medical director of the CLL Society on the last day of ASH 2017 in Atlanta, Georgia.

Dr. John Byrd – Hi, I'm Dr. John Byrd. I'm a professor at the Ohio State University and work in early drug development for CLL and other blood cancers.

BK – Dr. Byrd, one of those drugs that you've been involved in early development with is acalabrutinib, which is a second-generation BTK inhibitor. It blocks the B-cell receptors like ibrutinib does. Can you tell us... You presented some abstracts here and presented some of your research. Can you give us some sense of that for the patients?

JB – So it became very, very apparent, as ibrutinib came into the clinic and was really benefiting so many patients with this disease, both in relapse, and then in the upfront setting, where they needed treatment, that some people either were intolerant or, for other reasons, ibrutinib wasn't the right medicine for them, and that having a back-up, and a potentially a better drug is, generally, when we're developing drugs, the first one is going to have hiccups, and if we can improve on things, understanding the biology, we have the chance of making something better. Acalabrutinib is a second-generation BTK inhibitor that really goes much more after the target in CLL-BTK and spares alternative targets that may cause some of the side effects associated with ibrutinib, such as diarrhea, rash, and bleeding, and atrial fibrillation. Although, that's really… we can't say absolutely that there's a big difference until the two are directly compared. So, what was very fun at this meeting was presenting both the safety of over 500 patients treated with monotherapy, with acalabrutinib, and sort of looking over time as to how they do, and really, not seeing big signals of safety concern. And more importantly, because if you have a safe drug, it doesn't look as good, or it's not working, and who cares? But really, what you want is a real safe drug that's real effective. And we presented the long-term follow-up of the initial acalabrutinib study, which included 134 relapse and refractory patients who had had an average of two prior therapies. And what we saw with a follow-up now of over 24 months is that the responses continue to go up… over 90% of people responded… a small number of remissions, only about 3%, but at the time we did this analysis, 78% were still on therapy, still doing well, and there's very, very little discontinuation, very little safety concern relative to adverse events. There are some Grade 1, Grade 1/2 early diarrhea, which you see. There's a class of that…

BK – It should be mild when Grade 1 and Grade 2. Yeah.

JB – And the same thing with headaches, and headaches is probably one of the distinct side effects of both acalabrutinib and the other second-generation molecule that Gilead has, the . And it's really a headache that comes on during the first several weeks of therapy. It's responsive to Tylenol. In almost everybody, it goes away. There are a few people that get the headaches that come on later, but those individuals are quite rare. And so, it's really exciting,
because we've got a second-generation medicine that when you look at the objective data, comparing one study to another, it's really hard to tell. But I mean, I think, and I was just talking with another CLL expert... sort of at the bedside, in the clinic, and when you're talking with patients, it does seem to be tolerated a little bit better, and certainly the efficacy looks as good as ibrutinib, and one of the distinct differences of this BTK-inhibitor, as compared to ibrutinib, is because it has a short half-life, it can be dosed twice a day, and by dosing it twice a day, you put more pressure on the target BTK.

BK – Help me understand that. I'm not following you. Why would you put more pressure if it's got a shorter half-life? Help me understand that.

JB – So, ibrutinib and acalabrutinib are irreversible inhibitors. So, once they bind to the drug, once it gets in the body, even if it's there for 10 minutes, if it binds the BTK, that BTK is gone. And then the way the cell escapes that is that it remakes ibrutinib. It makes BTK.

BK – It regrows the BTK, yeah.

JB – Right, and so if you're giving the medicine every 12 hours, you occupy the target better. So when you look at acalabrutinib versus ibrutinib, you give acalabrutinib 24 hours... over 24 hours... at the end of 24 hours, 90 to 95% of the target will be occupied, but 5% has sort of regrown back. You look at acalabrutinib... 98-99% is occupied at the 24-hour time point, because you've given two doses. And that may be important for more aggressive CLL. I say may... and there's actually a randomized Phase III study that just finished that's directly comparing ibrutinib versus acalabrutinib... and that study will tell us, one, are there differences in safety between the two, because it's a direct randomized comparison, and two, is one potentially better than the other? But I mean, it's really exciting. This drug was approved, not for CLL, but for mantle cell on Halloween of this year. And that's made it available for people who get bad rashes, who developed recurrent atrial fibrillation or other complications. It makes it potentially available to prescribe. It's a very expensive drug, so one has to work through insurers paying for it and such, and it's totally off label. But I think we're moving toward having a second BTK inhibitor, which I believe is at least as good as ibrutinib, approved. It's going to provide something for the small subset of patients who are intolerant to ibrutinib, eventually, and I think as these new studies come forth with acalabrutinib versus ibrutinib, we'll see if we have maybe a better one. But we have to wait for the studies to know.

BK – Good. Yeah, that study just finished accruing, right?

BK – Right. So, you just...

JB – Right, and the amazing thing, I think it's like 700 patients were on that study, and it's still... it's going to take a long time to get the results for a good reason, because patients... and this is the great example, and every patient that participated in that trial, thank you, because as I say, it's going to help us arrive at an answer to this question. But everybody got a good therapy. They got a pill therapy, no chemotherapy. But it may take a long time to get the answer to which is better, because probably both arms are going to do well, but we're excited
to see that study readout. And I think the big debate at this meeting has been which of these is better? Patients asked me that, and some patients come and have their mind up that they want to receive acalabrutinib, because it’s a better BTK inhibitor. It’s better tolerated. And really, everybody’s making inferences, and when I presented this long-term data, I started at the beginning. I think you were there.

**BK** – You’re right, I was there.

**JB** – I said don't ask me the question which is better, because we're only going to be able to tell when that randomized study reads out, but let's just count our blessings that now we have two BTK inhibitors approved for patients with mantle-cell lymphoma and, hopefully, CLL soon.

**BK** – Dr. Byrd, thanks so much for the research you're doing.

**JB** – Thank you.