ASH 2017: George Follows Discusses Exciting Clinical Data for Venetoclax plus Rituximab for Relapsed Refractory CLL - Transcript

Dr. Brian Koffman – Hi. Dr. Brian Koffman. I'm a family doctor and a CLL patient, myself, and I'm here at ASH 2017 in Atlanta, Georgia.

Dr. George Follows – And Dr. George Follows. I'm a consultant Hematologist from Cambridge in the UK where I have the clinical lead for CLL and lymphoma.

BK – Dr. Follows, one of the most anticipated abstracts here is the MURANO abstract, which is a combination of venetoclax and rituximab verses bendamustine and rituximab. Can you tell us why you're excited about that paper and what you're expecting and seeing in that?

GF – Yeah, Brian. So, we've all been really waiting for this for quite some time. It's a relapsed/refractory trial and it's big. There are nearly 400 patients in that trial, randomized between venetoclax/rituximab against bendamustine/rituximab. And why is it important? Well, it's the first time one of the new drugs has been randomized against immune-chemotherapy, and its combination, as well. So venetoclax with the rituximab has won on every measure… primary end points, secondary end points, response rates, progression free survival. It's even read through into overall survival. So, this is a really big thing. As you know, the Phase III trials, we like to crawl all over them in detail and I'm just talking on the abstract because it's being presented tomorrow when we can get more details. But it's looking really promising… very exciting for our patients.

BK – So, in the past, often in these Phase III trials, or registration trials, where drugs are trying to get to market, sometimes the comparators have been a little weak so they're a little easy to knock down. But the bendamustine/ rituximab has a pretty good track record.

GF – Yeah, it does. And I think it is important to remember there's a bit of an international perspective. So, you could say, "Well look, maybe North American market, relapsed CLL, everyone's on ibrutinib. But internationally, I don't know whether that's the case because it is important, particularly that first relapsed phase, we know the mutated CLL, mutated immunoglobulin chains and long first remissions, these patients can actually do reasonably well re-treating with immuno-chemotherapy, and that's certainly common practice internationally. And so, the space there, I think, is real. I think testing against proper immuno-chemotherapy and showing actually we've got a combination that wins out, with good toxicity. And so, I think this is really is going be a game changer for CLL.

BK – So venetoclax on its own is a very potent drug. And that's how it's approved for use in the US and, as I believe, in the United Kingdom, too. Does adding an antibody add extra oomph to it?

GF – Well, this is the interesting thing, because we know from the BTK inhibitor studies that when you inhibit BTK, you throw in anti-CD20, and there's a good Phase III trial looking at that.

Yeah. it clears the lymphocytes, but it doesn't really push the remission down and it's very hard to show benefit.

BK – Right, It seemed to me you got there quicker, but you didn't get any deeper or longer remission.

GF – Exactly. And if you're risking on extra toxicity, well, what's the rush? But I think with venetoclax/rituximab, and if you remember a couple years ago at ASH when the Northwestern data came out showing how deep those remissions were, you know, pushing half of patients getting MRD negative and that's something really exciting for us because you add that anti-body to venetoclax you get deeper remissions and its giving the opportunity to stop. And that's where the MURANO trial is really exciting… two years of therapy and stop. Now, of course we've got to be careful. The median follow-up on this trial is about two years so we can't yet say, tracking those patients, whether that's going to be the right strategy for them. But it is really exciting that we can push remissions deep enough to allow patients to come off it.

BK – So I've got to push on a couple points. The first is that both venetoclax and the monoclonal antibodies like rituximab can drop your neutrophils, which are so important in fighting infection. And there's been some issues there.

GF – So, yes, of course. And it's a relapsed trial, so patients… there will be issues of cytopenias.

BK – Cytopenias being low cell count.

GF – Yeah, low cell counts, and that's absolutely right. Any CD-20 antibody, whether it's obinutuzumab, which probably has more readout in neutropenia, or rituximab, or some of the newer ones, ublituximab… really exciting drugs around. But they probably do come with adding a bit of toxicity… can't escape that. But I think still, you know, the treatment related mortalities were pretty similar between the arms, perhaps a touch lower. So, I think the signal readout in the Murano trial, I think is acceptable for me.

BK – And when you're talking about stopping therapy, is that just for the people who are MRD negative, or if you do MRD negative and wait six months for a second MRD negative?

GF – So that's a really good question. There's a lot of trial design and thought going into this, so, do you treat people until they get MRD negative, and then are they still MRD negative at a repeat test? In the UK we are modeling this and with our combination trials we're feeling perhaps it's safer to keep them on treatment for the duration it took to get them MRD negative. But the reality is we don't know. In these large Phase III multi-center trials, they've gone for a straight down the line stop at two years. And as we know the Germans have their own strategies, stop at one year. And I can see why, but then you can also see a patient might say, "Well look, I'd rather go for a tailored approach and if I'm not MRD negative yet, can I carry on?" But we just don't know the answers to that yet.

BK – Any final thoughts or things you'd want to share with a patient about this new, exciting combination?

GF – Yeah. I think, as we always say for the patients, it is and exciting era. There are so many promising things coming down the line. I mean we haven't touched on venetoclax with a BTK inhibitor plus anti-CD20. And you've got three drugs there. You can change how you use them. You can change combinations. There really is great promise. But I think from my perspective, this is potentially a game changer. I think it's going to come into practice and I think we'll see patients benefiting from them.

BK – Dr. Follows, I always learn something talking with you.

GF – It was great talking to you Brian.

BK - Thanks.