ASH 2017: Dr. Con Tam on BGB-3111 or Zanubrutinib for CLL Transcription

Dr. Brian Koffman – Hi. Dr. Brian Koffman. I'm the founder and medical director of the CLL society and I'm here, coming near the end of Day Two of ASH 2017.

Dr. Constantine Tam – Hi. I'm Con Tam from Peter MacCallum and St. Vincent's Hospital in Melbourne, Australia.

BK – Dr. Tam, the medications that block the signaling of the B-cell, the B-cell receptor inhibitors, have changed the way CLL is being treated and there's some new ones coming along and you've been involved with one of those molecules BGB 311 (corrected BGB 3111) and there's a number of papers on that that you've been involved with. Could you explain to patients what that is… what they should know about that?

CT – Yeah. Absolutely. So, as you know, Brian, ibrutinib, which is the first BTK blocker, has been very successful. However, ibrutinib can be improved in some ways and that's what the second-generation molecules are trying to address. So, the BGB 3111 actually has a name now. It's called zanubrutinib, z-a-n-u-brutinib.

BK – Okay.

CT – This is a drug that is a second-generation drug. It's better than ibrutinib in that it's more specific. It's more targeted against BTK and less against the other enzymes. Now what that means is that there may be the potential for us to be able to target BTK with less side effects because it doesn't hit the other enzymes quite so much. The other thing about this drug is that it is really well absorbed and because it is really well absorbed we were able to get blood levels much higher than we could with ibrutinib. So, we're looking at blood levels 6 to 10 times higher than ibrutinib. Now, what we don't know, of course, is whether these higher blood levels will mean that patients will respond better in the long

term. Only the clinical trials will tell us that. The studies that we presented at ASH this year is an update on our monotherapy experience, so this is the drug by itself. We have previously shown that the drug is very active in chronic lymphocytic leukemia. On this occasion we presented the data on non-Hodgkins lymphoma showing that it performs just as well, if not better than ibrutinib in those diseases, but we also show for the first time, some data of that drug with… in combination of some of the other antibodies. Maybe the first one I talk about will be zanubrutinib in combination with GA101 or obinutuzumab. So, this is a combination of the drug plus an anti-CD20. There is some information to suggest that ibrutinib and Rituximab may not be the best partners because ibrutinib blocks an enzyme called ITK which is important for the function of the immune cells. So, the Rituximab goes and tags the leukemia cell, and then relies on the immune cells to come and kill the cancer cell that's been identified. Ibrutinib, through its ITK action, can potentially impair the action of those cells in attacking the cancer cell.

BK – Let me stop you on that because we saw some data that's a different study on ibrutinib versus ibrutinib and rituximab and the data looked pretty similar, like it didn't add anything, take away anything. It was pretty much the same.

CT – It was and this is a really highly anticipated study that you just mentioned from MD Anderson where they issued a randomized study of ibrutinib versus ibrutinib plus rituximab, or Rituxan, to you. The long and the short of it is the Rituxan didn't do much, which is what we suspected. Now zanubrutinib, or the Beigene drug, is different in that it does not affect ITK. So, theoretically it should not interfere with antibody action. So, we did a clinical study combining zanubrutinib and obinutuzumab, and in patients with chronic lymphocytic leukemia, in the frontline, we are achieving a 35% complete remission rate even before the first year is up and in the relapsed setting we are achieving a complete remission

of 20%. Now, these rates are higher than what we expect for a BTK inhibitor and it suggests to us that, at least in this population, that the obinutuzumab was helpful in making the BTK inhibitor work better. However, this of course is not randomized data, so at some point this is... but it does confirm some of the suspicions that we've had about the way the drug works in the lab, and it's nice to see that it seems to be producing better responses in the patient.

BK – Any safety signals that you saw that were new or concerning?

CT – None at all. In fact, I was joking that the combination actually made… was actually safer than the drugs individually... and the reason why was the major side effect of obinutuzumab is the infusion reaction, which happens in about one in five patients in a severe manner and in this study our severe infusion rate was 2% instead of 20%. The reason why, we think, is because the BTK inhibitor, which was given only half an hour before the first dose of obinutuzumab, but the BTK inhibitor we think, made a big difference in reducing the infusion reaction rate.

BK – Modulates the T-cells in some way that may reduce the reaction to the foreign proteins?

CT – Possibly. Yes.

BK – Yeah.

CT – And this is not the first time that this observation has been made. We made the same observation with idelalisib, with ibrutinib, so I think it's a class effect.

BK – So, this new BTK inhibitor, it's also being combined with some other molecules, too?

CT – Yes. The company also has a potent PD1 antibody.

BK – So, tell us what a PD1 antibody is.

CT – Alright. So, the PD1 antibody is pretty hot right now, not so much in leukemia, but in cancer in general. The cancer cells hide from the immune system by expressing a molecule called PDL1. And what that does is, it makes the cancer invisible to the immune system. A PD1 antibody comes along and removes this cloak of invisibility and makes the cancer visible to the immune system...

BK – You're doing your Harry Potter stuff here!

CT – Yeah, yeah, yeah, yeah, Harry Potter. …and allows the immune system to find and destroy cancer. This group of drugs has been really active in melanoma, in lung cancer, and in fact of course, across all the fields of cancer and is really one of those miracles of modern medicine. Now, PD1s have been tested in CLL and to be perfectly frank, in CLL that they haven't done very much. However, we made the observation that patients who have Richter's transformation, simply respond quite well to PD1 and it may be one of the most active drugs in Richter's transformation. So, we have a combination of the Beigene BTK inhibitor with the PD1 inhibitor, given in combination, and we only presented early data just to show that the combination is active and that it's safe, but we're gathering more data. We've treated a number of patients with transformed diseases…. so, CLL that has become lymphoma, or follicular lymphoma that has become aggressive, and we have seen good responses in those patients… nothing that's curative, nothing that lasts forever, but certainly very encouraging signs. We are still working toward this combination. I think for patients with chronic lymphocytic leukemia, one day it may be a very good combination for patients who have developed large-cell or Richter's transformation. In particular if they haven't seen a BTK inhibitor in the past.

BK – Any final thoughts on this area of research and these new molecules coming up?

CT – No, except to say that I think it's a really good time. I'm very happy for my patients, that we have so many choices now. We've got ibrutinib, which is amazing. We've got venetoclax, which is amazing. We've now got second-generation drugs which are overcoming some of the shortcomings of the first-generation drugs. We've got combinations of ibrutinib and venetoclax, which you've heard all about in these sessions today, showing good tolerance and really encouraging activity.

BK – Dr. Tam, thanks so much for what you're doing. Thank you**.**