2017 CLL Ireland: Dr. Tal Munir on Combination Therapies in CLL - Transcription

Dr. Brian Koffman – Hi. Dr. Brian Koffman. I'm a family doctor and a CLL patient, founder and Medical Director of the CLL Society, and I'm here in Dublin, Ireland to help launch CLLI (CLL Ireland). Thrilled to be here!

Dr. Talha Munir – Hi. I'm Dr. Tal Munir. I'm one of the hematology consultants at Saint James's Hospital in Leeds. My main interest is CLL and clinical trials and I'm very excited to be here as a part of the team to launch CLLI.

BK – Dr. Munir, first, thank you for coming to Dublin for this. This is so important, what they're doing. Second, thank you for the research you're doing out of Leeds. I think it's groundbreaking. You're looking at combinations and I'm a big believer that combinations are the future. CLL tends to be a fast-moving cancer, not in terms of its clinical progression, but in terms of the way it can mutate around different therapies. One of the combinations that I'm interested in, and I know you're doing some research on that, is ibrutinib and venetoclax. Could you talk a little bit about some of the science behind that and if there are any early clinical results that you'd want to share with us?

TM – So ibrutinib and venetoclax, both these drugs have been used in clinical trials but not in combinations, although there's some early data in Phase Ib trials using the combination of ibrutinib, venetoclax and obinutuzumab.

BK – That's the Jeff Jones trial

TM – Jeff Jones trial.

BK – Out of Ohio State.

TM – That's very true. And we are very interested in looking at combinations right from the beginning, so we've got a Phase II program where we used ibrutinib as a model and looking at the biological markers, looking at the phosphorylation of the CLL cells, also looking at the genomic data.

BK – So, the phosphorylation, that's what proteins are turned on and off. Is that right?

TM – Yes, and also what is the blockage of the BTK and what impact it is having on the other kinases in the CLL cells, like the SYK kinase.

BK – The other enzymes, yeah.

TM – Looking at the other kinase and in real time when the patients are receiving the drug. Stemming from that data we constructed two trials which were looking at combination of ibrutinib with obinutuzumab and see how well we can get patients into deep remissions and that trial is ongoing at the moment. We have got 20 patients who are already on ibrutinib and we've combined obinutuzumab at a later date to improve the depth of remission. And we've had another 20 patients who've basically had combination of both drugs. And we will assess the biological end markers in that trial and we'll be presenting the data soon. The second trial, which is very interesting to us, is where we're combining ibrutinib with venetoclax and patients get ibrutinib pre-phase for about two months and then we're adding venetoclax on the top of that. And the main goal of that trial is to see what is happening to the depth of remissions and we're looking at the peripheral blood data as well as the bone marrow data to assist the depth of the remission and that is being assessed at different time points in this trial in a positive way.

We have got some preliminary data which we would be presenting at EHA this year and some more data at ASH this year. And it appears to us that this is the way to go to get the patients into deep remissions. Taking that from relapsed refractory patients, we are now hoping that we can use this combination in frontline setting as well.

BK – Do you see a time where this kind of combination could be used in a durable timeframe? I mean, one of the hits against ibrutinib, as good as it is, is that we don't know about the safety of stopping it. Is that built into your trials? Do you say you take it for a finite period or you take it until you're MRD negative? Is that built into your trials?

TM – Yes. Our trials are very, very MRD-focused and essentially the main point is that if the patient gets MRD negative say at six months or at 12 months in peripheral blood, we will continue the drugs for another six months, confirming the peripheral blood MRD to be negative and confirming, finally, that on the bone marrow. And once we have confirmed that they have achieved MRD negativity in the bone marrow, then we will stop the drugs.

BK – Both drugs?

TM – Both drugs. And we monitor both the MRD in the peripheral blood and as soon as patients become peripheral blood MRD positive again, then we will re-initiate therapy again.

BK – And is there any experience about whether people respond if you challenge them again with the same drugs?

TM – At the moment, no. But this is what is built into the trial at the moment and that's what we're trying to answer in this Phase II trial in relapsed refractory patients. The same thing will be applied to the frontline patients, as well, and essentially those patients will get this combination, get them into MRD negativity and stop the drug, and re-initiate the therapy when they start to become MRD positive.

BK – This is very exciting from a patient's perspective. Thank you so much for what you're doing. Any final thoughts you want to share with the CLL community?

TM – I just want to say that it is a very exciting time. We've got multitudes of drugs now which we want to use and the best thing to do is to combine them in a positive manner, but looking at the biological endpoints, and then translating that into clinical practice quickly for our patients.

BK – Thank you, so much, for what you're doing.

TM – No problem. Pleasure.