



## ASH 2017 Atlanta Dr. Adrian Wiestner on Combination Therapies for CLL

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

**Dr. Adrian Wiestner** – Hi. I'm Adrian Wiestner. I'm a physician at the National Institutes of Health, specializing in CLL.

**BK** - Dr. Wiestner, you've done a lot of research yourself, looking at different combinations of therapies for CLL. I wonder if some of the papers that you've heard so far at ASH got your attention... what you see is important, what you see is work that's left to be done.

**AW** - So, I think exciting really is the high rate of responses, and the very deep responses you can get with combination therapies, as reported in several papers... especially venetoclax with ibrutinib or venetoclax with antibody seems to really induce responses even better than what we had seen with chemo-immunotherapy. And what remains to be seen, I think, is, to some degree, the safety profile of those combinations... notably, we do get quite a bit of neutropenia... often

**BK** - So, neutropenia is low neutrophil count, and the neutrophils help fight off bacterial infections and other infections. Are we seeing infections with that too?

**AW** - Well, to some degree, yes. Some of the papers had maybe an increase in ... These are not randomized trials at this point, so you do see some infections. There was a case of aspergillosis here or there, so this is a fungus infection that's also associated often with low neutrophil counts.

**BK** - That's an opportunist infection like the HIV patients used to get, where your immune system is down, or your neutrophils are down.

**AW** - Your neutrophils are down... or you can see that with prednisone, with steroid therapy. So, there are something else here and there then maybe once that's a little broader... I'm not quite sure what the safety profile really is of longer-term therapy. I think that's, in some ways, the open question because the response rate... the depths of response or how low the CLL count really goes to undetectable levels... that's all very exciting.

**BK** - Now there are medications that hematologists can give... these growth factors. Do you think that's the answer? Is that going to solve the problem? Because you use those when you do traditional chemotherapy.

**AW** - So, the MD Anderson amended their study to incorporate the support with Neupogin... with this growth factor for the neutrophils. And that is only a recent change, but it seems like that will help prevent the neutropenia, yes.

**BK** - Do you see the future being a combination of these... I know this is speculative... a combination of these non-chemo drugs or do you think that there's still a role for a chemo-immunotherapy backbone, because Dr. Matt Davids presented some pretty impressive data on FCR adding ibrutinib in the 80% CR rates... complete remission rates. That was pretty impressive data.

**AW** - That is. That was six cycles of traditional-dosed FCR plus the ibrutinib. Again, the responses are actually very, very good. The tolerability of the regimen was the same as FCR. I think we will also have to face that maybe the long-term consequences of that regimen will be the same as FCR, and I'm one of the people who are concerned about the rate of two, three, maybe 5% of long-term bone marrow toxicity that can transform into a myeloid leukemia in its worst form, or just result in impaired formation of the neutrophils, platelets... so-called "myelodysplastic syndrome" (MDS). I don't know where we would set an acceptable level for that



toxicity. If you could get cured, but you have a 2% risk of actually having that serious complication within a few years... I think everybody needs to balance that risk for him, herself, but, I think we have to keep it in mind.

**BK** - Let me ask you a follow-up question on that because one of the other papers presented using less FCR... just three cycles. The question that I wanted to ask and didn't get to ask was, "Does that make a difference?" Do we know that these low-frequency, but very dangerous complications of chemo-immunotherapy are dose related or does it, if you get three dosages, are you less likely to get myelodysplastic syndrome than if you got six doses? Do we really know that or is that just our conjecture?

**AW** - I think we don't really know that, but I guess it is reasonable to think that you would at least halve the rate of that complication. One might even think that you'd reduce it even more than just half, because I think that there is some issue of the cumulative toxicity of repeated exposure to the FCR. And we know that a third of patients do not finish six cycles as planned, because of myeloid suppression. So, it seems like it does get more intense the more cycles you get. So conceivably, that will reduce that dangerous complication.

**BK** – Well coming back to where we started... the combinations without chemo... specifically venetoclax and ibrutinib or venetoclax with antibodies... I think that's pretty exciting, that efficacy data, and the safety will have to be looked at in bigger trials. Any final thoughts you wanted to share with the patient community about what you've heard about in terms of the combinations?

**AW** - I think we have to learn what are really the good combinations, so I think, what I've seen as really interesting combinations is venetoclax with an antibody, and ibrutinib together with venetoclax. I'm not so excited about ibrutinib with antibody.

**BK** - I agree.

**AW** – And some investigators are even changing ongoing clinical trials to remove the antibody from ibrutinib combination and put in venetoclax instead. I think there's still a learning curve how and what to combine to really get optimal results. I would make a little bit the case for the benefit, potentially, of long-term kinase inhibitor therapy, in the sense that this long-term therapy that is a little bit criticized for the need for continued therapy, also provides a continuous inhibition of the main driver of what happens in CLL, and that's B-cell receptor signaling. So, especially those patients who are in groups where this B-cell receptor signaling is very intense, I think long-term therapy with the kinase inhibitor may actually be able to suppress the clonal evolution we see in some patients that would lead to Richter's transformation or that leads to early relapse after treatment. So, I see the benefit of time-limited therapy with a combination regimen. If that leads to cure, wonderful! If it leads to regrowth of cells, then we're back to the question, "Would it be better to just turn that off?"

**BK** - The question that seemed to be raised by long-term therapy is that therapeutic pressure on the cancerous clone, leading it to mutate around the receptor site where the drug binds... and we've seen that develop. How do you balance that concern with the issue of keeping the cancer levels low?

**AW** - That is a very good question. And we know that patients do develop resistance, and in some cases, the CLL does develop resistance and escape from that inhibition, but the escape in some ways also tells us that's exactly what we need to inhibit, because the escape is reactivating the target of ibrutinib... reactivating BTK... reactivating the whole signaling process. In some ways, it tells us that that signaling process is really what's driving the evolution, and that will happen whether you are on treatment or not on treatment, because if you have a deep remission and your CLL regrows from that deep remission, that's millions of cell divisions. And that's where mutations come from... right?... from replicating the DNA to make new cells. Cell division is part of the evolution process.



**BK**- I always learn something, Dr. Wiestner. Thank you for your thoughtful answers. Thanks so much. Thanks for the research you're doing.

**BK** - Thanks.

**AW** - Thank you.