



ASH 2017: Professor Michael Hallek Molecular Evolution in CLL Transcription

Dr. Brian Koffman – Hi. Dr. Brian Koffman. I'm the founder and medical director of The CLL Society here at ASH 2017 in Atlanta, Georgia.

Professor Michael Hallek – My name is Michael Hallek. I'm from the University of Cologne and the chairman of the German CLL Study Group.

BK – Professor Hallek, I wish the CLL cancer would stay the same, but it's a moving target and it evolves over time. Our treatments are evolving too, but there was some new information on that molecular evolution of the CLL. Can you put that in a patient-friendly way so we can understand how that's important to us as patients and how it's important to you as a physician treating CLL?

MH – What we have learned in CLL is that it usually comes back. And this coming back was a phenomenon that we didn't really understand. Now we are starting to investigate the nature of the development of CLL by molecular tools, mostly sequencing. And we can see that ...

BK – So, sequencing is when you look at the ...

MH – ...the gene sequencing. So, we basically try to read, in the human genome, what gene is changed when a cancer comes back. So that's the “molecular evolution”, how it's called now. And so, there's only a limited set of genes that is usually important to drive this evolution. And they are called “driver mutations” because they push or drive this event. And we've learned over time, with elegant studies, particularly done at the MIT and Dana-Farber by Cathy Wu, that this is actually a very regular phenomenon in CLL. Now in terms of the novel therapies, there have been very elegant studies by the group at Ohio State, who could show that basically patients that are relapsing are developing these resistance mutations much earlier than they are clinically visible... sometimes months ahead... which is a frequent finding. Sometimes they are actually even preexisting. They exist when you start your therapy and then the selective pressure hits on the tumor cell and kills all the cells that are nonresistant, and the resistant cells remain. Now you can learn how to prevent it by simply adding something in combination and try to get rid of that resistance mutation. There's a been a new abstract here by our own group now on venetoclax, because we have learned how it works in ibrutinib resistance. There is a mutation in this pathway, or even in the target molecule BTK, preventing the action of ibrutinib on BTK... on the target. So that is causing the resistance for ibrutinib, and as I said before, it comes earlier. For venetoclax, it was totally unknown, but we also see resistance patterns in patients having relapses. So now here our group has presented the first patients with refractory disease... so, refractory to venetoclax... and we found that, unlike in ibrutinib resistance, there is a multitude of different mutations that come and develop and predefine transformation to Richter's or predefine resistance. Some of the genes are targetable. So, we have found one RAF mutation that could be targeted with a RAF inhibitor. In another case, we found amplification of PD-L1, which could be targeted by checkpoint inhibition. So, very interesting findings, and I think we will learn to exploit this molecular evolution for therapeutic purposes. So venetoclax, much more work needs to be done, but it's interesting as well, we did not find any mutation on targets. So venetoclax is, as you know, inhibiting BCL-2. It's a BH3 mimetic, inhibiting the action of BCL-2, a pro-apoptotic molecule that is actually preventing apoptosis. And the sequencing effort has not identified a single aberration on targets. So somehow ...

BK – So, it's not the binding like it is with ibrutinib?

MH – Absolutely. It's not the binding of venetoclax to this molecule, nor the direct interaction of some kind of ... It is much more indirect, creating a multitude of different mutations around that BCL-2 pathway that are



leading to resistance in these cases. And we could show also, in additional experiments, that when you added RAF inhibitor, you can actually overcome the resistance in vitro to venetoclax resistance. So, here we are beginning to learn how this resistance is coming, but in any case, the study of this molecular evolution allows us to now describe how these resistance mechanisms work. So, it's a little bit like with antibiotics, where we have learned in medicine decades ago that with prolonged treatment of one agent, you create bacteria that are getting resistant to the antibiotic therapy. And in tumor biology, or in CLL now, we are exactly at this same step. So, we are learning from failures, and we are learning very quickly.

BK – This is very exciting, and I know it's very new, the venetoclax resistance. I mean most of this information is a year old or so and it's going ...

MH – Yeah, even not half a year old... unpublished mostly.

BK – So... very exciting and I think very clinically important for patients. Any final thoughts on this area of clonal evolution or molecular evolution that you think patients should know about?

MH – So, I would say that if a patient has to face a situation where relapse is occurring under targeted therapy, he could entertain a dialogue with his doctor about a potential screening for mechanisms of resistance. In some of the therapies, including in, above all, in ibrutinib-treated patients, we now know that we can describe these mutations and therefore, they are meaningful because at this point you have to consider getting alternatives, or combinations, or changing therapy, and this is very helpful information for the doctors and for the patients. I think for the rest, it is probably at the moment in a very fast development and is not altering the standard of care, but I am relatively confident that in a year or two from now, we will use the information to guide therapies for the other drugs like venetoclax, idelalisib, and so on.

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

MH – You're very welcome.