



Transcription: iwCLL 2017: Dr. Pagel on PD-1 Inhibitors for Richter's Transformation in CLL

Brian Koffman, MD – Hi. Brian Koffman, a family doctor and CLL patient here at iwCLL in Manhattan, New York.

John Pagel, MD, PhD – Hi, I'm John Pagel. I'm a CLL Researcher and clinician and I'm in Seattle, Washington, Swedish Cancer Institute.

BK – One of the big unmet needs in CLL is Richter's Transformation and there's been some new, exciting research going on out there, and I know that you're familiar with this stuff. Dr. Pagel, can you share some of that with us?

JP – You bet. Well, Richter Transformation, as you know Brian, is an aggressive transition or switch or again transformation from CLL. Typically, it goes to what we call a diffused large-cell lymphoma that can behave very aggressively. And we've struggled with how to take care of patients with Richter's Transformation. Doesn't happen often, maybe 10% of the time, which is not insignificant. But the problem has been that we have limited tools in our tool box to approach patients with Richter. We know that the data is really not incredibly impressive with the use of BTK inhibitors, like ibrutinib in Richter Transformation. But now, at least two groups, the MD Anderson Group in Houston, as well as the Mayo Clinic Group in Rochester, Minnesota have explored the use of PD-1 inhibitors for patients with Richter Transformation.

BK – So let me stop you there. What's a PD-1 inhibitor?

JP – Yeah, PD-1 inhibitor. You also hear it called “checkpoint inhibitor”. These are antibodies just like rituximab or obinutuzumab, antibodies that the CLL community knows well. But these are antibodies that target a receptor on the surface of the cell called PD-1. Now, what PD-1 does is, it actually is used to interact to a ligand on T-cells and actually send a signal to the T-cell, the powerful immune system cell, that T-cell. That signal is to tell it to be turned off. Why would this happen in our body? Why would we want to turn off T-cells? Well, we have to keep things under control. We have to check these things. We have to, it's like a check and balance. We don't want T-cells to be doing crazy things, attacking our own tissues. So, we have these mechanisms to put the brakes on T-cells. But, unfortunately, when we put the brakes on T-cells, they're not finding the malignant CLL cell, or the Richter cell, and they're not killing those cells. We know that T-cells are particularly, in fact, probably the most powerful part of our immune system for controlling cancer. So, if we can take an antibody and block this interaction between the PD-1 and its ligand and if that interaction is blocked, we're not turning off the T-cells. In fact, we're taking our foot off of the brake of the T-cells and allowing those T-cells then to find the malignant cell, the Richter cell, and actually to eradicate it and kill it. So, very importantly, the Mayo Clinic Group has just now published a brief exploration into treating patients with Richter Transformation with PD-1 inhibitors and shown that, not only can you get responses in these patients, but you can get complete remissions in these patients, that can be relatively durable and provide benefit to patients. It's not going to be the end. We need to



think about combinations and maybe this is a way to get people to more aggressive treatments that might be curative: allogeneic transplant or chimeric antigen receptor t-cell (CAR-T) therapy. But, certainly an exciting start for us.

BK – The trial at MD Anderson with Nitin Jain combined ibrutinib with a PD-1 inhibitor. At Mayo, did they use that same model?

JP – They did not. And I think, and I just alluded to this, it's really combinations of drugs that are going to be critically important. It's not just a PD-1 inhibitor. And the reason for that, is that, if you remember, that Richter Transformation evolves out of CLL. The underlying CLL is still present and, actually, PD-1 inhibitors don't work in just regular old garden variety CLL. So, if you're taking care of the Richter cell with a PD-1 inhibitor you still need some other agent to, hopefully, control the CLL and keep that in check, and so combinations, like with ibrutinib, make a lot of sense. And I think the more combinations we could have in this difficult situation, the better.

BK – So, this can knock down the disease. I've had personal experience with a fellow CLL patient who's gone through this therapy successfully and then went on to a successful allogeneic stem cell transplant where they harvested somebody else's stem cells and used that other person's immune system to wipe out any remnants. Is that part of the future that you see that maybe this is the first step and then you have to consolidate this with a transplant or you mentioned CAR-T?

JP – I think that's where we're at now. We don't believe that PD-1 inhibitors will provide long-term survival benefits. These patients that are in the Mayo's trial that I just alluded to, recently published, they do relapse. But at least this gives us a chance to control disease and get to something like an allogeneic transplant or CAR-T cell therapy. But, hopefully, what we learn, I guess I'd say two things: Number one, hopefully, we can learn that some combinations, in different ways of attacking Richter Transformation, may keep us from having to do transplants. And maybe if we can continue to learn a lot about the biology of this transformation, hopefully, our ultimate goal is to keep it from happening.

BK – Alright. Well, Dr. Pagel, thank you for the research you're doing and thank you for the care that you're taking the patients. Thank you.

JP – My pleasure Brian. Thank you.