



ASH 2016: Professor John Seymour on Using Venetoclax in Combination to Treat CLL Transcript

Dr. Brian Koffman - Hi, Dr. Brian Koffman, I'm a family doctor and CLL patient here in the last hours of the American Society of Hematology, ASH 2016 meeting in San Diego.

Dr. John Seymour - Hi, I'm John Seymour from the Peter MacCallum Cancer Center in Melbourne, Australia.

BK - Melbourne was the birthplace of Venetoclax, ABT199, and we've seen that develop and now be approved, at least in the USA. For the first time we're looking at some data being published on Venetoclax in combination with other drugs. They looked hard at the safety, a little, numbers were small so efficacy is hard to comment on, but could you share what your take is, having watched your baby grown up a little bit, and seeing how it's doing playing with others.

JS – Yes. Yes. So Venetoclax is a single agent. Andrew Roberts has published that data in the New England Journal. So great to see that getting a high profile. Clearly the drug is very effective, but as always, we are wanting to optimize and enhance that. So as a single agent the complete remission rate with Venetoclax is 20%, which is, of the new targeted drugs, the highest complete remission rate as a single agent. So we're beginning from a high base, but we want more. There's good data now with safety and effectiveness together with Rituximab, where the complete remission rate is now up to 51% in the relapsed setting.

BK - And Rituximab is a long-standing monoclonal antibody that's been used in all kinds of lymphoma and in CLL and has really enhanced the quality of almost everything else it's been joined with, yeah?

JS - Correct. There's very clear data that when combined with other agents, chemotherapy agents, a new antibody, obinutuzumab, (In the US, it has the trade name Gazyva, and used to be called GA101.) or Gazyva, is a more effective antibody against CLL than Rituximab. Inevitably and naturally, then, the desire to add obinutuzumab, the more effective antibody, to Venetoclax was clear. But as with all of these things, we need to be conscious of toxicity. One of the concerns, a very valid, real and manifest concern with Venetoclax is the risk of Tumor Lysis Syndrome: rapid, very effective cell killing with leading to chemical imbalances. Obinutuzumab (Gazyva) has a similar risk and also has a risk of infusion reactions, chills, fevers, shakes, sometimes shortness of breath and low oxygen levels with the first infusion. So, there was appropriate caution and care in combining the two. But both the US study as well as a German cooperative group study and a study in the UK have shown safety from combining the two together. Where the antibody begins first, the infusion reactions are dealt with, and then after a few weeks, the gradual ramp up of Venetoclax is begun. So, we now have very good information that, when done with care, with vigilance, and with attention to detail, that combination can be given safely.



BK - And wasn't one of the rationales that if the antibody is given first, it would knock down the tumor, and we know this Tumor Lysis is based on the amount of cancer that's killed, so if there's less cancer, or lower tumor burden, then there's a lower risk. I know that you stratify your patients and whether they're high risk or low risk for Tumor Lysis Syndrome. So wasn't that one of the hopes, that by giving obinutuzumab early, you could lower the risk of Tumor Lysis later?

JS - Yes, correct. That's very accurately the rationale. Now, obinutuzumab rapidly clears the peripheral blood, but the main bulk of disease is present within lymph nodes. At the early time point, there isn't a dramatic reduction in the bulk in the lymph nodes. There's some improvement, but it's not profound. Now the flip side, the converse element is that a CLL cell that has obinutuzumab on its surface has received, let's call it a flesh wound, and it's closer to dying. So, at a given dose of Venetoclax, there may be greater cell killing when the--

BK - Ah, I see where you're going with this.

JS - ... when the CLL has the antibody present.

BK - So, there is potentially a greater risk of Tumor Lysis if these cells already have a mortal wound that takes them one step closer to death. So, we can't automatically apply the same predictors for Tumor Lysis Syndrome when Venetoclax is given as a single agent to the situation where a patient's CLL may be partially killed ...

BK - I know, it's more on the tipping point of being able to...

JS - That's a good analogy.

BK - ... to be pushed over into cell death.

JS - Yes, so my caution here is that for example, let's say, because the predictors for Tumor Lysis Syndrome with Venetoclax as a single agent were peripheral blood lymphocyte count greater than 25,000, or lymph nodes greater than 10 cm in diameter. So, let's say you've received your Gazyva and you're no longer in that high-risk group. It would be reckless to assume that you are no longer at risk for Tumor Lysis Syndrome because the playing field, the parameters are different. So, caution and vigilance still needs to be used.

BK - Thank you so much for that, I think that's a really important point. What kind of safety, did we find any new safety signals, putting these together? Were there any concerns, other than what we already knew about the two drugs, when they dance by themselves?

JS - Yeah, no, no clear or new safety signals. We will need to watch neutrophil count. Both of these--

BK - Those are a different white blood cell that is not part of the CLL disease, but can be an innocent bystander from these medications.

JS - And is important for protecting against infection. In the early months of treatment with Venetoclax, about one-third of patients will have a low neutrophil count. When used on its own,



low risk of infection. But about 15% of patients, when treated with Gazyva, will also have a low neutrophil count. Again, on its own, low risk of infection. But we need to check carefully to see whether we may have additional risks of infection with the two. So still early days, but very encouraging that these can be given safely. Very, very small numbers of patients, but Barbara Eichorst from the German group, presented information on the peripheral blood, not bone marrow, where 14 out of the 14 patients treated with this combination had achieved no detectable minimal residual disease by this flow cytometry assay at, I believe it was week twelve, so quite early in the treatment, three months into the combination treatment.

BK - That's certainly, again, early news, but that's amazingly exciting.

JS - Very encouraging.

BK - And I'm going to push you a little bit because Jeff Jones presented some data, adding ibrutinib to those. And if you could comment a little bit about any safety or maybe just take us through that trial a little bit, because it was a different group of patients who were being looked at, and safety and efficacy data, your take on that.

JS - Wonderful work from Ohio State, and adding in a third ingredient. So, we talked about the anti-CD20 antibody. We know about Venetoclax and this was adding a third component, ibrutinib. There's very good information that ibrutinib pushes CLL cells out from the tissue compartments, out from the lymph nodes, out from the bone marrow. It's becoming quite clear that those locations are not simply a passive storage site. They're locations that nurture, stimulate and protect the CLL cells from killing from a number of treatments, antibody treatments, and also, it's emerging probably to Venetoclax in drugs that act through apoptosis. So, this is very strongly appealing, that we're adding cell-killing signals that work in different ways, but we're also removing protective shields from these CLL cells that we predict will make them more vulnerable to killing by these agents. Again, very early information, and again, only about a dozen patients treated, so we cannot draw any conclusions about effectiveness. But it showed the principle that these three drugs, again, with careful sequencing, so they don't all begin at once, and with careful monitoring, can be delivered safely. So, gives a platform to then allow comparison of these approaches, which both the German group and Peter Hillman in the UK are doing, and of course, we then want to see whether the effectiveness in the real world in a patient will fulfill what our experimental studies suggest should be the most effective combination of drugs that we have available.

BK - Any final thoughts on these combinations and what you would say to patients from ASH 2016?

JS - It's an incredibly exciting and optimistic time. The tools that we have available are unprecedented in their precision and unprecedented in their capacity to target key pathways in CLL. We know that from other diseases, that when we acquire agents that have this degree of effectiveness on their own, the combinations have the potential for cure. I believe that that's a very realistic goal to be pursuing in CLL. And the other very appealing element for patients, for



the community, and for payers is that, if this potential is fulfilled, these combinations should be effective in a time-limited delivery. Now, whether that ends up being two years or 18 months, or three years, of course we need to do the trials. But the paradigm of moving away from an old drug suppressing the disease and used forever, is one of the other appeals of these highly potent combinations.

BK - I'm with you with that. Dr. Seymour. Thanks so much for the research that you're doing and have done and what you've done for the CLL community. Not just in Australia, but around the world. Thank you so much.

JS - Thank you. A pleasure.