



ASH 2017: Dr. Ian Flinn on Venetoclax and Obinutuzumab for Frontline Treatment of CLL

Dr. Brian Koffman – Hi, Dr. Brian Koffman, founder and the Medical Director of the CLL Society, here on the last day of ASH 2017 in Atlanta, Georgia.

Dr. Ian Flinn – I'm Dr. Ian Flinn. I'm the Director of the Blood Cancer Research Program at the Sarah Cannon Research Institute in Nashville, Tennessee.

BK – Dr. Flynn, you presented some very exciting data on two of the most powerful drugs, in my opinion, for treating CLL: Venetoclax and Obinutuzumab. Can you talk to us a little bit about that research and what's got you excited, and help patients understand why you think this might be an important combination in the future?

IF – Sure, I'm glad you think of it as exciting, because I really thought it was exciting, as well. I mean, this was a study looking at the combination of Venetoclax... so Venetoclax, being this BCL2 inhibitor that...

BK – Which helps cells commit suicide, essentially.

IF – Exactly. It's now approved in the United States for relapsed patients that have... you know, second or third line... on patients that have had... patients with 17p deletion. But it's a very powerful tool. Obinutuzumab... the other name for it is Gazyva... this is a drug that's approved for the front-line treatment of CLL in combination with Chlorambucil. We think it's a better anti-CD20 monoclonal antibody.

BK – And it's in the same class as Rituximab, or Ofatumumab, but it's a kind of a third generation that seems to have a little extra oomph to it.

IF – You summarized that well. That's right. So-called glycoengineered to be... more efficacy. And we know that, from clinical trials, that it looks like it is a better antibody in CLL. So, this study combined these two powerful agents together. One of the things people worry about with Venetoclax is tumor lysis syndrome. And we always think about killing off CLL cells quickly seems like it should be a good thing. But it can cause some problems... problems with patients' electrolytes, and it can be a life-threatening issue if you get very significant tumor lysis syndrome.

BK – Right. It can affect the kidney function, and, in worse cases, if too much of the stuff that's supposed to stay inside the cells, but when the cells are killed, spills out into the blood, the potassium levels, the uric acid levels can damage the kidneys and even damage the heart.

IF – Exactly. And so, one of the important findings of the study was that we looked at two different schedules of giving the drugs together. First, we looked at giving Venetoclax--

BK – Remind me. I'm sorry to interrupt. Remind me which population you're treating here.



IF – So, we previously looked at the combination in relapsed and refractory patients with CLL...patients that had already been previously treated. In this presentation, this year, we looked at patients who had no prior therapy.

BK – Okay.

IF – So, we found one, that we examined two schedules, but we ultimately chose a schedule where we were giving the Obinutuzumab, the CD20 monoclonal antibody, first... getting some of the white count down... getting some lymph nodes to shrink a little bit... then adding in the Venetoclax. And with that combination, there was no synergistic toxicity, and there was no tumor lysis syndrome, at least no clinical evidence of tumor lysis syndrome. So, it was a very safe combination. That's important, but it's important that we also had increased efficacy. And so, we saw (that) everybody on this regimen responded. Right? And more than 2/3 of patients, nearly 3/4 of patients actually, achieved a complete remission. So that was pretty exciting too. That, combined with... we looked at what's called minimal residual disease. In this case, what we're looking for is just the rare cell in either the blood or in the bone marrow.

BK – Less than one in 10,000.

IF – Right. Right. less than one in 10,000 leukocytes (white blood cells). And everybody became MRD negative, and was disease negative in the blood.

BK – Everybody?

IF – Every patient, at some point

BK – Wow!

IF – And then the other thing that was interesting is that that persisted. So, we looked at various time points after giving the Obinutuzumab, and we found that at three months after the last dose of Obinutuzumab, and nine months after it, 90% of patients were still MRD negative. And then at a year after, it was probably more than 70%. We were missing some samples, but even with all the missing samples, it was more than 70%.

BK – Wow!

IF – And then some people wonder, "Well, maybe the blood isn't as important as the bone marrow." And so, we looked at the bone marrow, as well. In this case, 3/4 of the patients were MRD negative in the bone marrow at some point. And it turns out, even in the patients... the small number of patients that were not complete remission patients, but they were at partial remissions, it really didn't matter. They were just as likely to be MRD negative as the patients that were in complete remission. Kind of makes us wonder whether our response criteria is as accurate as maybe they could be.

BK – And when you say they're partial remission, that's usually because, on imaging, you see a lymph node that's slightly bigger, but that, from what I understand, could be just scar tissue... fibrotic changes... and the node just hasn't shrunk from five centimeters back down to less than 1.5 centimeters.



IF – Exactly.

BK – There may be no cancer left in it, it just hasn't gone back to normal size.

IF – Exactly. Four of the seven patients that were MRD negative, but were considered partial remissions, that was the case. They otherwise met all criteria for a complete remission. The other thing I think that's exciting about this regimen is that it's basically a fixed-duration, one-year treatment. There are some patients that went on to receive a little bit more Venetoclax because it allowed patients to go on afterwards, but you know I think that's really where we need to be in the treatment with these novel agents in the front-line therapy. Hopefully being able to get people in such a deep remission that we can actually get people off of therapies.

BK – Do you have any data about how durable the responses are... I know it's very early... in the people that did stop after a year?

IF – Right. So, you're right. It is early, but we have about an 18-month follow-up on patients, and in that 18 months of follow up, more than 90% of patients were still in remission.

BK – Wow! What about increased toxicities? I'm thinking (of) the risk of infection. Venetoclax reduces your neutrophils, which are the white blood cells that help fight off infections, bacterial infections particularly, and so does Obinutuzumab, (Gazyva). So, did you see this, what we call neutropenia, of these low neutrophil counts in patients and was that an issue, and did you have to intervene to help those patients?

IF – Yeah. We did see neutropenia. So, about half of patients developed what's called grade three or four neutropenia, when it gets to the point that we start worrying about it. And in many patients, we had to hold for a period of time, allow their counts to come back up. But it didn't look like we had synergistic toxicity, synergistic lowering of the counts. It looked like, consistent with what we would see with two individual therapies. And so, I think that was pretty gratifying.

BK – Increased risk of infections, or any other troubling signals that you saw in terms of the adverse events?

IF – No, it really didn't look like that. I think it was right in line with what we'd expect of the individual agents, so that was particularly good news.

BK – Well, this is pretty exciting. I mean those response rates are amazing, of complete remissions and MRD negativity. Any thoughts about how you see this evolving in the future and what patients can look forward to in terms of this combination?

IF – So, this combination is currently being studied in a large trial in Germany. And those results will probably come out in a year or two. But I think that it... I think it's very likely to make its way forward into the front-line therapy for patients with CLL.

BK – Dr. Flinn, thanks so much for what you're doing.

IF – My pleasure. My pleasure.

BK – Thank you. Thanks.