ASH 2017: Dr. Brander on Umbralisib (TGR-1202) in CLL - Transcription

Dr. Brian Koffman – Hi. I'm Dr. Brian Koffman. I'm a family doctor and a CLL patient myself and a founder and the medical director of the CLL Society, here at the first day of ASH 2017 in snowy Atlanta, Georgia.

Dr. Danielle Brander – Hi, and I'm Dr. Danielle Brander. I'm at Duke University where I'm a CLL expert.

BK – Dr. Brander, you've been involved in some of the research of a new molecule to help CLL. It's not approved yet, umbralisib. Can you tell us a little bit about that and what your experience is with that?

DB – Sure. So, umbralisib, which some patients that participated in trials might know it by its previous name which was TGR-1202, has been in clinical trials with us since the Phase I/II Study, so for when it was first being tested for the dose. And now has been moving forward in CLL, by itself and in combination in Phase II and Phase III studies. So, I think the big thing that's come out of it is that umbralisib is a PI3 kinase delta inhibitor, meaning it targets that important protein inside of the CLL cells.

BK – And, let me stop you there. What does PI3 kinase do, and why is that important in stopping CLL from progressing?

DB – Sure. So, what's really important in CLL and some other lymphomas is for the cell to get signals from the outside that tell it to continue to grow and survive and live. And so PI3 kinase is one of those inside of the cell that's important. And so, when you block that, the signaling stops. It can't take the signals from the outside of the cell that CLL normally depends on to continue to live and survive and eventually grow.

BK – So, when you block that signal, the CLL cell loses its purpose in life, which is to communicate with other cells.

DB – Correct. And so, one of the things is it can't go to what I call the hiding places, the lymph nodes, the spleen, the bone marrow, as easily. It's pushed out in the blood, and eventually it doesn't have the signals it needs to survive.

BK – So umbralisib blocks that, so it's going to slow the growth of CLL and kill the CLL cells off.

DB – That's correct.

BK – And idelalisib does the same, but there's been some toxicity issues with idelalisib.

DB – Correct. And that's actually what I was going to point out, t,,hat some patients will have been familiar with idelalisib which targets the same isoform of PI3 kinase, which is PI3 kinase delta. However, when we talk about what a drug or a treatment's purpose is to block, often it not only blocks that but probably some other proteins. We call that “off-target effects”. And sometimes that off-target effect has side effects. And so, we know blocking PI3 kinase delta is very important in patients when idelalisib had very promising results in terms of responses. Unfortunately, because of the side effects, many of them immune-mediated, it was very difficult for patients to stay on that drug long term and therefore get the benefits long term.

BK – And is the picture different with umbralisib?

DB – Exactly. So, umbralisib is a next-generation PI3 kinase delta inhibitor. And it also is felt in some of the animal studies to target certain other proteins that will help with keeping the immune response from getting out of control. And so, therefore, you cut down on the side effects. And there're a couple posters at ASH and presentations where they've pooled all the studies using umbralisib or TGR-1202 to look at safety and efficacy. And what we see is that it works really well, but it doesn't have the same side effects. And now

hundreds of patients that have used the drug, either as their second or third treatment, or even as their first treatment.

BK – Even as their first treatment? Because weren't there bigger problems with idelalisib front line, and then in relapsed refractory? And I always thought that was because the immune system was more intact and more aggressive.

DB – Exactly.

BK – But you're not seeing that with umbralisib?

DB – Correct. So that's again why we think that it's not hitting some of the same-- it's off-target effects, and maybe also what it also does is important in keeping the immune system in check. And I would say in addition to allowing patients to stay on the medication longer and get the benefit, one of the really good benefits of the toxicity is that it allows us potentially to combine it with more medications. And, I think one of the promising things with what we'll see at ASH this year with CLL is a lot of these combinations of promising drugs that are getting even better responses for patients, and then hopefully that will have less resistance.

BK – I'm going to, push a little bit on the adverse events that I know about with idelalisib, and that was colitis. Does that seem to be less, the inflammation of the bowel?

DB – Yes.

BK – And the liver inflammation, or what we doctors call transaminitis, are we seeing less of that?

DB – That's correct.

BK – What about the pneumonia and the pneumonitises? Do we have any data on that?

DB – So, we're not seeing those at high rates, certainly not the high rates either with the idelalisib. And I think what's new and Dr. Matt Davids is presenting the integrative safety analysis for umbralisib, is that now patients have been on this medication longer. Because as you know with idelalisib, one of the stories that came out of that unfortunately, was that these side effects don't just happen when you're first starting the medicine, we actually worry about it later on after patients have been on six, seven, longer months. And so now that more patients have been on umbralisib for longer periods of time-- I think the longest patient from one of the first studies has been on several years, over three years-- that we have that longer-term follow-up, and it's continuing to look promising in terms of side effects. And like I mentioned, in addition to allowing patients then to stay on a medicine that gives them benefit, it means we can combine it with more. The very last thing I'll point out, as you might know, is that with these newer targeted drugs, sometimes some of the difficulty is that they interact with a lot of other medications. And umbralisib is somewhat unique in that is that it doesn't either activate or inhibit one of the key liver enzymes that can make it difficult to use with other medicines. So, there's really no drug-drug interactions we have to worry about as much with umbralisib, which allows us to combine it with a lot more medicines.

BK – Well, this is always very exciting.

DB – Yeah.

BK – And as a patient, I'm always looking for more options. So, to have another option in this critical pathway and to be able to use it in combinations-- because I see combinations as the future.

DB – Exactly.

BK – Yeah.

DB – Yeah.

BK – Any final thoughts, Dr. Brander?

DB – Well, I think as you just ended very nicely is that it's great to have more options because as those of us that focus on helping patients with CLL, each patient really is different. Their other medical problems they might be having are different. The medicines they're on might be different. And even though rates of what we call intolerance, or not tolerating some of these drugs might be low, it's important if it's your patient sitting in front of you. And so, the more options, I think, the better, both to get better responses in combination and also so that patients aren't having to go through side effects that another medication might not overall overlap with and be able to give them the same benefit.

BK – Dr. Brander, thanks so much for what you're doing for the CLL community.

DB – Thank you very much.

BK – Thanks.

DB – Thank you.