# CLL Global Research Foundation Virtual Town Hall | January 30, 2025

Jeff Folloder: Hello, and welcome. I'm Jeff Folloder. Thank you for joining us for our very first CLL Global Research Foundation virtual town hall meeting of 2025. Today, we're going to hear about research and treatment updates from leading CLL experts, including promising clinical trial developments. And as usual, we're putting aside 30 minutes of the town hall to answer your questions.

As I mentioned, my name is Jeff Folloder, and I'm going to be your host. I am a CLL patient, and I'm heading towards year 15 of living an excellent life with CLL. The reason why I'm living that excellent life is because of the work of CLL Global Research Foundation. We are doing wonderful things to make sure that all patients have a better shot at living a great life.

Before we dive in, let's review just a few housekeeping items. We have received many questions for our experts. We will do our very best to get as many of those answered as possible.

Please keep in mind that we cannot answer specific questions about your medical treatment. Those should be discussed with your own health care team. You're also going to receive a survey following this town hall. Please, please, please share your experience with us so that we can continue to improve and produce programs that best serve you, our audience.

Now it's time to meet our experts. I'd like to introduce a familiar face to many of you, Dr. William Wierda. Dr. Wierda is the president and CEO of CLL Global, and the executive medical director at the University of Texas MD Anderson Cancer Center. Wow, that was a lot to say. Dr. Wierda, welcome. Do you have some opening words for our audience?

Dr. William Wierda: Good afternoon, or evening, or whatever time of day it is. Morning for Dr. Tam. I'm happy to be here. And thank you, Jeff, for your willingness to participate in this activity and support our efforts to the foundation. The foundation continues to be vibrant and engaged in important research for our patients with CLL, with the goal of improving and curing the disease. So, thanks everyone for coming.

Jeff Folloder: Fantastic. And we're also joined by Dr. Constantine Tam. Dr. Tam, can you introduce yourself and tell us about your role in caring for CLL patients?

Prof. Constantine Tam: Thank you, Jeff. Thank you, Bill. It's a real pleasure. I am a CLL doctor from Australia. And I was very fortunate to have benefited from the mentorship of Professor Michael Keating and Dr. Bill Wierda, who taught me everything I need to know about CLL.

And I also want to say that the CLL Research Foundation is really a unique organization. I would still remember when I first saw the concept explained to me by Professor Keating, where patients are fast tracking research in the targeted areas for the direct benefit of CLL patients.

I thought that was an amazing model. And I think the fact that we've made really some very important progress, which is directly relevant to the patient care, is testament to the success of these foundations. So, thank you for the invitation to be here today. It's been a real pleasure.

Jeff Folloder: Fantastic. I can echo your sentiments about Dr. Keating and Dr. Wierda, because both of those gentlemen have been instrumental in my care. So, I take that just a bit personally. Thank you both for being here today. What people want to know is about what's happening, what's new. So, let's move on and learn about the emerging research and treatment developments.

Just a little over a month ago, blood cancer experts from around the world met in San Diego for the annual American Society of Hematology meeting, or what we call ASH. And at this meeting, researchers reviewed CLL research, treatment, and technology advances. Dr. Wierda, are there highlights from the meeting that you would like to share with our viewers?

Dr. William Wierda: I would love to. This is one of my sort of favorite things to do, and that's just to highlight and touch on some of the important abstracts or presentations that were made at our meetings. Typically, our foundation town hall that we're having right now, this time of year, is the opportunity to summarize the ASH results, because the meeting is in December.

And then the other meeting that we have later on in the year is the opportunity to review data that's presented at the

European Hematology Association. And the American Society of Clinical Oncology meeting, as well as some others. And I have a list of the ones that we're looking forward to the later on this year as the last slide. But this slide summarizes the presentations that were made that I think were important and relevant for our patients with CLL.

The ones in black are for previously untreated patients, and the ones in blue are for previously treated patients. So, I'm going to walk through each of these and just briefly give you a flavor of what was presented and discussed at ASH, and some of the very important and noted presentations and findings.

So, the first one there is a trial that we've been anticipating. It's what's called a Phase III randomized trial, where patients who need treatment are assigned to one of three different treatments on this trial. Acalabrutinib (Calquence) plus venetoclax (Venclexta) or acalabrutinib plus venetoclax plus obinutuzumab (Gazyva). Or a chemotherapy-based treatment, either FCR or bendamustine-rituximab (Treanda-Rituxan).

And the goal of this trial was to identify outcomes for patients with each of those treatments. Now, those are time limited therapies or fixed duration treatment. The acalabrutinib-based treatment was a year of treatment, and the chemotherapy was the standard six cycles or six months of treatment.

That trial was a positive trial, showing improved what's called progression-free survival. You can think of it also as the duration of response or showing that that was improved for patients who received either acalabrutinib-venetoclax or acalabrutinib-venetoclax plus obinutuzumab over chemotherapy. And so, here we have another clinical trial done with targeted therapy in a randomized fashion demonstrating improved outcomes for the targeted therapy over chemotherapy. And the treatment was well-tolerated.

Now, one of the things that we saw with ASH this year was some of the complications of the pandemic. And those were patients who had developed COVID, and some of whom had died on these trials as a result of the COVID while they were on treatment. So, there was a fair number of patients on the trial that did have COVID and/or succumbed to the COVID infection. It was generally higher for patients who received the CD20 monoclonal antibody.

And we know that's a risk. We knew that at the time. Many of us were avoiding obinutuzumab or rituximab during the pandemic in patients who hadn't been vaccinated. Because we knew that there was an increased risk for severe infections and problem. But this trial was a positive trial. We're anticipating its inclusion in the NCCN guidelines. We're anticipating its approval by the FDA. It being AV or AVO.

The next trial was a trial that we've been doing at MD Anderson. Also targeted therapy. This is a Phase II trial, so all patients received the same treatment on this trial. They were all previously untreated. And they received a combination of pirtobrutinib (Jaypirca), Venclexta, and obinutuzumab. And with that combination – which is a year of treatment, six cycles or six months of obinutuzumab, and a year of pirto and venetoclax – we're seen extremely high remission rates and very high rates of undetectable MRD with that combination.

Now, that's not a comparative trial. We do tend to make cross-trial comparisons. But it gives us an idea about the potency and the activity of that combination. I would anticipate at some point it will be studied in a Phase III trial.

The next trial, which is the third one on the list, is a trial that was presented by Jake Sumarai, which is a combination of zanubrutinib (Brukinsa) plus sonrotoclax (BGB-11417). Now, sonrotoclax is a new BCL-2 inhibitor. It's not yet approved by the FDA. It's being developed by Beijing. And this combination has been studied in previously treated patients and also previously untreated patients. And this was an untreated cohort who received zanu plus sonrotoclax, and demonstrated significant activity, and that this was a well-tolerated combination.

And there's a large, randomized trial that's looking at this combination that's ongoing and enrolling. Actually, I think it's just recently completed enrollment. So, we'll hear about data from that randomized trial.

And then the last of the untreated trials was a trial that we presented. It was in Anderson. A trial of venetoclax plus obinutuzumab plus atezolizumab (Tecentriq). This was a Phase II trial. Atezolizumab is a checkpoint inhibitor. And we were looking to see if we can improve outcomes with the addition of the checkpoint inhibitor. We saw very high

undetectable MRD rate. And these patients are doing very well, and we're continuing follow up on that trial.

Among the trials and data that was presented for previously treated patients, there's a lot of activity and a lot of interesting things going on in this space. The first was a Phase III randomized trial of pirtobrutinib, which is a noncovalent reversible BTK inhibitor versus idelalisib (Zydelig) plus rituximab or bendamustine plus rituximab. That was a positive trial that showed improved outcomes for previously treated patients who received pirtobrutinib as their next therapy over idelalisib or rituximab.

Now, all of these patients enrolled on the trial had to have had a prior covalent BTK inhibitor. And so, this was a trial looking at patients who had been previously treated with a BTK inhibitor, a covalent BTK inhibitor. The activity and efficacy of those treatments among those patients.

The next study was an update that I presented, which was the liso-cel plus ibrutinib (Imbruvica). We've many times presented in the past liso-cel as a single agent. Now this is the CD19 CAR T-cell therapy. And this trial looked at liso-cel combined with ibrutinib. And we reported higher complete remission rate with that combination compared to liso-cel by itself on the TRANSCEND CLL 004 trial.

The next two abstracts that you see there are new drugs that are in development Phase I clinical trials. These are a category of drugs called degraders. There are more than just those two. These molecules are small molecules that are taken orally, and they induce degradation of BTK in the leukemia cells. And in doing that, they cause the CLL cells to die.

And so, these were two abstracts, early clinical trials looking at tolerability, and toxicity, and activity of these two agents, NX-5948 and the Beijing BGB-16673 compound. And we're very excited in seeing activity with those compounds.

And then finally, epcoritamab (Epkinly). We've heard about epcoritamab on the trial that was presented. This was an update. And they made some changes in terms of the premedication and to improve the tolerability of epcoritamab for CLL. It's also being studied in Richter transformation. And we've seen the abstract for Richter transformation presented recently also.

So, a lot of activity in previously treated patients. A lot of very exciting work and exciting agents that are – we look forward to moving forward in treatment and getting approval for our patients with CLL.

Jeff Folloder: Sounds very exciting. I'm very excited to hear that its duration is one of the premier issues. I know that when we move from traditional chemo to the next wave of treatment, people were worried about being on meds for the rest of their life. And it just does my heart well to know that we're looking at fixed duration.

So, thank you, Dr. Wierda. Dr. Tam, let's turn to you to hear your thoughts on the conference.

Prof. Constantine Tam: So, Dr. Wierda has really summarized the highlights of the conference. I just wanted to highlight, to get different angle, and just talk about – expand the way Dr. Wierda talked about the BTK degrader, and why that's such an important treatment.

So, this is a summary situation of a new area, which is basically BTK mutations. So, we know that patients who take the traditional BTK inhibitors – such as ibrutinib, zanubrutinib, or acalabrutinib – they respond well, but ultimately, they develop resistance. Usually due to a mutation where the drug binds. And that's where the new drugs like pirtobrutinib comes in, because it binds to different points. And it gives us a second opportunity to treat using the BTK pathway.

Now, we've now realized that while the cancer is quite clever, and while we can block the traditional points where the mutation occurs, but with the new drugs like pirtobrutinib, we're now getting multiple mutations in new areas. So, the BTK degraders are a really exciting new class of drugs, because the way they work is they actually destroy the BTK protein. So, where the cancer has a chance to mutate the protein to basically shake off our traditional drugs – including acalabrutinib and including pirtobrutinib – the degraders actually destroy the entire protein.

So, we think that this is exciting for two reasons. Firstly, it gives us a third opportunity to treat BTK. So, a patient can have now potentially three goals at treating the BTK pathway, and get an extended period of benefits from that treatment. And secondly, it also gives us a way to hopefully treat the BTK pathway with a reduced risk of resistance.

So, this is an active area of research, both worldwide. As Dr. Wierda mentioned, there are now two lead compounds in this area. And what's really exciting to me is that it worked when traditional BTK inhibitors have stopped working. So, they're clearly effective in patients with resistance.

And also, the fact that the side effects are in fact very mild. So, the side effects are exactly as expected for the traditional BTK drugs, showing that we can actually destroy the entire protein and get cancer control, but not induce any new side effects. So, that's a really exciting area for us.

Jeff Folloder: Fantastic. This is exciting stuff. There are options for when even the new treatments are failing. We're exploring new things. These are great overviews. I appreciate that very much. Dr. Tam, are there areas of CLL research that you in particular are involved in? What would you like to share about that ongoing work?

Prof. Constantine Tam: So, we have been very involved in the study that Dr. Wierda – well, actually, we are involved in the whole spectrum of new therapies for CLL. Including the next generation of BTK inhibitors, the combinations with sonrotoclax, as well as epcoritamab and CAR T cells. So, we're working on exactly the same areas as Dr. Wierda's group. And we're aligned because these are the most exciting, the most effective treatments that we have. So, we align pretty much our research direction very similar to that of our Houston colleagues. And it's…and probably the one thing that we have a special interest in is actually defining, in great detail, the mutational profile of our patients. So, we've had a tradition of looking very carefully at our patient's samples to try and find reasons for why they don't respond to drugs anymore.

And our group had been very fortunate in making discoveries about what the mutation that causes resistance to venetoclax. We're able to identify the new mutation that affects zanubrutinib. And we're now working on some of the mutations that affect our newest generation of drugs, including degraded. So, once we workout, how cancer has managed to evade our treatments, we can then develop a new therapy for it.

So, that's all I wrote. And I think it really emphasizes the global nature of CLL and advancement. That we can be on different ends of the world, and yet, we're providing best

therapies to our patients, and we are complementing our research step by step.

Jeff Folloder: It sounds like personalized medicine is the absolute rifle target for all of this, and I appreciate it. Dr. Wierda, I know that every time I see you in clinic, I ask the same question over again. "If I had to start treatment today, what would it be?" And it seems like over the years, every time I ask that question, I get a different answer because things are moving so fast. What are you working on?

Dr. William Wierda: So, my answer usually is a clinical trial. Now, I realize that not everybody has clinical trial options available to them. So, we dedicate a lot of time, and we have a lot of interest in developing our regimens and our clinical trial work in new combinations.

I mentioned the PVO trial, which is pirtobrutinib, a triplet that we're seeing very good activity with. There is some increased risk for infection and suppression of the normal marrow. But right now, that it looks to be like our most active and effective combination. Which has been well-tolerated across our patient population. We've recently expanded it to 120 patient trial. And currently working and thinking about, "Okay, what's the next thing that we're going to do? What do we want to study for previously untreated patients?"

And it's becoming more and more challenging, because we've done a great job in making progress. And it's the goal. The thought and the challenge is moving the undetectable MRD rate up above what it is now. And if you're starting at 90 percent, it's hard to improve on that. There is room for improvement, but – so, we struggle. And I work to think about, "What's the next advance? And how can we improve our outcomes for our patients with CLL?"

And I think because of the high MRD undetectable rates we're seeing, that we really have to pivot and think about cure. And that has to be the focus right now for our newer trials. Particularly for patients with high-risk features.

Jeff Folloder: You said the word that I was waiting to hear. The four-letter word called "cure". When I first started my CLL journey, that word was not part of the landscape. The general response was, "You may pass with this, but you may not pass from this." But now, more and more, we're hearing about the word "cure," and that just makes me feel really, really good.

Dr. Wierda, we're going to move on to audience questions in just a minute. Thank you for your thoughts, Dr. Tam. Thank you for your thoughts. To our participants in this program, I want to mention that if you missed anything presented by the panelists today, the slides, a replay of this town hall, all of this is going to be made available on the CLL Global website at CLLGlobal.org within just a few days.

This is the part where everybody that's watching us wants us to get to. There's a host of questions, so we're going to get to the Q&A. As I said at the beginning of the program, we have received many questions in advance, and we're going to try to get to as many of them as possible. We're going to start off with the questions that came in.

Let's see. Leanne wants to know, what percentage of patients stay in remission? She's 77. It's a good question to ask. How many of us are going to stick in remission? Dr. Wierda, you're up first.

Dr. William Wierda: That's a complicated question. I think you have to start out with the discussion that there are two strategies that you can take for treatment. One is a maintenance strategy. And you can achieve a remission with a maintenance strategy, but it's not deep enough to get you off treatment. But it is considered remission, and you stay on treatment. In that setting, with the data that we have currently available, the average duration that a drug like ibrutinib works as a maintenance is about nine years. And that's pretty good. And that's pretty good, especially since there are other options that we have available if that fails, if ibrutinib fails.

I expect that the outcomes will be even better with acalabrutinib and zanubrutinib, because they're better tolerated. And I think in general, patients probably fare better with those drugs than they have historically with ibrutinib.

The other strategy is fixed duration or time-limited therapy, where the goal is to get patients in a good deep remission, and have a period off treatment in remission. And then if the disease comes back, we can retreat with that same strategy. If patients have a very short remission or if they don't respond to the treatment in that setting, then we switch to a BTK inhibitor-based therapy. So, we can switch in that instance where we don't get long enough remission or we're not getting a remission with venetoclax-based therapy.

So, the time limited or fixed duration. The data that we have right now available is with the CLL-14 trial. That trial showed that the average duration of remission, or the median progression-free survival was overall six years. It's a bit shorter for patients who have an unmutated immunoglobulin gene. It's a bit shorter for patients who have 17p deletion.

But on average, the median progression-free survival is six years. That doesn't mean patients who have progression need treatment. So, the time to next treatment is longer. And again, as I said, if patients have their disease come back, it is a reasonable option to go back to venetoclax. We don't yet know what the average duration of remission is with our combined target therapies. Ibrutinib plus venetoclax, acalabrutinib plus venetoclax, or the triplets. I'm confident that it will be better than what we've seen with CLL-14.

So, it's a tough question. And, unfortunately, or, fortunately, it takes a long follow-up to have an understanding of what the remission duration is and how long these treatments are effective. But you can, as you can tell, it's a long time. And to the point where I think we have so many options and we have such effective therapy, that somebody who's over 65, even if they need treatment, their lifespan's probably not going to be shortened by their diagnosis of CLL.

Jeff Folloder: That's what we need to hear. Dr. Tam, Peggy has a great question. Is there any new information on treatment protocols for CLL, specifically with folks who have the TP53 feature and the 17 deletions?

Prof. Constantine Tam: So, for the audience, the 17p deletion or P53 mutation, they go hand in hand. Basically, means that there has been disruption of a key gene in the CLL cell called P53. And that gene is responsible for response to chemotherapy. So, in the era where we used to use chemotherapy, there was a really important gene. If you have P53, you are not going to respond to chemotherapy, you get all the side effects, but you won't get any of the benefits.

So, in the modern era where we have targeted therapies, in general, the BTK inhibitors, such as acalabrutinib is thought to largely overcome the bad impact of P53. So, a patient who goes on to acalabrutinib with P53 is going to have a similarly good outcome as their patient who doesn't have P53. And that's not exactly true of the venetoclax-based regimen.

So, if you take a venetoclax-based regimens and you have P53, your response duration tends to be a bit shorter than patients who do not have P53. So, there is a general trend to go towards the continuous BTK therapy for patients who have got P53, and slightly away from the venetoclax-based fixed duration regimens. But that comes with important a caveat. So, just in general.

I think in my practice; the most important thing is patient preference. And for my patients, the question is, "Do you want to have a continuous, easy-to-take, suppressive therapy? Or do you want to put in the work for a slightly more cumbersome, but a fixed duration therapy, with venetoclax?" And if my patient has P53, and says to me that they strongly about having venetoclax because they don't like continuous therapy, I don't think that's a wrong option. Because you will still get approximately four years of venetoclax-based therapy.

And as Dr. Wierda has already alluded to, the important thing about the fixed duration therapy is, at the time when you relapse, yes, you may actually stay in remissions for longer. It's so long, compared to continuous therapy, but when you relapse, you do not carry recessive mutations. And you can still be re challenged with the same drug, and be retreated, and go back into remission. Okay?

So, if you take a BTK inhibitor continuously, and yet, your CLL gets worse, well, you've developed resistance to a drug, and you can't ever go back to that drug again. For venetoclax, you just take it, you stop it. If some years later, it comes back, you can be retreated and go back into remission. So, the first remission duration may be shorter, but there's an option for retreatment. So, I think overall, it balances to be about the same.

Jeff Folloder: That's good information to have. I know people with TP53 and 17 are always concerned about how they're going to fare in treatment. So, this really is good news for that segment of the CLL population.

Dr. Wierda, Brian brings up two words that can invoke an awful lot of trepidation in patients. He mentions that Richter's transformation is one of the major unmet needs for CLL. What's the current state of research in terms of dealing with Richter's transformation?

Dr. William Wierda: Well, I think I would agree with the statement that it's an

unmet need. I think most of us who are working in this area have some focus on Richter transformation. And we all know and understand the need for more laboratory investigation and understanding of the process under which patients develop Richter transformation, the risk features, and also effective treatments – developing effective treatments for patients with Richter's transformation.

And so, this is an area. This has been a challenge. From a therapeutic perspective, it probably is the biggest challenge for our patients with CLL. Because we have some treatments, but they're not – we're not satisfied with the outcomes with those treatments. And short of a stem cell transplant, most of the treatments that we have some activity, but it's not very long-lasting effectiveness.

So, we're working at Anderson. We have several laboratory investigators working on animal models, so we can better study and understand the Richter cells that we can grow in mice, and understand and identify agents that may be effective in putting into a clinical trial and treating them. So, there's a lot of activity, and a lot of interest, and work going on right now in Richter's transformation.

Jeff Folloder: Good, good, good. There are over 16,000 members of the CLL support group on Facebook. And I know many of them were listening in just to hear that information about Richter's transformation.

Dr. Tam, this may be a leading question, or it may be something else entirely. Kathleen wants to know about UMRD. Let's assume that a patient has achieved UMRD. What are the important things they can do to maintain that status?

Prof. Constantine Tam: So, that's an excellent question. And I think it comes in two parts. But let's first explain what UMRD means. So, UMRD is short for undetectable minimal residual disease. And it came about because our treatment has become so good. So, if you go back to the chemotherapy age, most patients will have a reduction in the number of cells in the blood. The bone marrow may even be clear. But if you use a very sensitive test called MRD, where you look for cancer cells at a rate of one in 10,000, or one in 100,000, you can usually find some with older therapies.

But with the new therapies that we have, we're doing such a good job that the scans are normal, the bone marrow is

normal. And we're having to go to the MRD test to look for disease. And with combinations, the clearance of all detectable leukemia, even at the one in 10,000 rate, can be as high as 90 percent. Such as Dr. Wierda had studied with PVO, for example, has an extremely high MRD clearance rate.

So, you want to achieve UMRD if you are taking a fixed duration treatment. It doesn't matter if you're taking a continuous treatment. But you're taking a fixed duration treatment, you want to be in UMRD at the end of treatment. Because it means that we can't find any cancer in you, and hopefully it'll be a long, long time before it grows back.

Now how can you maintain yourself in UMRD? As a patient, there is no strong evidence for what the patient themselves can do. However, in general, we believe that patients who remain active, physically fit, has a healthy diet, and healthy lifestyle, that almost healthy immune system, and therefore it helps to keep things under control. So, I will always advise that for my patients. But there is no magic vitamin or herb that you can take that will help that.

What we can do from our side is to understand which patients are the ones who are most likely to relapse with UMRD. And we have some clues. So, these are patients who have got and retain their IGHV **g**ene, they have got P53 mutation. Those are patients who are more likely to relapse earlier. And at the moment, at least in Australia, we are starting a study of consolidating those patients.

So, these are patients who are at high risk of relapse with UMRD, and we are now putting them on a clinical trial with epcoritamab. Which is a bispecific antibody. And what we're hoping to do is that if the residual CLL cells are on, then we can recruit our own immune system to go, and control, and destroy the remaining CLL cells to give us a longer UMRD. But that's a clinical trial.

At the moment, we are very lucky to be able to get people in UMRD on the available therapies. It's an important endpoint for the patients. And we're working on ways to identify which patients relapse faster, and try and intervene early.

Jeff Folloder: That's excellent information. I always advise people when we're chatting on social media or in-person at these types of events. I tell them, “As a patient, you must take care of your comorbidities. Anything that's going on in your life, other

than the CLL, deserves your attention. So, get a little exercise in. Watch what you're eating. Be healthy. Be active. Do everything that you can to keep your body in the best possible shape."

I've got a question from Nick, which is something that I think is really, really important. Dr. Wierda, what are the most common forms of cancer due to having CLL in the past?

Dr. William Wierda: So, the most common form of cancer that patients with CLL can get – that's probably related to the immune dysfunction that they experienced because of the CLL – are skin cancers. Basal cell carcinomas and squamous cell carcinomas. And there are melanomas that we also see in patients with CLL. But skin cancers are the highest risk among other cancers for our patients with CLL. But they are at increased risk for solid tumors like colon cancer. And prostate cancer we see frequently in patients with CLL. Male patients with CLL, of course.

And so, because of that observation that there is an increased risk for other cancers, we recommend diligent screening for other cancers. Seeing a dermatologist, regardless of your age, at least once a year. If the dermatologist feels like they need to see you more often than once a year, then that would be what I would recommend for patients to follow. PSA check for men every year. Annual mammography for women. And then screening colonoscopy every five to 10 years, depending on if there's polyps or not.

And so, there are things that you can do – proactive things that you can do for early detection for other cancers. And that's very important. But the answer to the question is skin cancers. Fortunately, those are things that you can see relatively easy, and you can remove relatively easy with surgical procedure.

Jeff Folloder: I can confirm that Anderson is very good about asking about all of those things. Your office just sent over the pre-visit questionnaire. And you asked about the dermatologist. You asked about the gastroenterologist. You asked about the PSA testing. When was the last time I had one? So, yes, this stuff is important. We need to stay on top of it.

We have a question – actually, a couple of questions that came in about the BTK degraders. So, Dr. Tam, a patient from Uruguay asked do BTK degraders affect the tumor cell microenvironment?

Prof. Constantine Tam: Excellent question. So, the BTK degraders block the BTK pathway in much the same way as a traditional BTK inhibitors do. So, everything that the traditional drugs do, the BTK degraders do exactly the same. Obviously, expected they do the same. And we do know that traditional BTK degraders – the traditional BTK drugs block the nice sort of nourishing signal that the tumor microenvironment gives to the CLL cells.

So, the CLL cells like living the lymph nodes, in the bone marrow, in the spleen because that's where they get all the nourishment, and care, and protection from treatment. And the BTK degraders cut that link, and basically stops the CLL cells of survival. So, they do exactly the same as BTK degraders.

Jeff Folloder: So, good information. Let's stick with the BTK degraders for just a moment. Deb has what I consider to be an awesome question. What happens to healthy cells that are off target cells with the BTK degraders? And if something does happen, is that a permanent negative effect?

Prof. Constantine Tam: That's a wonderful question. So, firstly, it is not permanent. So, the BTK degraders, while they are still in the body, will get your body to destroy the BTK protein. But once you stop taking the medication, it washes out. Now, what happens to normal cells? And that's always a big question, right? As a patient, you go on to medication that damage your normal cells. And that's what causes side effects.

So, the BTK degraders, much to our comfort, didn't have any new side effects compared to the traditional BTK drugs, which is fantastic. And that's partly backed up by what we know about BTK. So, there's actually a human disease where children are born without BTK. Okay? It's called Bruton's agammaglobulinemia. These are kids who are born without BTK. And what do we know about these kids? We know they have no B cells. So, the B cells are where CLL comes from.

The B cells also make immunoglobulins, which defend against the infection. And that explains why BTK-deficient patients require immunoglobulin replacement. But those kids live normal lives otherwise. They do eventually succumb to infection in the 40s, because they have lifelong lowered immune system. But the heart, the lungs, everything else is normal. So, we do know that in a human, that you can

actually be missing BTK for most of your life, and it doesn't do anything bad to you, except that you will not have any B cells.

Jeff Folloder: Got it. I have a question for Dr. Wierda. And it's going to sound innocent, but I suspect that the answer is a little bit more complicated than we think. This is a question that I had when I first started my CLL experience. How do you know when common symptoms are CLL-related or something else? I'm talking about random coughs, itching, fatigue, bleeding. How do you know it's CLL-related, or it's nothing to worry about?

Dr. William Wierda: That's a great question. And it's something that I talk a lot about in my clinic with patients, because it's oftentimes not clear. And it's oftentimes not clear particularly for the troubling symptoms of things like fatigue, and occasionally night sweats. Things like that, that are reasons that we would start treatment for patients if we think that they're from their CLL, and causing significant impact on their quality of life. So, it's not an unreasonable question, and something that we talk about a lot in the clinic.

I think probably a couple principles that I would encourage patients to keep in mind. And with CLL symptoms, particularly, they don't usually happen overnight. They are usually things that start out – they're not very frequent. So, for example, fatigue or night sweats. And they sort of escalate. But they don't escalate in a rapid fashion. They usually escalate gradually, over weeks, months, even sometimes years. So, if there's something that happens that's abrupt, and unexpected, and – then it's probably not the CLL. And those are situations where I aggressively look for other explanations and other causes.

Sometimes we're at a point where patients have had fatigue for months, and they say well – and they don't have a high white count. They don't have enlarged lymph nodes. So, from my perspective, it's a little bit confusing, because they have these significant symptoms, but they don't have a lot of measurable disease. Usually, the symptoms correlate with the amount of disease that's present. The larger the lymph nodes, the higher the white count, the more likely patients will have some symptoms.

But occasionally we'll see patients, they don't have a lot of lymph nodes enlarged, they don't have a high white count, they've got significant fatigue. And sometimes you get into

a situation where you – I have a discussion and say, "Okay, well, I'm not sure 100 percent. All treatments have risks. If these symptoms are bothering you enough, we can do a trial of treatment to see if your symptoms improve with the treatment. If they don't improve with the treatment, then they're not coming from the CLL. If they do, then great, we're on the right track. And we can proceed with continuing the treatment." But it can be a challenging situation and can be challenging.

The other thing I would say is that enlarged lymph nodes or rapidly enlarged lymph nodes, if there's pain and tenderness, it's not usually from the CLL. CLL doesn't usually cause tender painful nodes. That's usually something related to an infection.

Jeff Folloder: Got it. Dr. Tam, we've been talking a lot about pills, inhibitors. We've been talking about the BTK approaches. T cell transplants, is that a mainstream treatment for CLL? And once we know that, how mainstream is it? And how risky is it?

Prof. Constantine Tam: Sure. So, that really opens up the new field of CAR T cells and allogeneic bone marrow transplant. So, we know for quite a long time now that if you have a bone marrow transplant from another person – so not a bone marrow transplant from yourself, but from a brother, sister, or unrelated donor – and you put a new immune system into a CLL patient, that you can cure CLL. Okay? So, that is the one area where we know we can cure. But that's a high-risk procedure, because the transplant may recognize the patient's body as being foreign. It causes something called graft-versus-host disease, which is a very difficult situation.

So, traditionally in CLL, we have known about transplant, but we usually kept it in a back pocket for very difficult situations. Where patient has stopped responding to our drugs, or patients have Richter transformation, or something similar.

And more recently, your audience will have heard about CAR T cells, which is where we do pretty much the same thing, but without the risk of graft-versus-host disease. Which is where we get the patients' own immune cells, T cells, and we genetically hijack them to attack cancer. And that's now a mainstream treatment for lymphoma.

But what people actually don't remember was that the first

three patients ever to be cured of anything in the world with CAR T cells were infected CLL patients. So, these are patients with advanced CLL who got CAR T-cell treatment at University of Pennsylvania, and who were cured of the disease.

Now we've subsequently done CAR T-cell trials in CLL. And there's now liso-cel, which is now licensed in the US by my country, but in the US for treatment of advanced CLL. And you do get very good responders as Dr. Wierda reported, especially in combination with ibrutinib, you can people who have very long remissions, often cured.

But those are small numbers. And why are they so infrequent compared to, let's say, other types of lymphoma? And we think it's because the starting material, the T cells in the patients, are not all that healthy. And we do CAR T cells in patients where the CLL has been present for a long time, the patient has had many different types of treatment for the CLL. Their immune system is no longer healthy. And we're getting really damaged T cells to make our foot soldiers to fight CLL. And we're not going to have very good outcomes.

So, I think a future research area will be, how can we identify those really high risk patients for which we think eventually they will need some sort of cellular therapy? And how can we bring in CAR T cells at an earlier stage? How can we improve the fitness of T cells, so that when the patients do get their CAR T cells, they're getting a good active product rather than a product that is damaged by the fact that the T cells were not good to start with?

And I think that is a really exciting area, that a single infusion of a CAR T cell may be the permanent solution to a patient's CLL and cause cure. But obviously, it's very expensive. It's complex. We need to have ways to identify which patients are the best suited for it, and well-suited for it. Also, we need to find a way to produce the best cells possible.

Jeff Folloder: So, that's a lot to consider. Stephanie has a question that's near and dear to my heart. When a CLL patient is first diagnosed, most of us are put into a program that the medical community calls watch and wait. The patients call it, watch and worry. Myself, I'm in my second pass with watch and wait. Stephanie wants to know, are there new approaches to watch and wait? Dr. Wierda, what do you think?

Dr. William Wierda: Well, no, there's not new approaches to watch and wait necessarily. Watch and wait continues to be watch and wait. And we haven't changed the iwCLL criteria for when to start treatment. We have a lot of new exciting agents that are very effective. I think that tends to make people want to move forward potentially earlier with starting treatment, but there's no recommendation that's come from anybody.

And I think the CLL community, and leadership in our community particularly, are still persistent with we need to treat when patients need treatment. There isn't really any clinical benefit that we know of so far with early treatment. And so, for patients who don't have active CLL, they're better off being observed and monitored, and treatment be initiated when their disease is active, and when our aim is to get rid of the disease and get the patient in remission.

That's always been a difficult conversation. It's a little bit easier today, because our treatments are evolving very quickly. And we have new treatments, and new clinical trials, and research that's ongoing. And so, my opinion is if you wait a year, you may have something better, some better treatment opportunity, in a year than you do today. We got great things today, but if you don't really need it, you're probably better off sitting tight, being patient, and waiting until you truly need treatment, and starting treatment at that time.

Jeff Folloder: That makes a lot of sense. And you and I have actually had that conversation on more than one occasion. You don't tell me what I'm going to do right now because I don't need treatment right now. And who knows what's going to happen in six months? A year? Or five years? In the meantime, I go and do all the stuff I can to enjoy life.

Anne has got a great question for Dr. Tam. Where are we heading in terms of next generation sequencing and CLL?

Prof. Constantine Tam: So, there are two aspects to that. So, the first aspect is looking for new genes that may predict the outcome of CLL. So, mixed generation sequencing have uncovered some key genes that allow us to determine how risky the CLL is. In particular, P53 have been very useful for that. But there are other genes like NOTCH1 and SF3B1, which provide information but doesn't change therapy.

So, with respect to that, I think we've pretty much understood the CLL generics as well as we can. So, we're now looking

at finding infrequent genes, but we're not finding any new genes that would change treatment.

Now, the other role of mixed generation sequencing, of course, is to monitor response to treatment. So, there are two aspects. So, firstly, mixed generation sequencing allows us to look at the MRD status in a much more sensitive manner than flow cytometry. So, instead of finding one cell in 100,000, we're finding one cell in a million, or one cell and 10 million with mixed generation sequencing. So, as our treatment gets better, mixed generation sequencing allows us to look even deeper, and to find the very few remaining CLL cells in the body. So, that's a really exciting new technology.

The other aspect of mixed generation sequencing that is exciting is understanding why patients become resistant. So, by looking at the entire BTK and BCL-2 gene, we can understand why some patients stop responding to the drugs. And then we can hopefully use that information to look at other drugs, even within the same class, but you might find other drugs that are actually active against a mutation, and then prescribe another drug within the same class to overcome that mutation.

So, as you pointed out before, Jeff, this is really personalized medicine. This is about finding out within the individual patient what mutations they carry, and how we can target our treatment to cover those mutations.

Jeff Folloder: Fantastic. We're getting near the end of our Q&A session. I have a last question for Dr. Wierda. COVID is still a thing. What is the current recommendation for CLL patients in terms of getting COVID boosters? Once a year? Twice a year? Only when things rage? Tell us what the plan is.

Dr. William Wierda: We're getting into a period probably where if you ask several different doctors, you might get different recommendations. My recommendation is if you've had a prior vaccination, and/or you've had an infection that you have recovered from, you do have some immunity. And so, we're not in a situation today like we were in the beginning of the pandemic, where we had patients who had no protection, and their immune system doesn't work. And we were losing patients at that time with COVID.

So, we do have a population where many or most patients have had either an infection and they've recovered, or they've had a vaccination. We also have drugs that treat COVID, like

nirmatrelvir (Paxlovid). And so, that's a new tool, and is a tool that also has helped prevent patients from getting sick, very sick, and succumbing from their disease. There are other drugs that we use. We have vaccines for COVID that are mRNA-based vaccinations. And we have a protein-based vaccine – or we've had a protein-based vaccine.

One of the concerns I have is that we don't have a long-term understanding of the side effect and toxicity profile from the mRNA vaccines. If you're giving one every six months in perpetuity, I don't know that that's as important as it would have been in the very beginning of the pandemic. So, that's not really my recommendation these days. Maybe at most once a year, a COVID booster. If a new one comes out and they're covering strains that have not been identified, and are emerging as important new strains, then that would be – and it's a once-a-year time.

If you've had a recent infection and recovered from that within the last six months, I don't think there's a need for reboosting. Because, in fact, an infection itself is a boost to the immunity once you've recovered. Because your immune system has been exposed to a recent COVID virus and is reactivated against the COVID virus.

So, I would say once a year. And if there's a new strain particularly, get the booster. I don't usually, for my patients, recommend more than that. Like every six months. And we do have monoclonal antibodies for prophylaxis. And there are very rare patients that I think I have recommended that for. Patients who can't get a vaccine and patients who haven't had a COVID infection and recovered would be probably the small group of patients that I would think about recommending the monoclonal antibody for.

Jeff Folloder: Excellent. Thanks to everyone who has submitted questions for this program. Before we wrap up this town hall, we're going to get some final thoughts from our experts. Dr. Tam, I'm going to give you less than a minute. How do you feel about the future for CLL patients?

Prof. Constantine Tam: It's never been better, Jeff. We are at the cusp of hopefully providing cure with less and less side effects.

Jeff Folloder: Fantastic. In other words, what you're saying is the future is so bright, time to put on some sunglasses. Right? Excellent. Dr. Wierda, what would you like to leave our audience with as we close the program?

Dr. William Wierda: Well, I would agree with Con's statement. We have a lot of activity, a lot of things that are going on. We have a lot of new drugs that are in development. There's a lot of excitement. And we've made a huge amount of progress in treatment for patients with CLL. We can't be complacent. My focus right now is immune restoration, and vaccinations potentially, and ways to improve and reduce the risk for infections and complications from infections. As well as reduce the risk for second cancers.

We also intend to work on Richter transformation, which is a big unmet need. So, there still are things for us to work on. We've made a ton of progress, and we continue to be extremely dedicated to curing patients with CLL.

Jeff Folloder: Love hearing that word? I'd like to thank both of you for taking the time to join us today. And I'm thanking everybody who's watching us online. Don't forget to fill out the survey. It's really, really important. All that information that we get off the survey helps us deliver better programming for you.

And stay tuned, we're planning our next town hall already, and that's going to be held a little bit later this year. We hope you can join us. As I always say, you may have CLL, but you can still live a great life. Thank you everyone.