

CLL Global Research Foundation Virtual Town Hall | October 10, 2025

Jeff Folloder: Hello and welcome. I'm Jeff Folloder. We're back again for this year's second CLL Global Research Foundation Virtual Town Hall. Today, we'll start by hearing all about emerging CLL research and treatments straight from the experts.

And, of course, we'll be answering as many viewer questions as we can possibly get to. As I mentioned, my name is Jeff Folloder, and I'll be your host. I am a CLL patient, and I've been dealing with CLL for over 15 years. I've been through watch and wait. I've been through a clinical trial. I've been through complete remission, and I'm currently relapsed back in watch and wait. So, I'm just as interested in what's new as you are.

Now, let's meet our experts. First up, I'd like to introduce the president and CEO of CLL Global, Dr. William Wierda. Dr. Wierda, would you like to welcome our audience?

Dr. William Wierda: Sure. Thank you, Jeff. Welcome to you, Jeff, and to Cathy Wu for participating in our event this afternoon, and welcome to all our participants. We hope to have a great session this afternoon.

Jeff Folloder: Fantastic. As Dr. Wierda mentioned, we're also joined by Dr. Catherine Wu from Dana-Farber Cancer Institute. Dr. Wu, can you please introduce yourself and tell us a little bit more about your areas of specialty?

Dr. Catherine Wu: Thank you so much for inviting me. It's such a pleasure to be here. I'm the chief of the Division of Transplant and Cellular Therapy at Dana-Farber Cancer Institute, which really just simply means that I'm deeply involved in cancer immunotherapy. I've been involved in CLL for quite some time now. My areas of specialty are in genomics and in the study of cancer heterogeneity and trying to understand the scientific mechanistic underpinnings of CLL. I'm very deeply interested in seeing how we can bring immunotherapy to CLL. Thank you.

Jeff Folloder: That sounds fantastic. Thank you both for joining us. Okay. Now we're going to jump right into this. We have a discussion about evolving CLL research on deck. There have been a few research meetings since our last town hall. These include the American Society of Clinical Oncology and the European Hematology Association meetings.

Dr. Wierda, are there highlights from these meetings that you'd like to share with our viewers?

Dr. William Wierda: Yes. Thanks, Jeff. I'm going to just very high-level introduce some of the topics that have been discussed this year. Then I think in the question session, we can

get into some of the more detailed content. Over 2025, there have been several important meetings; those are summarized here. There's the American Society of Hematology meeting. That was last December. We had our town hall after that, so we did cover content from that meeting.

Subsequently, in June, there were two important meetings: the European Hematology Association meeting and the ASCO meeting, or American Society of Clinical Oncology meeting, in June. And then, just last month, we had a large meeting in Kraków, Poland, which was the International Workshop for Chronic Lymphocytic Leukemia, which was a two-day meeting; well, actually, it was more than two days discussing various aspects of the disease and new developments and new therapies.

I made a list of sort of the hot topics for this year that have been discussed. There's data, and there will be more data. We're very excited and interested to see the data that's presented at the American Society of Hematology meeting that's coming up in December.

We've recently been notified of the presentations and the posters, and there's going to be a lot of very good and interesting content, but hot topics for the year include maintenance therapy for the first-line setting; this is a BTK inhibitor-based therapy, and we're getting long-term follow-up data from our BTK inhibitor-based treatments demonstrating very long and durable responses with continuous single-agent BTK inhibitor therapy. There's been discussion around the choice of which BTK inhibitor.

In general, we have been directing therapy towards second-generation BTK inhibitors over ibrutinib (Imbruvica) or the first generation because of a reduced side effect and toxicity profile with those newer agents, but that is one area that's been updated, and again, that's the long-term exceptional outcomes that we see with continuous BTK inhibitor-based therapy.

Also, there's been a lot of work done and published and reported recently on combination therapy. We have, for all intents and purposes, eliminated chemo, chemoimmunotherapy from our treatment strategies for our patients with CLL, both in the front-line setting and in the relapsed setting, and in the front-line setting, as well as in the relapse setting, we're working on developing combined targeted therapies, so these are oral drugs for the most part that target specific proteins. Through blocking those proteins, they will induce apoptosis and killing of the leukemia cells and put patients in remission.

And so, there are a lot of different options in terms of therapeutic agents that we have. And are combining and working on the most effective and potent combination strategy to get the highest percent of patients in remission and the

highest undetectable MRD rate with our newer treatments.

And we've made a lot of progress. We started with venetoclax-obinutuzumab (Venclexta-Gazyva) and moved into all-oral treatment with ibrutinib plus venetoclax, acalabrutinib (Calquence) plus venetoclax. There has been some data presented with regard to sonrotoclax and zanubrutinib (Brukinsa) as an effective combination, and then we've reported also on our data with a triplet of pirtobrutinib (Jaypirca), venetoclax, and obinutuzumab, and again, we're seeing very high rates of remission and undetectable MRD, and over the next five or more years, we'll be sorting through that data and hopefully will arrive on what's the most effective treatment in those combinations.

Pirtobrutinib: We've seen more data coming out on pirtobrutinib, which is referred to as a reversible BTK inhibitor. It was approved for patients who had failed a prior covalent BTK inhibitor and venetoclax, but we're seeing that it has activity in an earlier line of treatment.

So, not necessarily restricting it to use for patients who've failed all prior treatments, but we're seeing activity when it's used earlier. Updated data on CAR T-cell therapy, and particularly CAR T cell combined with ibrutinib, and higher rates of complete remission with that combination compared to liso-cel (lisocabtagene maraleucel [Breyanzi]) or CAR T by itself.

And then there are several drugs that are in development that we're very excited about and I think will be the next advance and wave of approvals in therapies for patients with CLL, and that's these drugs that bind to BTK, which is an important protein in the cells that is associated with their long-term survival. These are agents that bind to that protein and induce its degradation or removal from the cells, and in removing it, the protein from the leukemia cells, that is another mechanism of killing those leukemia cells.

The inhibitors bind to that protein and block the function, but these degraders bind to that protein and completely eliminate it from the cell, which is proving to be active, and patients are tolerating these compounds in early clinical trials.

And then the bispecifics are also in development, for example, epcoritamab (Epkinly), which recruits the immune system to kill leukemia cells through engaging the immune cells of patients with CLL, T cells, for example. These agents are administered intravenously or subcutaneously, and upon doing that, they bind to the CLL cell and also bind to the T cell and induce the T cell to kill the leukemia cells. And so, that group of compounds, and particularly epcoritamab and mosunetuzumab (Lunsumio), are in development.

So, there's a lot of exciting work. We've never had more progress. We've never

had more agents available, and we're very excited to see what we're going to hear about at ASH this year, because it just keeps getting more and more exciting, and we see more and more promising results. And that just highlights the ASH's – our next meeting that's coming along. So, thank you.

Jeff Folloder: Outstanding. Let me see if I can play back what I just heard. Chemo is pretty much done. There's lots of new things coming, and we should all be hopeful, right?

Dr. William Wierda: Absolutely.

Jeff Folloder: Fantastic. Thank you, Dr. Wierda. Dr. Wu, let's turn to you to hear your insights.

Dr. Catherine Wu: Wonderful. I'm going to see if I can bring up some slides. So, I think, you know, what we heard from Dr. Wierda is that it's an exceptionally – can you see this?

Exceptionally exciting time in terms of the choices that are available for our patients. And I think it does give us a lot of hope that patients' disease can be controlled for long periods of time, and dare we think, for one's life's duration. But there's still a lot of challenges that are faced.

And I think for that, we have to continuously think about how we can understand CLL better. So, what are the sources of relapse? Why is relapse happening? And how, and if the current drugs are not working for us, what are new options that are available? And so, I'll just take you through. There's kind of five points here. And what I do want to say is that there is a lot of active basic research that is going on so that we can better understand CLL. And in doing so, that is going to help us think of better therapies.

So, the first thing, Number 1 there, it's written, "Basis of CLL Heterogeneity." So, this is a concept that not all leukemia cells are the same. So, when patients have leukemia, there are little different variations. And that happens because of the way that cancer arises in general. It's also the seed for why we have resistance that develops later, because there's so much variation.

We hope that our medications can kind of get rid of every single cell. But if there's one that escapes, then that's the source of relapse. So, we have to understand a little bit better why heterogeneity happens. What are the characteristics of those escaping cells? And the good news for all of us is that we have better tools than ever that allow us to directly profile and analyze patient leukemia cells.

We can profile their DNA, we can profile their RNA, we can look at their proteins, we can look at all the peptides that are displayed on their surface. So, we are not

only in the age of immense drug development, like Dr. Wierda just said, but we are also in the age of human biology, where we have the tools that can really crack these sorts of secrets open. So, that's No. 1, Basis of Heterogeneity.

Number 2, what got us there to begin with? So, how did a normal B cell actually turn into a CLL cell? What were the steps that kind of took place, if we kind of do a little bit of archaeology, that got us to the CLL? Other than an academic interest, I think the reason why that's important is because if we can get to dealing with the problem earlier, then maybe we can change the natural history of disease. Maybe we can even prevent full-throttle CLL from happening if we understood where were the levers, where were the areas that we could actually intervene.

Number 3, Nature of Immunodeficiency in CLL. We all know that CLL comes with its risks of immune dysfunction, but just knowing about it, we need to know more. So, what exactly is the nature of that immune dysfunction? How much of those changes are permanent? How many are temporary? So, if we use the drugs that Dr. Wierda talked about, and we actually get the disease under control, are there still areas of the immune system that's dysfunctional that we can't change? How much of it is temporary, and how much of it is permanent? How much can we modify? What can we replace? How can we restore immune health? This is something that Dr. Wierda and I talk a lot about.

Number 4, Defining Key Pathways of Disease. So, we're doing wonderfully with the drugs that we have, but for sure, there are other important pathways that are out there that – it just broadens our toolkit if we understand a little bit more about what are the other possible therapeutic avenues that can be developed.

Finally, one thing that has been concerning for all of us is Richter's transformation. That is, at some level, a manifestation of resistance. This is, as this group knows, a very difficult, to treat, situation. So, again, can we understand why that happened? Can we understand what were the seeds that got one to Richter's transformation? What can we do about it? What are the right pathways to get at? What are the right combination of drugs to go after?

So, I think that we're at an exciting time because these are the questions we have to answer. But better than ever, we have tools that allow us to attack each of these areas. My other slide is just to say that I think for us, one can say, our goal is precision oncology. We want to make sure that therapy is personalized for the individual, that it's going to be effective; that it's going to minimize any sort of toxicity.

So, we're doing great right now, but to fully realize that vision, there's still a lot we have to do. So, this is just a schematic. How do we cross that bridge?

Certainly, I mentioned some of the things that we're hoping to understand, but I do think that in the future there'll be a moment where we have what we call molecular taxonomy of CLL. So, that's really precisely knowing on a per-individual basis, what are the characteristics?

Can we kind of look in the crystal ball? Can we understand what is the right combination for that individual given the characteristics of the CLL that you have? I would love to figure out ways that we can understand how we can, at an early point in disease, intervene and prevent any toxicities or side effects that might happen down the road.

And all of these different aspects require, as everyone can imagine, funding because we need support for that for the discovery science; collaboration because we always get more out of increasing interactions and access to data and being able to pull it all together, systems that help us integrate all that information.

And then, again, like Dr. Wu said, all these important practice-changing clinical trials that are going to make a difference for our patients. So, I'll end there.

Jeff Folloder: Thank you. Dr. Wu, I know that you're involved in ongoing CLL research. Since we're in the middle of the Major League Baseball playoffs, I'm going to ask you for a little inside baseball information. Is there anything that you'd like to share with us that you're working on?

Dr. Catherine Wu: Let's see. Well, I think that myself, personally. I think that we are – one of the things that really excites me is the tools that we have that allow us to dissect that heterogeneity, like I said. So, looking at each cell one by one, not only that, but we can look at cells now kind of in a spatial configuration. So, we can look at how different normal and leukemia cells are interacting in lymph nodes or in bone marrow.

And I think we're going to get a lot of clues and answers from those types of analyses. And I'm excited about really understanding from these exciting trials that are effective in patients, but also in patients who develop resistance, what the differences are. So, how can we understand what are those troublemaker cells that are still there are, even despite the best therapies that we have? And if we could figure out what the troublemakers are doing, then we would know what to go after and think about better combinations.

Jeff Folloder: I love that term, "troublemakers." I would love to refer to my cells as troublemakers and make sure that they just go away. Dr. Wierda, before we move on to our audience questions, are there any additional updates from you that you'd like to share?

Dr. William Wierda: Sorry, not necessarily anything specific to add.

And I think I reflected my excitement about all of the new treatments that we've been able to work on and the progress that we're seeing. I have said this before, and I continue, and it becomes even more apparent to me that we are on the brink of developing curative therapy for most of our patients with CLL. We are having more and more discussions about, well, what does a cure look like? Is there this functional cure? Or how would one define cure? And I think that's a more and more relevant topic and something that we're working towards, and I think approaching for most of our patients.

Jeff Folloder: I love hearing that four-letter word, cure. At the beginning of the program, we talked about getting rid of chemo. Now we're hinting at the word cure. It makes my day. Thank you both.

I want to mention that if you missed anything presented by the panelists today, the slides and a replay of this town hall will be made available on the CLL Global website at cllglobal.org in just a few days. Okay, let's get to the Q&A. As I said at the beginning of the program, we have received a bunch of questions in advance, and we're going to try to get to as many of them as possible. So, I'm going to start off with a question for Dr. Wierda. Betsy wants to know what research is being done on how to build the immune system of CLL patients?

Dr. William Wierda: That's a great question. There's a lot of work that's going on, Dr. Wu – both Dr. Wu and I have a strong interest in this particular area.

We at MD Anderson have received some donor funds and have a program that we're working on to first understand what are the fundamental aspects of immune dysregulation for our patients with CLL? CLL is a very unique disease. That was what drew my interest many, many years ago, and that patients don't have a normal immune system, a normal immune function.

And so, getting that understanding – why that is and how we can correct and fix that – is something that we've talked about and worked on for many years. So, we have laboratory investigators here at Anderson who are working on various aspects of that. Others are working on it, I'm sure. I know Cathy's group is also working on it. We're interested in developing vaccinations or vaccines directed at the leukemia cells. There are multiple components to the whole effort.

And again, that in my view is to understand what are the fundamental abnormalities that result in the immune dysregulation. Then we can start thinking about and talking about, okay, how can we intervene and correct those? Historically, we haven't had a lot of therapies that have been effective at fixing

immune dysfunction.

We talk about steroids and using steroids for patients who have overactive immune systems, but there haven't been really any good therapeutic strategies to fix immune dysfunction. Stem cell transplant has been used for patients who have severe immune deficiencies. But we have a group that's – members of our group that are working on agents that may have some immune restorative potential. And then we have a group that's working on various aspects of vaccination.

Dendritic cells are a cell type that one of our collaborators who works with Dr. Allison is working on with us as well. And maybe I can invite Cathy to speak on her work because I know they have been doing exciting and interesting work in this area as well.

Dr. Catherine Wu: Yeah. Thank you. Thank you, Bill. I totally agree with everything he said. I think that in the current age, again, because we have the tools to do so, it becomes really fascinating to see, for example, on clinical trials, as patients eliminate their disease, can we understand what impact that has on restoring the functionality of our immune system, of the immune system of patients with CLL. I've had a long-time interest, and our group has had a long-time interest in vaccines. Back in the day, we were thinking about using whole tumor cells, so leukemia themselves, as a vaccine agent.

And then there's a trial that I was involved in already more than 10 years ago, where we took CLL cells; they were irradiated so that they would not expand, but the patient's own whole tumor cells were given back as a vaccine for patients with CLL who went through stem cell transplants. And we were able to show that there were very nice, strong immune responses against the patient's own CLL cells that happened after whole tumor cell vaccination.

That inspired me to try to get a little bit more specific. So, with a whole tumor cell, it's hard to know what are all the components that are in that cell. And so, with the availability of next-generation sequencing – DNA and RNA sequencing – we were able to be one of the first to create a pipeline that allows one to identify each tumor's specific mutations.

And then also to predict what – which one of those mutations might be something that the immune system could attack. So, this is kind of the road toward getting toward personalized vaccines. And, in fact, we've already completed clinical trials for that in melanoma, in glioblastoma, renal cell. We're just finishing a trial on ovarian cancer, but I've always been interested in trying to bring it back to CLL.

So, we have an ongoing study right now where one arm is patients who are just getting vaccine alone. Again, one arm is getting vaccine with anti-P – PD-1 antibody; sorry. The second arm is actually the vaccine with what we call metronomic cyclophosphamide (Cytoxan). And this is cyclophosphamide, given at very small doses to alter the immune milieu and get rid of some of the suppressive – immunosuppressive – cells.

And then the final arm is to add the vaccine together with the metronomic cyclophosphamide and anti-PD-1 therapy. I will say that again: the vaccine starts with the patient's tumor being sequenced. We analyze the sequencing for mutations; from those mutations, we do some prediction, and, ultimately, we generate a series of personalized peptides that we administer to the patients as a shot, and they're given in series, and they're very well-tolerated. But we're already seeing some immune responses. We'll have to see how the results pan out, but certainly this is a larger effort to try to think about personalized vaccines.

Jeff Folloder: Excellent. Although you wouldn't know it here in the Houston area, fall is upon us, and many of us are getting our flu boosters. I'll direct this to Dr. Wierda first. What is your recommendation for COVID boosters right now?

Dr. William Wierda: I've written a few things about this recently, and I've gotten some interesting responses. I worry a little bit about repeated vaccination with an mRNA vaccine that we don't have a lot of long-term understanding and knowledge on the safety. And so, that's sort of one component to what my recommendation is. So, if we're talking about a COVID vaccine, it's nice to talk about the protein-based vaccine that's been difficult for patients to access. And again, I have seen patients whose disease has flared with the mRNA-based vaccine. So, I'm a little bit apprehensive. Most of our patients have been vaccinated at some point. Most of them have had boosters and haven't had problems with their CLL.

Most of them actually have had a COVID infection and cleared a COVID infection. My opinion is that if you've had COVID within the last year or at least within the last six months, it may not be critical to get a vaccine right now. And once a year to once every other year, a vaccine should be enough. But I, again, worry a little bit about the repeated stimulation that's seen with the mRNA vaccines.

And it's a different clinical situation right now than what it was three, four years ago, where patients don't die from COVID infections nearly with the frequency of what we saw early on. We have nirmatrelvir/ritonavir (Paxlovid), we have remdesivir (Veklury), IVIG tends to have some coverage for COVID. So, we're not in the dire situation that we were early on in the COVID pandemic.

= And I think we need to be a little bit thoughtful about this repeated vaccine with

a vaccine that doesn't have a lot of long-term data yet. I mean, we've had flu vaccines for a long time since I've been practicing medicine. So, we know those are safe. The flu vaccine is a protein vaccine. And we do recommend annual flu shots for our patients with the updated new version of the flu vaccine.

Jeff Folloder: Dr. Wu, would you like to add anything to that?

Dr. Catherine Wu: I don't have a whole lot to add. I think Dr. Wierda gave a very thoughtful, well-measured response. I will agree that today's scenario is quite different than we were at several years ago. That was really everything was on fire. And I think that the vaccines really helped us get out of the tough spot we were in. But I think we are in a different situation now.

Jeff Folloder: Gotcha. When I first started my journey with CLL, I was told that most patients will never know how they got CLL. But there are a few cases where we do have some insight. Dr. Wu, Ron wants you to know that his father-in-law and his wife have CLL, and now he's been diagnosed. What do we know about familial CLL? And along the lines of what causes it, what about environmental exposures in CLL?

Dr. Catherine Wu: Yeah. So, I do think that there have been some very, very interesting and well-done rigorous studies looking at familial CLL. And I think with more and more numbers of patients that have been profiled genomically, by now, from the work of our colleagues evaluating tens of thousands of patient CLLs, there begin to emerge some patterns, which is that there are areas of our genome that do provide some susceptibility to CLL.

All of them are what we call low effect sizes. So, any individual one of them probably doesn't cause CLL, but an accumulation – it does set you on a path, and that there may be an accumulation of changes that happen that gets you to CLL. I think that that's what we can say about the genetics. And I think there was just a study published this year that kind of was the accumulation of all the work that had been done in the 10, 15 years before. And really quite definitive. I think that environmental exposure is tougher to pinpoint. Bill, I don't know if you had any comments there.

Dr. William Wierda: No, I mean, we just know that the exposure to herbicides such as Agent Orange has been associated with the risk for developing CLL.

And that's why the VA has made it a service-connected illness. So, there are associations, but just as you said, there hasn't been as clear a delineation of exposure and developing the disease as there has been with, say, smoking and lung cancer or other such associations.

Jeff Folloder: So, Dr. Wierda, earlier in the program, you mentioned the acronym MRD, Minimal Residual Disease. David wants to know, what does that actually mean?

Dr. William Wierda: Mm-hmm. So, this is an area that I'm extremely interested in now and doing a lot of work on. MRD means minimal residual disease or measurable residual disease, and it refers to a very low level of disease that we can test; we can detect with some of our more sensitive tests than, say, a blood count or a CAT scan.

We apply these tests to either the blood or the bone marrow, and we're able to sort through the cells there and say, "Okay, yes, there is one CLL cell among 10,000 normal cells" or "one CLL cell among a million normal cells." That level of detection refers to the sensitivity of the test that's being used. So, flow cytometry is one of the tests that we use to detect minimal residual disease. The flow cytometry is more limited in its sensitivity than next-generation sequencing or a molecular test. So, the flow cytometry allows us to detect one in 10,000, one leukemia cell in 10,000 normal cells. The next-generation sequencing platform allows us to detect one leukemia cell among a million normal cells.

And you can imagine that if we're talking about that very low level of disease, we're talking about very effective treatments that can get rid of almost all of your CLL. And so, in the past, we've talked about response to treatment being measured by how big the lymph nodes are and what the blood counts are. And if we see any CLL cells under the microscope in the bone marrow, now we're talking about remissions where we've gone beyond that, where we need to use these very sensitive tests to pick up very small levels of CLL.

And so, our new clinical trials are aimed at eliminating minimal residual disease. We feel that if we can get patients into an MRD-negative or a minimal residual disease-free remission, this is going to be correlated and associated with the longest remission and potentially a cure of the CLL.

Jeff Folloder: So, that begs the question, how far away are we from MRD-directed, time-limited therapy in standard community settings around the world? How far on the horizon is this?

Dr. William Wierda: Well, that requires us to have data, clinical trial data that will support doctors doing, practicing, and providing treatments according to how it was done on a clinical trial. Right now, there are ongoing clinical trials where patients are getting MRD-directed therapy. We've seen some data already where outcomes are reported with regard to MRD-directed therapy. There's a large trial that the British did called the FLAIR trial where patients received ibrutinib plus venetoclax that was MRD-directed, and outcomes were superior for patients who became MRD-undetectable with that treatment.

So, we will see treatment options on the NCCN guidelines that are MRD-directed in the very near future, and I'm sure at this coming ASH, we'll see new data out for clinical trials where treatment was given in an MRD-directed fashion. I think that's where we're going in general in the future for all of our time-limited therapies.

Jeff Folloder: Can you comment on the NIH spending cuts and how they're going to impact basic science research and progress in CLL? Is there reason for concern, or is there still hope?

Dr. Catherine Wu: I think we're in unprecedented times, and it's very, very difficult to have clarity on what is going to happen down the line.

I think for better or for worse, some of the things that are going on are already having an impact, and the reason I say that is that already – we're all attached to our iPhones and our newspapers, and there's a lot of tough reports that are coming down, and I think the group that is most concerned are our young people. I think trainees, people who are on the brink of trying to decide whether or not they're going to commit to really making their lives' work about – for example, CLL research. They're scratching their heads going, "Maybe I don't want to sign up for this, and maybe I just step away from this thing that I've been working on all my life, and I'm not going to continue on this career." I've already seen that happen, so.

Some of my most promising what-would-be future leaders in biomedical research have decided to take a step aside and do other things. I've also seen that currently young people who have really poured blood, sweat, and tears to put together a good proposal for funding, who were funded in the blink of an eye – moment, they received a letter, and the government shut down their funding. And so, of course, I can support them, and I'm not even the worst hit. I have a lot of colleagues who have lost up to nine grants, which is a lot, you can imagine, so it's a tough time, so you have to really need to keep the faith to keep going and be of an optimistic nature and look at it as a glass half-full, but it's not half-full right now.

It's actually quite difficult. And so, I think I'm talking about young people, and I'm talking about currently the day-to-day looks very similar, but I think in order to really do the important stuff, you need a little bit of a runway. You need to have a Pax Romana, a period of peace and tranquility, for all of that fundamental work to happen, and it's a little bit hard to plan that right now. I think this will also deeply affect the biotech sector, because a lot of the ideas and kind of the personnel that go into the pharmaceutical industry are coming from academia. So if you turn off the tap for young people, then you won't have a supply chain

to go into making drugs, which is what we care about.

I think also within the hospitals, we have to also – I think so far, there is a concern of kind of turning off the tap for support of clinical trials, and that we know is what is really needed in order to change practice. The final aspect is that from where I stand, Bill and I, Dr. Wierda and I, both go to many, many national and international conferences, and all our international colleagues have never received more applications from Americans than before that are really trying to look for job opportunities.

Because they're being shut off right now by our current crisis. So, I think our loss is someone else's gain, but I'm not sure that that's a loss that we really want. So, it is an unprecedented time, and we're all keeping our eyes on the prize, but you have to kind of turn off some of the noise, because there is a lot of noise right now.

Jeff Folloder: Gotcha. While I've got you talking, as a leader of one of the largest support groups on social media, CLL Support Group, there are two words that tend to still strike fear into CLL patients' hearts, and those two words are Richter's syndrome. Are there any new trials looking specifically at Richter's?

Dr. Catherine Wu: Bill?

Dr. William Wierda: Sorry, I thought that was directed to you. You mentioned Richter in your introduction also, and we've done a lot of work together also on Richter's transformation. There are interesting clinical trials. We've done a lot of work with chemoimmunotherapy. It does not work well for patients with Richter's transformation, so we have turned our attention towards more immune-based treatments, bispecific antibodies are being studied.

CAR T cells are being studied for patients with Richter's transformation. And so, we will continue that work. We're most optimistic about the immune-based strategies for patients with Richter's. Even allogeneic stem cell transplant – that is the one situation where I will be more proactive about referring patients for a stem cell transplant if we can get control of their Richter's transformation with treatments that we have, and they have a donor, and they're fit enough to get a stem cell transplant.

So, this is an area that we're doing a lot of work on. In order to conduct our clinical trials, we need referrals, and we need to be able to put patients on clinical trials, so we can do that with the patients that we follow closely here at our institutions of excellence. It would be helpful if we had more referrals from the community, if community physicians were referring us to those patients with Richter's transformation specifically for our newer treatments and clinical trials.

That would be helpful for us.

Jeff Folloder: Dr. Wu, would you like to add to that?

Dr. Catherine Wu: Yeah, I agree that it's not the traditional treatments that we've been using that are working. You know, and ironically, there are some immunotherapies that don't work in CLL, but appear to have a fighting chance in Richter's. And I think there is some really interesting ongoing research that is beginning to delineate the differences in the immune microenvironment of CLL compared to Richter's that might provide us with some answers as to why that is the case.

Dr. Wierda mentioned all these new bispecific antibodies that are kind of coming down the pike right now. These are being actively tested in Richter's, and I think this is kind of an exciting new frontier, and we'll see if we can see a lot of – see some success. My clinical area is an allogeneic stem cell transplant. And so, I am very cognizant of both the benefits, but also the toxicities that happen with transplant.

It's really quite a blunt instrument. So, whatever we can do to keep the good parts and fend away the bad parts, I think would be beneficial. And fundamentally, allogeneic stem cell transplant is an immunotherapy. It is really trying to harness the donor immune system to eradicate leukemia cells. It comes with other attendant kinds of toxicities, but if you remember that aspect, then what is it about that immune response that was so important to get you to eliminate the leukemia? So, keep that part and try to build on it and make it less toxic, and I think that would be a path forward.

Jeff Folloder: Very good. Very good. Back when I started this CLL thing, FCR was referred to as the gold standard of care, and I know we're not doing chemo so much anymore. I guess that the gold standard now is the combination of venetoclax and ibrutinib. Dr. Wierda, just how effective is that gold standard, and more importantly, what comes next when that gold standard fails?

Dr. William Wierda: Yep. So, maybe just back up a little bit. I would say that in terms of first treatments, we have two gold standards. One is maintenance treatment with a second-generation BTK inhibitor. That's a continuous treatment. It's extremely effective. We know from our work with ibrutinib that the average duration that that treatment will work, although patients have to stay on the treatment all the time, is about nine years, and it's probably better with the second-generation drugs, acalabrutinib, zanubrutinib.

And so, that is a gold standard. It's a maintenance. It comes with specific side effects and toxicities, and it requires the patient to stay on treatment continuously, but it's extremely effective and would be considered one gold

standard. The other gold standard is time-limited therapy. And particularly, venetoclax-based therapy, venetoclax plus obinutuzumab, which is an IV medicine.

The venetoclax is given in that combination – one year. The IV medicine, obinutuzumab, is given for the first six months. And we've done work with other combinations, as you indicated, that are venetoclax-based treatment. Ibrutinib plus venetoclax, acalabrutinib plus venetoclax, acalabrutinib plus venetoclax plus obinutuzumab. And then we've most recently done a trial with pirtobrutinib, venetoclax, obinutuzumab.

Those combinations are very active, very effective. We've been able to put those combinations, venetoclax plus ibrutinib and venetoclax plus acalabrutinib, into the NCCN guidelines. So, one would consider them the gold standard because they are in the NCCN guidelines. However, they're not FDA-approved. We can get access to them for our patients because they're in the NCCN guidelines. But most of the clinical trials now and the new data that we'll see relate to those combinations of targeted therapies.

And I expect that we will eventually have not just two gold standards or – that being BTK inhibitors and venetoclax combination with obinutuzumab – but multiple gold standards as first treatment. And those being venetoclax or a new drug that will likely get approval in the next few years, sonrotoclax, that works similar to venetoclax combined with a BTK inhibitor with or without a CD20 antibody. So, that tends to be the challenge. There's more than one gold standard. There are different strategies that we can take with our patients, and optimizing and selecting therapy for individual patients is more the discussion these days with regard to getting the best outcome for our patients.

Jeff Folloder: Excellent. Excellent. Dr. Wu, I've got three minutes. It's just you and me talking here.

So, very personal question. Why can't doctors start CLL treatment right away? Why put them on watch and wait?

Dr. Catherine Wu: That's a great question. I think this is something that's been studied for some time. I mean, there has long been a thought to do that, but there have actually been studies that showed that there wasn't actually any clinical benefit to do it earlier. I think that one reason when we get to the genomics and start to study that CLL heterogeneity that I talked about before is that we still need to try to understand this better. But what we do know is that when we come in with something like a therapy, it actually changes the composition of the CLL. And so, it almost is a fuel to select for more resistant versions of the CLL.

So, the question kind of becomes like, "Do you want to start that process earlier or not?" That's not to say that with the newer agent. On the other hand, the other side of that is treating earlier; shouldn't it be better? And I think it will depend a little bit on what we're treating with. So, if we have more tools, more drugs, better complementary ways to get at it from the very beginning, maybe that kind of selection won't happen, but that's to be seen.

Jeff Folloder: Got it. Dr. Wierda, I'm going to sneak in one more question. Elizabeth has got a great question here. She's a newly diagnosed patient. Is there an opportunity to harvest and bank her healthy T cells for possible future CAR T-cell use?

Dr. William Wierda: That's a great question. The easy response is not really unless you pay for it out of pocket.

Because insurance companies will require there to be some clinical need for the pheresis, which is the procedure for collecting the cells and banking them. And that usually includes a CAR T-cell therapy. So, if you want to pay for it out of pocket, you can probably have it done. As a standard of care option, it's not an option at this point. Now, I will say in our work with the CAR T-cell treatments, we're able to collect T cells from almost all patients, even if they've had a lot of prior treatment, and generate an active product for CAR T-cell therapy even in the previously treated relapsed/refractory setting. So, we haven't had a big challenge with collecting the T cells. And we know that even in patients who are newly diagnosed, their immune system and their T cells are not normally functioning.

So, if you're looking to harvest T cells when you're first diagnosed because you're thinking that they're normal and that you'll have a better product, that's not necessarily the case. The CLL disrupts the immune system and makes it so that those T cells, even if you haven't had any treatment for your CLL, don't work normally.

Jeff Folloder: Okay, I lied. Dr. Wu, there's one more question, and it's another really, really good one. What recommendations do you have for CLL patients who relapse really quickly, like within a year? What can we do for them?

Dr. Catherine Wu: I think currently, and I'm looking at my colleague Dr. Wierda here, I think we would still probably go with all the other treatment options that there are, because just because it's not great that they relapsed early in one year, but you would probably choose a complementary therapy in hopes that you would gain benefit.

The problem becomes when there is resistance to the "new gold standards." And if you develop resistance to that, then it becomes actually quite challenging. And

maybe we're talking about allotransplant or something like that, but or new clinical trials.

Jeff Folloder: Thanks to everyone who submitted questions, including those great last-minute questions. Before we wrap up this town hall, I'd like to hear some closing thoughts from our guests. Dr. Wu, you're up first with all of your insights into current CLL research. Are you optimistic about the future of CLL treatment?

Dr. Catherine Wu: I am absolutely optimistic. You heard about all the amazing choices that are in front of us. There's an active community trying to get at the answers to those questions that I mentioned. We do have threats to our funding, and that's at the federal level, but that's where, again, I think an organization like CLL Global is so important because I think this is where philanthropy support, foundation support really make a huge difference from top-down, from the most – the youngest investigators to have that vote of confidence that that direction is the right one to take to senior investigators like myself, just making sure that we can feed the mouths to keep things going.

But immensely appreciative of all the support because there are, it is an exciting time. So, why wouldn't you want to go for a cure, right? Why wouldn't you want to keep reaching forward and extending ourselves so that we can get to that goal?

Jeff Folloder: Indeed. Dr. Wierda, my doctor, my friend, any final thoughts for the audience as we wrap up?

Dr. William Wierda: Sure. Just a few brief thoughts. First, I'd like to thank Dr. Wu for participating with us today and sharing her knowledge and understanding. And to you, Jeff, for moderating, as you do a wonderful job every time you do it. And we really appreciate you giving your time and supporting our patients, and you're in your advocacy role for our patients. I'm an optimistic person. I'm a glass-half-full type of person. We've made a lot of progress. I am a little concerned, as Dr. Wu indicated also, about the current research environment that we have, and this will probably result in a slowing of our progress.

That said, we are determined, I am determined, and my colleagues, I know, are determined to make progress. That progress may be made outside of the U.S. temporarily. We've been traditionally – the U.S. has traditionally been really on the brink and forefront of medical progress. And we've been the world leader in biomedical research and therapeutic development. And again, we may see that slowing because of the current environment.

And it is striking to me how important it is to be engaged, involved, and knowledgeable about politics and involved to the extent that you're participating

in the process and voting and expressing what's important to you. And so, with that, I'll say that again: we are determined, and we are persistent, and we'll continue with our efforts with full force as we have all along, and we will persevere.

Jeff Folloder: Excellent. I want to thank our experts for taking the time to join us today. And a reminder, don't forget to fill out the survey following today's town hall. It will help us provide information that's important to you, and stay tuned. We're planning our next town hall, which will be held early next year. Please continue to send in your questions, and thank you for joining us.