CLL Global Virtual Town Hall: February 7, 2024

Jeff Folloder: Thank you for joining us for the CLL Global Research Foundation's very first virtual town hall of 2024.

We're excited to hear the latest in research from CLL experts, including news from December's American Society of Hematology Meeting, and we've received so many questions for this webinar that we've extended the Q&A portion of the town hall, so we've got lots to cover today.

As I mentioned, my name is Jeff, and I will be your host today. I am a CLL patient. I am currently relapsed after going through treatment just one time in a clinical trial, and I am honestly living my best life ever. Even as a CLL patient, I'm doing everything that I want to do and more. Couple of weeks from now, I'll be in the high desert of New Mexico doing the Bataan Memorial Marathon March. So, if I can do it, you can do it, and let's figure out what you need to know.

Before we get started, let me cover just a few housekeeping items.

Many of you have submitted questions for our expert panel when you registered, and we are going to do our very best to answer them all. You can also submit questions via email to townhall@cllglobal.org. Please keep in mind that we cannot answer specific questions about your medical treatment. Those should be discussed with your own healthcare team.

You are also going to receive a survey following this town hall. Please share your thoughts with us, so we can continue to produce programs that are helpful for CLL patients and their caregivers. Remember, your feedback is crucial for us delivering the best events that we can.

Now it's time to meet our experts. First up is Dr. William Wierda. Dr. Wierda is the president and CEO of CLL Global.

And he's also the executive medical director of the University of Texas MD Anderson Cancer Center, to name a few of his roles. There's a lot to say there. Dr. Wierda, welcome. Would you like to say a few words to our audience?

Dr. William Wierda: Thank you, Jeff. Yes, I'm happy to be here, and I'm looking forward to the discussion. These types of meetings are always great for me because it does give us a connection with our patients, and that's

what it's all about for us. So, I'm grateful to be here, and happy to have you here, Jeff, and Patrick here for the discussion.

Jeff Folloder: Thank you. Also joining us today is Dr. Patrick Reville, who is an assistant professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. Dr. Reville sees CLL patients in clinic and is also involved in research. Dr. Reville, can you please share a little bit about yourself and your work with CLL

Dr. Patrick Reville: Yes, thank you, Jeff, and the CLL Global for the invitation. I'm happy to join and share a little bit, both about myself and help answer some questions here today. Yes, I'm an assistant professor in the Department of Leukemia, clinically focusing mainly on treating and caring for patients with CLL, although we treat a range of leukemias as well.

Research-wise, we have sort of a growing research group that's really looking at the intersection of leukemia and the immune system, and so what we're really focusing on in CLL is sort of how that impacts immune dysfunction, trying to understand immune dysfunction.

And then I think sort of translationally, it's looking to see if we can turn any of those insights into treatments in terms of immunotherapies or strategies to improve the immune system.

Jeff Folloder: Great to hear from both of you. And in the spirit of being completely candid, I'm a patient at MD Anderson.

Dr. Wierda is my doctor, and Dr. Wierda was straight up involved in taking care of me last week when for the first time, I managed to come down with COVID. The nirmatrelvir/ritonavir (Paxlovid) worked just fine, Dr. Wierda, so thanks, and my wife thanks you as well.

Let's get started. Let's go to treatment and research news. Back in December, the annual American Society of Hematology, or ASH as we call it, this meeting was held in San Diego, California. Researchers from all around the world attend this meeting and shared their hematology research. Dr. Wierda, can you explain a little bit about ASH, what's going on there, what it's all about, and maybe some of the research highlights from that meeting?

Dr. William Wierda: Sure. Thanks, Jeff. I have just a few slides. So, as Jeff said, the ASH, or American Society of Hematology meeting, is an annual meeting that we have.

It's usually the first or second week in December. That's where clinical scientists and laboratory scientists from all over the world come together and share their research and new results in presentations. Those presentations can be oral presentations, which are about 10 minutes of a lecture or speech with slides, or they can be posters, where their data is displayed in poster format. And there are educational lectures during the sessions. And it's something that we all look forward to every year, and it's the really the place where new research is presented. New data, it's – there are other meetings during the year, but it is our main big meeting.

A couple other meetings to just touch on, one is the American Society of Clinical Oncology, or ASCO. That does have malignant hematology data presented.

But it's mostly made for solid tumor, solid tumors and ongoing research, clinical research in solid tumors. That's in June every year. We do attend that.

And then around the same time is the European Hematology Association, or EHA, ee-ha, and that's the European meeting. That's the European hematologist meeting that's a bit smaller, but it's every year, and we do see important data reported at that meeting as well.

So, if we go to the next slide, what I wanted to do is just touch on some of the key presentations. Now, the important data that is presented is usually selected for oral presentations. So, I have three slides here that summarize the oral presentations and the data that I'm going to talk about, the data that was presented with them and sort of the highlights for those data.

The first two slides have more abstracts or presentations listed on them, and then the last one just has one.

So, this slide summarizes the oral presentations that related to first treatment for patients with CLL. And just briefly to review them, the first one was a long-term follow-up presentation that Adrian Wiestner gave on outcomes with ibrutinib (Imbruvica), particularly as first-line therapy. What we learned from that 10-year experience

is that the average creative time that ibrutinib maintains control of the disease in the frontline setting is nine to 10 years. That's maintenance, it's continuous until it doesn't work any longer. But patients, if it's used as the first treatment, are doing extremely well with maintenance upwards, on average, of a 10-year period of disease control.

That's the first time we've seen sort of the average reported because it takes a long time to collect that data, and we don't have the median, for example, for acalabrutinib (Calquence) or zanubrutinib (Brukinsa) yet. We do anticipate that it'll be as good if not better than ibrutinib, and those data will be forthcoming.

The ELEVATE TN trial is a frontline trial with acalabrutinib. It was three arms, and it compared treatment with acalabrutinib by itself, acalabrutinib plus obinutuzumab, or chemoimmunotherapy. And that trial demonstrated improved outcomes with acalabrutinib or acalabrutinib plus obinutuzumab (Gazyva). This was a long-term follow-up report, and really not any significant additional conclusions from that report compared to what we already knew about. It does appear that patients with 17p deletion, while they do very well with acalabrutinib-based treatment…

…the addition of the CD20 antibody probably doesn't add a lot to the treatment for that particular population of patients with 17p deletion.

The GAIA trial was a large, randomized trial looking at four different treatments, three of which were venetoclax-based (Venclexta) and one of which was chemotherapy. That trial demonstrated improved outcomes for venetoclax-based treatment over chemotherapy if venetoclax is given with obinutuzumab. Either venetoclax plus obinutuzumab or venetoclax, obinutuzumab, plus a CD20 antibody. Venetoclax, obinutuzumab, and ibrutinib.

That trial illustrated – and we've seen the data before – that obinutuzumab is a better CD20 antibody compared to rituxumab, so we prefer obinutuzumab, particularly in this trial, demonstrated when given with venetoclax.

There doesn't yet appear to be a difference in terms of outcomes for venetoclax/obinutuzumab with or without the addition of ibrutinib, but longer follow-up and subsequent reports may show something different.

The CAPTIVATE trial is a trial that has been going on for several years. This was a five-year follow-up. The important point from that report was for patients, for the few patients that have had their disease return and has needed to be retreated, for those patients – and this trial, CAPTIVATE was ibrutinib plus venetoclax for one year of treatment – but for the patients whose disease has come back after they've been in remission, we didn't see mutations in BTK. And so the important point there is that patients should maintain their sensitivity to treatment, whether we're talking about ibrutinib or venetoclax or the combination.

And, in fact, those patients who have been retreated with either ibrutinib or combined ibrutinib/venetoclax have responded to treatment, and that was the important follow-up from the CAPTIVATE trial.

A longer-term report for the GLOW data, which was ibrutinib/venetoclax compared to chemoimmunotherapy, really not any new conclusions from that, but longer follow-up.

And the FLAIR trial was an important trial that P. Hillmen presented, which was a comparison of ibrutinib/venetoclax versus chemotherapy, the FCR regimen. That trial demonstrated improved outcomes with ibrutinib/venetoclax over chemotherapy or chemoimmunotherapy. And that trial allowed treatment for two years, up to six years with combined ibrutinib and venetoclax combined therapy. And patients could stop earlier than the six-year time point if they became MRD undetectable.

So, that trial is important, and continued follow-up for that trial will be important because of this ability to treat longer with the combination, and the discontinuation of treatment based on MRD status.

If you go to the – so, that's the summary for frontline. For relapsed disease, I'll go in the interest of time a little bit quicker. If you go to the next slide. There were several abstracts that were presented for patients who had previously received treatment. There was an update from ALPINE that was a comparison of zanubrutinib versus ibrutinib and demonstrated improved tolerability for zanubrutinib, and a bit better efficacy with zanubrutinib compared to ibrutinib.

The CLL2-BAG study is a trial with acalabrutinib, venetoclax, and obinutuzumab. That showed impressive outcomes in relapsed patients with that combination.
There were two abstracts presented with pirtobrutinib (Jaypirca), one demonstrating activity in patients who had had a prior covalent BTK inhibitor. Most of them had had prior ibrutinib, but they could also have had prior acala or zanubrutinib.

But very good activity with pirtobrutinib after a covalent BTK inhibitor. High response rate of 80 percent response and median progression-free survival of about a year-and-a-half.

And then we also reported on mutations associated with pirtobrutinib resistance. With the covalent BTK inhibitors, ibrutinib, acala, and zanubrutinib, the predominant mutation of BTK that arises that's associated with resistance is the 481 mutation. It's different from pirtobrutinib, and that was the important presentation with regard to that abstract that Jennifer Brown presented. Patients who go on pirtobrutinib will lose that 481 mutation, but when they develop resistance, they'll acquire a couple of other different mutations in BTK as a resistance mechanism.

Tanya Siddiqi presented an update on the Liso-cel trial, the CD19 CAR T-cell trial. That was not – it was more patients who had been treated and longer follow-up on that trial, but definitely clinical activity in patients who are refractory to BTK and BCL2 inhibitor-base therapy with Liso-cel. And we know Liso-cel is currently under review by the FDA for potential accelerated approval.

Jennifer Woyach presented an abstract on a drug referred now to as LP168. It doesn't yet have a name. It's another BTK inhibitor. And there was a bispecific ROR1 monoclonal antibody that was presented, a Phase I clinical trial referred to as NVG-111.

And then finally, on the last slide is a trial that Othman Al-Sawaf presented, which was a combination of the PD1 antibody with zanubrutinib for patients with Richter's transformation demonstrating activity.

There are other trials that have studied similar combinations and have demonstrated activity. The novel aspect of that, I'm not going to go through the rest of these slides because there's not adequate

time, and these trials are trials that we have open and activate at MD Anderson, so we'll skip those.

And that's really a highlighted summary of what was presented and discussed at the ASH meeting in December. We can talk about the data more during this session, the question session if we like.

Jeff Folloder: So, I think what I'm hearing is every day that goes past, we're getting further and further away from chemotherapy.

Dr. William Wierda: I have moved completely away from chemoimmunotherapy. I almost never use it. So, yes, the answer to your question is yes, we still see it used in the community a bit, but I have a harder and harder time justifying that selection.

Jeff Folloder: Very good. Dr. Reville, are there some highlights from ASH that you'd like to discuss? What would you like to add?

Dr. Patrick Reville: You know, I don't think that I have a whole lot to add. I think Dr. Wierda did a very good sort of broad overview of the highlights of ASH. I mean, I think for me, it was the majority of what I took away from the ASH presentations was really the continued follow-up of sort of the newer non-chemotherapy options, both on the frontline and the relapse setting, showing really good activity and sort of good safety profile with some emerging data, I think, over time that helps us decide between different therapies for different patients, and then different combinations.

That space is starting to become a little bit more clear as we think about personalizing therapies for individual patients.

And that's really only kind of known as we get this longer data, so I think at this stage here and moving forward, we've got really good, long-term data on a number of these agents to really help us decide.

From a scientific standpoint, like I said, I have strong interest in the immune system and sort of its interaction with CLL, so the other thing that's really nice about the ASH conference from my standpoint is that in addition to the clinical research, there's a lot of basic and translational science presented at that meeting. So, there were a number of abstracts that really looked at the immune system and its function within CLL, and that's really an emerging space. So, there's a number of people that are working on that, and

I think that there's some stuff that will be coming down the road that will be helpful there.

Jeff Folloder: Up until now, I haven't had the opportunity to pick your brain, so I've got a question for you. What other areas of CLL research are you particularly interested in?

Dr. Patrick Reville: Yes, I mean, I think there's a few things. You know, like I said, I think this aspect around the immune system, and in particular as it relates to immunotherapy is interesting. CLL kind of stands a little bit uniquely in the lymphoid malignancies, and that includes the other lymphomas as well as ALL, where immunotherapy really hasn't been a major player, and the activity rates of things like CAR-T cells or some of these other immune-based agents to date hasn't been as well explored in CLL as it has in some of these other settings. And so I think that there's a lot of room for that to grow over time.

I think as I think forward, there's a number of aspects. Since we're doing in a lot of ways better at treating CLL and getting away from chemotherapy-based treatments, there's a large focus that is on survivorship and trying to optimize these treatment strategies such that we're maximizing sort of patient outcomes and incorporating that sort of mentality into the way that we're studying these drugs to really sort of optimize patients' well-being sort of at a more global level, in addition to their CLL-specific outcomes.

Jeff Folloder: Sounds fantastic. It literally is a brave new world. Dr. Wierda, before we get to Q&A, we'd all be remiss if we didn't discuss research that was funded by CLL Global Research Foundation. That's an organization that I hold near and dear to my heart, mostly because it's very, very personal to me.

Can you give us an update on what CLL Global Research Foundation is doing in terms of research?

Dr. William Wierda: Sure. So, the CLL Global Research Foundation was started by Dr. Keating many years ago, more than 10 years ago, and it was founded with funding and donations that had predominantly come from patients. And that funding has been used to support research – laboratory research, clinical trial research, and also to support meetings like this and annual meetings we have with our colleagues to discuss our research.

Most of the funding that we collect for the Foundation goes to research. There is very low overhead or administrative cost to that, where some other funding and granting agencies, you'll see a lot of cost going to the infrastructure.

We have a great administrator, Sam Pace, who does all of the administration for the Foundation, and we have for many years now supported quite a bit of research. I don't remember what the number is up to now, but I believe it's upwards of $30 million over 10 years in terms of research funding for work.

And that's been very beneficial because you know, over the last 10, 15 years, we have made remarkable advances to treatment and outcomes for our patients with CLL. That's sort of the work of a village, not an individual person or group, and CLL Global Research Foundation has been part of that research village that has contributed to the progress that we've made.

Jeff Folloder: And that village is not just local at MD Anderson. It's all over the world, isn't it?

Dr. William Wierda: Right. So, the Foundation funds investigators all over the world, collaborators that we have both in the U.S. and in Europe.

Jeff Folloder: Fantastic. Thank you very much for that update. I'd like to mention that if any of you miss anything that's presented by the panelists today, if you missed their slides or anything that they have said, there will be a replay of this town hall that will be made available on the CLL Global website at cllglobal.org within just a few days. We'll also have that website listed there on the screen.

If you've got questions, this is your reminder to send them to townhall@cllglobal.org. We have a bunch of questions, and the first question on the list is one that I am so looking forward to hearing the answer to because I think I know the answer, but I always doubt myself.

This comes in from Barbara. Barbara wants to know, "Is CLL now a treatable disease, just like diabetes?"

Dr. William Wierda: Who's going to take that? Patrick, you want to take that?

Dr. Patrick Reville: Yes, I can. I think it's a bit of a difficult question to answer. I think yes, it's a very treatable disease. I would not necessarily liken it to

diabetes in the sense that I still think that it requires a lot of attention, especially early on. And so it is something that I think requires a lot of back-and-forth, both between the patients and the physicians and the healthcare teams that are managing it.

I think the treatments that we're using to manage CLL and the way that we think about CLL really requires still a decent amount of expertise, and so is something that is particularly managed by experts in the field.

Whereas I think in terms of diabetes, again, they're both chronic conditions. I think the outcomes, though, are a bit different between the diseases. So, sort of yes and no, I guess.

Dr. William Wierda: That's interesting. I had a long discussion yesterday with Tom Kipps, Dr. Kipps at UCSD about this, and we're putting together a perspective paper, several of us, on cure of CLL and what does that mean.

And in our conversation, Tom and I had, sort of he struggles with the introductory that Dr. Tait Shanafelt and I wrote about cure and what does it mean to have a cure, and what is a cure, and is cure important or is it as important to transition into a situation where you can manage the disease long-term.

So, I mean, I would agree with what Patrick is saying. I didn't like the analogy of diabetes with CLL, where we're at with CLL now, because they're different illnesses and different concepts apply.

I would say that for many, probably most of our patients with CLL, their lifespan is probably not shortened by their diagnosis of CLL, even if they need treatment.

Now, they can have infections, they can have second cancers, they may need treatment for their disease. But by and large, we have agents now that we can control the disease for their lifespan and not anticipate a shortened lifespan because of their disease that's uncontrolled.

There are some patients that develop resistance that are high risk that we struggle with still, but that's a smaller fraction than it used to be, certainly when we had only chemotherapy to treat.

Jeff Folloder: I think that is a very crucial takeaway that everyone should keep in mind. I've got a question for Dr. Wierda from Susan. This is a great question. "Does cytogenic testing direct doctors to the best method of treatment?"

Dr. William Wierda: So, I would say yes. I would say, if I were to choose yes or no, I would say yes, and the reason I say yes is when we talk about cytogenetic testing, cytogenetic can fall into several categories. Metaphase karyotyping is a form of cytogenetic testing, meaning we generate chromosomes in the lab that we can look at and count and determine if there is a change in the number or the structure of the chromosomes.

Another genetic test would be FISH. That tests for specific chromosome abnormalities. The one that is the one that we key into for the FISH test result is the 17p deletion. That's a high-risk feature. That's loss of part of chromosome 17, and that's also frequently associated with a mutation in the gene that's lost when you lose part of that chromosome, which is TP53. Patients with 17p deletion and mutated TP53 are high risk. They should not receive any chemotherapy. The target therapies improve outcomes for those patients, but we still have work to do in patients with that feature of 17p mutated TP53.

They're at risk for developing resistance, they're at risk for developing Richter's transformation. Those are patients we don't like to be in remission and off treatment if their disease has been active.

So, the answer to the question, and the very specific answer is yes, chromosome studies do matter. 17p deletion particularly will direct us to a maintenance strategy with a BTK inhibitor in preference over a fixed duration, venetoclax-based therapy. So, it is useful in terms of treating patients and managing the disease.

Jeff Folloder: And tell your puppies that I have treats for them. It's not a problem. I have another question for you that just came in from online. "At a previous CLL symposium, Dr. Nicole Lamanna said that if you do well with CAR T, you tend to do very well. But on the other hand, if you don't respond to that treatment, it's significantly less effective therapy."

"I've also heard that the average remission from CAR T is only about two-and-a-half years. Do you find that to be correct generally, and

what about the percentages of patients that do well with CAR T?" That's a whole lot to lay on you, but it's your turn.

Dr. William Wierda: You want me to answer that question, or Patrick? Was that a question for Pat?

Jeff Folloder: That's for you, Dr. Wierda.

Dr. William Wierda: Okay. So, I have been involved in the Liso-cel trial for a long time. I don't know that I would agree with Nicole. I respect Nicole and I love Nicole and she's a great friend, but I don't know that I would necessarily agree with what she's saying. The Liso-cel trial and the data that we have presented thus far has been in patients who have failed a BTK inhibitor and venetoclax. That's two agents, and those are the targeted agents that we have that have any reasonable activity, and patients have failed those. So, we're talking about a very high-risk population of patients who are getting CAR T that have been reported on so far.

Now, the TRANSCEND 004 trial is a very large trial. There were other patients enrolled that we haven't had a lot of information on yet, but we will probably in the near future. Patients who haven't necessarily failed both treatments, but perhaps have failed only a BTK inhibitor or only venetoclax-based therapy.

We also have a cohort on that trial of Liso-cel plus ibrutinib, where the activity seemed to be very good when you are using it in combination with ibrutinib.

The patients who are doing very well on the Liso-cel that we've reported on so far are patients who achieve a complete remission, meaning all their lymph nodes are less than 1.5 centimeters, and their counts have improved. They may have not had full recovery of their counts, but they have had clearance of their marrow and their nodes are all down to 1.5 centimeters. That happens in about 20 percent of the patients. All of those patients have been MRD negative.

All of those patients that we've reported on so far have maintained in remission. They haven't relapsed.

So, I think the data that we have seen so far has been, again, in a high-risk population, and the patients who respond do exceptionally well. There is some suggestion that there's clinical

benefit for patients who don't get a complete remission. Patients who have a partial remission, and even those who have stable disease. But it's not durable as it is for patients with a complete remission.
So, we need to see more data. We need to see more data from the TRANSCEND trial. We need more follow-up from that data. I think once we have some direction from the FDA in terms of approval, that information will come out for the trial.

Jeff Folloder: Fantastic. Dr. Reville, apparently COVID is still a thing, and it's still top of mind.

William would like to know if there are any forthcoming preventative offerings for CLL patients to prevent COVID, sort of like what tixagevimab/cilgavimab (Evusheld) did.

Dr. Patrick Reville: Yes. This was actually – I saw this question ahead of time, and I don't know if there's anything coming that would be sort of new antibodies. I mean, there are certainly continued developments from a vaccination standpoint, and so there is some ongoing research both looking into sort of new antibodies from products such as Evusheld with sort of the newer variance.

In addition, sort of ongoing work with updating vaccination. Today, there's nothing new that's approved compared to, I think, this time last year, for instance.

I don't really know sort of the timeline of kind of where that is in development. I don't know, Dr. Wierda, if you have any better understanding of the development there?

Dr. William Wierda: So, AstraZeneca, who produced Evusheld, pulled it from the market because it was no longer active. They have another drug that they have been running clinical trials on that hopefully will be approved. It's particularly important for patients who don't respond to the vaccination and/or can't tolerate the vaccination. So, I do anticipate – I don't know what the timeline is, but I do anticipate a replacement for Evusheld becoming available in the near future.

Jeff Folloder: Great. Dr. Reville, I want to follow up and go off on just a little bit of a tangent. We're talking about COVID. The subject of vaccines and boosters and all that wonderful stuff. Apparently there's a new kid on the block.

And that new kid on the block has initials RSV. Should CLL patients be getting RSV vaccines, and how should they be dealing with the RSV situation?

Dr. Patrick Reville: Yes, I mean, I think a lot of these respiratory viruses have been an ongoing problem for CLL. I mean, even obviously pre-COVID. The RSV has been around, other coronaviruses were around. Influenza. So, the respiratory viruses in particular have been an issue for patients with CLL, and that has to do with a number of issues related to the immune system, both intrinsic issues related to them having CLL but also issues with antibody production for patients that are on treatment, either previously with chemotherapy or currently with in particular CD20 antibodies or BTK inhibitors that might affect the way that the body is able to mount an immune response.

So, in terms of vaccines, I mean, that would be a vaccine that we would recommend for patients with CLL. They would sort of fall into the category for which it's now approved, and would be a group of people that can have more severe complications related to RSV infections that we would hopefully like to prevent by having them vaccinated.

There are some issues from time to time around when to administer those vaccines to get an optimal response, and so for a lot of patients, if possible, timing it when people are maybe not receiving the CD20 antibodies in particular could help to have them mount a better immune response.

At the same time, there are a lot of patients that are on continuous therapy, either with BTK inhibitors or even continuous venetoclax in some settings, in the relapse setting.

And so if therapy can't be interrupted, then I think giving the vaccines when it's reasonable to give the vaccines is a good approach.

We don't have great testing usually to really look specifically at an individual level about the response to the vaccine, so I think a lot of it is just sort of giving the vaccine at sort of the optimal time points to try to maximize your responses.

And then I think the other part of your question is sort of dealing with RSV. We see a decent amount of RSV in our leukemia patients

and across hem malignancies in general, so that is something that we manage, either on the inpatient setting or the outpatient setting, if it's reasonable to do so.

So, I think as patients are not feeling well, getting sort of testing for a variety of viruses, it's nice we kind of have some targeted antiviral therapies for different things, including RSV, that are potentially reasonable to consider in the right setting.

Jeff Folloder: Gotcha. Dr. Wierda, this is a great question. I'm thrilled with all of the questions that we've got coming in. "Can someone really know how long before actual diagnosis they had CLL?" I mean, I know MD Anderson told me yes, you have CLL. How can I know how long I had it before that moment?

Dr. William Wierda: I don't think there's any way right now that we can tell how long somebody's had it before their diagnosis. Most of the patients who are newly diagnosed are diagnosed based on an incidental finding of a routine blood count. It's uncommon for patients to come in with symptoms or with significant problems and not have been previously diagnosed with CLL.

But there are different rates at which the disease grows between different individuals. Some individuals probably have had it a lot longer than others at the time of diagnosis because of the rate of the growth being different between individuals.

Some of the factors that we measure these days kind of give us an idea about how rapidly growing the disease is, which would mean if it's a more rapidly growing form of CLL, it would be a shorter time that they had it prior to their diagnosis than a patient who has very slow-growing, chronic disease that doesn't change notably. But we don't really know, from most patients, how long they've had the diagnosis.

How long they've had the disease before they have the diagnosis.

Jeff Folloder: Gotcha. I know that for many patients, a diagnosis of CLL is a spontaneous thing. It comes in from out of the blue. Dr. Reville, Yvette asks, "My father and mother both had CLL. Could this be why she's developed it, and should my daughter be tested? Are there actually genetic markers that can be tested?"

Dr. Patrick Reville: Right. So, this is another good question. So, we know that there are some sort of clustering of CLL within families. We also know that people that have relatives with CLL, first degree relatives, there is an increased risk for CLL in those patients.

There is no – there really aren't very well-defined genetic or genes that have been defined that really confer that risk. So, while we do know that within certain populations or within certain families, there can be this elevated risk for CLL, we haven't really narrowed that down to like a very specific gene.

Now, we do – and at MD Anderson, we have a leukemia genetics clinic. There's a number of other centers around the country that have genetics clinics and cancer genetics clinics, and some of them even have more specific leukemia genetics clinics. And so these would be the types of patients that would be I think worth having a referral to a clinic such as that for some of this testing.

To see if any of these genes that we do look for that can be inherited, that confer leukemia risk or lymphoma risk, they could be tested. But you know, there's other cancers that people think about, like breast and ovarian cancer with the BRCA genes, that there's a very specific high-risk gene that can run in families. With CLL, even though we can see the disease in families sometimes, this case that we're discussing, we haven't really been able to find that very specific high-risk gene. And it may be that there just isn't one that occurs at sort of a large frequency.

Jeff Folloder: That makes sense. Dr. Wierda, you mentioned MRD status, or MRD-negative status earlier. Britt wants to know what she can expect from the immune system after MRD negative status has been achieved.

So, one, again, what is MRD status, and two, can we hope that our immune system actually gets jump started?

Dr. William Wierda: So, MRD stands for minimal residual disease, or measurable residual disease. It refers to testing that we do either in the blood or in the bone marrow in individuals who have normal-appearing blood, normal blood counts, normal-appearing blood cells under the microscope, normal-appearing bone marrow under the microscope, but may potentially have some low level of CLL still there that we can't identify on those rather crude tests that we do,

blood counts and microscopic examination of the blood or the bone marrow.

So, MRD sort of refers to a state of very low level of disease that's detectable, but you have to use special, very sensitive tests to detect it.

We do know that if you can get a patient in remission and to a level where you can't even detect that minimal residual disease any longer, that's referred to as undetectable residual disease or undetectable measurable residual disease, and undetectable MRD. If you get a patient in a deep remission where you can't detect any MRD, that is the best quality of remission that we have currently, meaning the deepest remission.

The importance of that is that the deeper the remission, the longer – the deeper the remission or the deeper the response, the longer the remission is expected either on or off therapy. So, if we have a patient who has still residual disease detectable at the end of their treatment, at the end of a year, for example, of ibrutinib plus venetoclax.

If they're detectable, they're going to have a shorter remission than a patient who is undetectable who's had that same treatment. And the question is a complicated question in terms of what happens to the immune system in patients who are undetectable. We think there's some improvement. We do know that the T-cell counts will improve. We have not seen full recovery of patients' immune systems, even if they become MRD undetectable.

We don't know why that is. Maybe it's because it takes longer than the period of time that we've had to observe patients after ibrutinib venetoclax who are becoming MRD undetectable. Maybe it just doesn't restore to the normal function, and for some reason the CLL has disrupted things so much that they don't recover their immune function. And as Patrick said earlier, that's an area that we're very actively interested in and investigating in our patient population.

What are the immune dysfunction characteristics before they get treatment? Do they restore their immune function when we get rid of all the detectable leukemia? And if they don't, what are some strategies that we can use to accelerate or improve that immune restoration?

That's an area that in medicine, there's not a lot of data that's been generated, there's no other diseases that we can use, so we're sort of on the forefront of clinical research and investigation in that area. And that is really a big unmet need for our patient population because of the risk for infection and other cancers.

Jeff Folloder: That's very interesting. Dr. Reville, I have a question that's come in regarding watch and wait, or as us patients call it, watch and worry because no matter what you guys tell us, we're still going to worry when we're doing nothing. We know we're doing something, but it just doesn't feel good.

When they're in watch and wait, when a patient is being observed, what white blood cell count elevation would prompt a therapy, or is it just the WBC that does that?

Dr. Patrick Reville: Yes, so actually the white blood cell count by itself is usually not the main reason that we would think about initiating treatments. And so the white blood cell count all on its own can actually get very high before it would ever cause any significant problems on its own. And so the mainstay, really, of thinking about treatment initiation, and there's clear sort of guidance on this in different settings. But it's mainly based on symptoms.

So, how patients are feeling I think is really the biggest consideration. So, the numbers, especially the white blood cell count all by itself, is usually not something that I am looking at as sort of the immediate decision point to start treatment. There are other blood counts that we're looking at. In particular, we look at sort of the red blood cell indices and the hemoglobin or the platelet count, which are kind of the other two major blood components.

So, if we start to see issues with those, in particular those going down, that could be a sign that the CLL is starting to disrupt the way that the normal blood system is being formed, and so that might be an indication for starting treatment.

And then I think lastly is around lymph nodes. And so lymph nodes that are getting large, growing rapidly.

Or again, coming back to the symptom piece, lymph nodes that are starting to cause symptoms or starting to impede on the function

of sort of other organs or other things there. That would be another reason.

So, the white blood cell count is a piece of that, and we do look at that as we're investigating, but that all by itself is not usually the sold determinant for starting treatment for patients.

Jeff Folloder: That's great information to get out to the CLL patients and their caregivers. Dr. Wierda, a question came in just a few moments ago. It's in regard to the 10-year average that you were talking about earlier in the presentation. They say, "I saw where you had the 10-year average of effectiveness for ibrutinib. Do you mean by this that that is the average number of years that you have seen ibrutinib continue to be effective?" Question.

"Or" – well, the reason is – the reason why he's asking is that he's been on ibrutinib for nine years now and wants to know what comes next.

Dr. William Wierda: Yes. So, it's a little bit complicated to explain. So, it's a median progression-free survival of 10 years. So, progression-free survival means no – and there are specific criteria we use for progression, no progression, and the median means if you take 100 patients and put 100 patients on ibrutinib, patient number 50 will have progression of their disease at 10 years.

So, you'll have patient 1 through 50 potentially progressing before 10-year time point, and then you'll have the other half of the patients, patient number 51 to 100, who are still having good disease control on ibrutinib at that 10-year time point.

So, it's the median. It tells us the time that – it's not the average. It's sort of where that middle patient, how long that middle patient has disease control or progression-free survival. So, the answer to the question is it's easier – because I think people understand – lay people understand it a little bit better by just saying the average length of time that the drug works is 10 years.

That means that on average, half the patients will have a shorter response duration, half of them will have a longer response duration.

And the other thing to keep in mind is that with ibrutinib, we see a fair number of patients coming off of ibrutinib for some side effect

or toxicity. That doesn't mean that a BTK inhibitor won't continue to work for those patients.

So, now we have a situation where, okay, if a patient is on ibrutinib for five years or four years and they have to come off ibrutinib because they have some muscle pains or joint aches and pains, they can switch over to acalabrutinib or zanubrutinib in that situation and expect to have a long period of response to treatment, at least that 10 years or longer.

And that's a little bit different than the way those data were generated because if a patient comes off ibrutinib for intolerance in that trial, they're monitored for progression on observation, not additional treatment, and so that 10-year time point also includes patients who have stopped early because of intolerance. And their disease progressed, and then they to on to a subsequent therapy.

Hopefully that's – it's a complicated concept, or several complicated concepts, but I think the important point is that you can expect, on average, a response duration of 10 years or more with the BTK inhibitors.

It may be better for the second generation BTK inhibitors, acala and zanu.

Jeff Folloder: Fantastic. Dr. Reville, we have a question that came in that I haven't heard before. "Is there a risk of CML or AML from CLL, and what about from CLL therapies?" And before you answer, tell us what CML and AML are.

Dr. Patrick Reville: Right. So, CML and AML are two other types of leukemia. So, CML is chronic myeloid or chronic myelogenous leukemia. It's sort of in some ways analogous to CLL, just in a different immune cell. So, CLL happens in the B lymphocytes, and CML happens in myeloid cells. So, it's a chronic leukemia of myeloid cells.

AML is an acute leukemia, so a quicker moving, more aggressive leukemia of myeloid cells.

In terms of the risk for CLL to CML, there is none that I am aware of in terms of risk of CLL to CML. In terms of AML, I'd say that there is no direct risk from the CLL per se, meaning that going back to the sort of genetic question, I think the genetics of CLL and AML are very different.

But AML, acute myeloid leukemia, can occur in some patients that have received chemotherapy in the past. And so any chemotherapy agent, or certain chemotherapy agents do carry a risk of causing damage to the bone marrow, and then damage to the bone marrow can result in AML.

Those risks sort of vary study to study and regimen to regimen, but are generally low. But maybe somewhere in the 1 to 5 percent risk for the various types of regimens.

So, there are patients with CLL that would have gotten chemotherapy or chemoimmunotherapy for the CLL, or allotransplants in which part of the transplant preparative regimen was chemotherapy, and that can injure the bone marrow in a way that can cause a secondary leukemia, and sometimes that secondary leukemia is AML.

So, in that way you can have this link between CLL and AML, but it's usually through the chemotherapy component.

Jeff Folloder: Thank you for answering that, and thanks to all of you that submitted your questions. I know that even though we have an extended Q&A period, there was just no way we were going to get to all of them. We tried.

I promise, we tried to get to as many as possible.

Before we wrap up this town hall, let's hear takeaways from our distinguished experts. Dr. Reville, you've shared your promising research. This is a common question that we ask. It's simple but it's important. Why are you hopeful about the future of CLL care?

Dr. Patrick Reville: Yes, I think for me, I highlighted some of this at the beginning and some of the updates from ASH, but you know, we're moving into a space where we've been able to move away from chemotherapy. We have really good, targeted therapy options that work well, and for most people work for a long time.

So, I think we're getting to the space – and Dr. Wierda mentioned the word "cure" – it's still an open question mark whether we can really, truly cure CLL, but I think we're getting to a point where people are living normal lifespans with CLL.

And I think moving forward, we're really hopeful that we can get to a place where people can spend more time off treatment than on treatment with some of these newer combinations that are coming down. So, really trying to focus on improving people's quality of life in addition to improving the CLL outcomes. I think that those are some of the major goals over the next several years.

Jeff Folloder: That's great to hear, and it's actually very comforting to hear. And as a CLL patient, I love the fact that we've moved away from chemo, and I also love the fact that because of all the research that's going on, because of the work of CLL Global Foundation, every day that I wait to do treatment again means that it's more than likely that something even better is coming along.

Dr. Wierda, we've talked about your foundation, we've talked about research, we've talked about all this good stuff. What would you like to say to our audience to close out the program?

Dr. William Wierda: I'm an optimistic person, and I've remained optimistic, and I continue to be optimistic about curative treatment for CLL. I think we have the tools, we just need to figure out how to use them. And I'm also intellectually curious about this immune dysregulation that we see, and I think part of the cure, we have immune-based strategies, but they don't work quite as well in patients with CLL compared to other types of cancer, like lymphoma.

So, figuring out what the reason is for that and to modify it so that it is as effective, if not more effective, for our patients with CLL to develop curative therapies are things that get me up in the morning and get me excited about working with young investigators like Patrick and individuals who are excited about the disease that we work with in doing our translational study.

I think since this is a – transitional studies, I think since this is predominantly a group of patients, I think CLL historically has had a community that's unique compared to other diseases. We don't see a similar community of patients for other diagnoses, like AML or CML. Patients tend to be very educated about their disease and knowledgeable. They have time to research it, they have time to investigate, they have time to search and find doctors.

I think educating them and educating each other about the importance of research, the importance of participating in clinical trials, right now that's a bit of a barrier for us. We have suffered a

little bit from our success, which is a good thing because we have many patients who are in remission and who are doing exceptionally well.

And at the same time, we have a lot of clinical trials open with new and exciting drugs that we are very excited about and would like to work with and advance and integrate into use in treating patients with CLL.

So, I think thinking about clinical trial options, investigating clinical trial options, we aim to design it, in our MD Anderson CLL program, we aim to design trials and treatments for patients that are potentially better than what they can get as standard of care.

So, I would like patients to think about clinical trial options not as a guinea pig option, but potentially a better option for them, and also an option that allows us to learn and understand and advance treatment for our patients with CLL. So, that's my brief advertisement for clinical research, and it is a very important topic for our patients to be thinking about and to be considering as an option.

Jeff Folloder: Excellent. Excellent words, doctor. I want to thank both of you for taking the time to join us today. Don't forget to fill out the survey. It will help us provide information that's important to you.

And stay tuned. We're planning on our next town hall, which will be held later this year. We hope that you can join us. Again, my name is Jeff. I am a CLL patient. I want to hear this information. I know that you want to hear this information. Thank you for joining us.