CLL Global Virtual Town Hall: September 12, 2024

Jeff Folloder: Hello and welcome! I'm Jeff Folloder. Thank you for joining us for another CLL Global Research Foundation Virtual Town Hall. Today, we're joined by two leading CLL experts as they share the latest in research, treatment updates, and clinical trial developments. We've already received so many questions from our viewers we've decided to dedicate 30 minutes to pose them to our guests.

As I mentioned, my name is Jeff Folloder, and I'll be your host. I am a CLL patient. I've been through "watch and wait." I've been through clinical trial. I'm back on "watch and wait" again, and I'm a passionate patient advocate. My goal is to make sure that everyone knows it's possible to live a great live with a CLL diagnosis. Now, before we start, I need to cover just a few housekeeping items. Thanks to those of you who have sent in questions for our expert panel. You did this when you registered.

We are going to do our best to get as many of those questions answered as possible. You can also submit last-minute questions to the email address found in your Zoom reminder email. That is production@thehccollective.com. Keep in mind that we cannot answer specific questions about your medical treatment. Those should be discussed with your own healthcare team.

You will also receive a survey following this town hall. The survey is very, very important. Please, share your experience with us so that we can continue to improve and produce programs that best serve you, our audience.

Now, let's meet our experts. Many of you are already familiar with our first guest, Dr. Dr. William Wierda. Dr. Wierda is the President and CEO of CLL Global and the Executive Medical Director at the University of Texas MD Anderson Cancer Center where I am a patient.

Dr. Wierda, how would you like to say welcome to this audience?

Dr. William Wierda: Thank you, Jeff. Welcome to our participating audience. I'm very happy to be here and happy to share our new insights and new data. Happy to be with here with Erin so she can share with us her new data and excitement. I think before we move on, I would be remiss if I did not also thank our CLL of Global Research Foundation Founder, Dr. Michael Keating, who has been a dedicated patient advocate through his career and his dedication and commitment continues. So, we thank Dr. Keating also for his

leadership.

Jeff Folloder: Indeed. Dr. Keating was my very first CLL doctor, and he is very near and dear to my heart. Also joining us today is Dr. Erin Parry, who is at the Dana-Farber Cancer Institute.

Dr. Parry, can you please introduce yourself? And tell us about your role at Dana-Farber.

Dr. Erin Parry: Hi. It's so nice to meet everyone, and thank you so much for having me here today. So, I'm an instructor of Harvard Medical School. I run a lab and see CLL patients and patients with B-cell lymphoma at Dana-Farber Cancer Institute.

Jeff Folloder: Fantastic. There is a lot that has been happening in the world of CLL. I marvel at how much has happened since the time I started almost 15 years ago. So much good stuff is happening, and so much is happening so fast. Now that we've met our guests, let's move on to learning about the latest research and treatment developments. Dr. Wierda, what highlights would you like to share with our audience from the recent big scientific meetings?

Dr. William Wierda: Great. Thanks, Jeff.

Yes, I'd like to give a little bit of a summary and an update to patients and colleagues who join us on these town halls in terms of what's been happening new in CLL. We usually learn about data early through meetings and presentations at meetings, and then those works usually get published after a process of reviewing. So, what I wanted to do was go over two meetings and just highlight what was presented at those two recent meetings, which have happened since our last town hall.

The first one is ASCO 2024. That's a meeting that occurs typically in June in Chicago. That's the American Society of Clinical Oncology. There's one presentation from that meeting related to CLL that I'm going to highlight and then the European Hematology Association, which is a meeting also that occurs around June every year. This is obviously in Europe. This year it was in Madrid.

I have several abstracts that I wanted to touch on that relate to that meeting, and we can talk about the data in a little bit more detail in the question-and-answer session. But, again, I just wanted to give a brief highlight. So, the ASCO presentation that was made this year that was relevant for CLL was an update on the

CAPTIVATE trial. This was an abstract that I presented and an updated analysis of the CAPTIVATE data.

Now, the CAPTIVATE trial was a trial of ibrutinib (Imbruvica) plus venetoclax (Venclexta), so a combined targeted therapy, all oral, which was given for one year of treatment, three months first of ibrutinib by itself and then 12 months or 12 cycles of combined ibrutinib plus venetoclax. This data has been published and reported at previous meetings.

But the new analysis that was done was to look at the outcomes for patients who are considered high-risk patients with 17p deletion, mutated TP53, or complex karyotype and also an unmutated immunoglobulin gene. The summary was that we get good deep remissions, including for those patients with high-risk features.

We did observe that the remission was shorter for those patients with 17p deletion and/or mutated TP53. But the duration of remission was reasonable that you could think about giving that combination, including to patients with high-risk features. Those without high-risk features have done exceptionally well with one year of combined targeted therapy.

This treatment is not yet approved or isn't approved in the U.S. It is approved in Europe, but we do have it on the NCCN guidelines. So, it is a potential option for the patients in the U.S.

Then, the other meeting is the EHA meeting, which again was in Madrid and in June, and there were several abstracts that were reported at the meeting. I'm just going to touch on each of those very briefly. So, the first one was a plenary session. Plenary is sort of the highest level of attention and importance when it comes to presentations at meetings, and this was an analysis of a large cohort of patients and looking at the outcomes for patients who have mutations in TP53.

So, this has been thought of as a high-risk feature, has been highly associated with 17p deletion, and this analysis was a large retrospective analysis over many years that were different treatments that these patients had received. We know patients who have these features should not get chemotherapy. The report essentially highlighted the fact that patients with TP53 mutations do do well with targeted therapy, particularly ibrutinib-based therapy.

I'm sure we'll hear more about that with subsequent analyses and updates on this data. The next abstract was a randomized trial done by the French group looking at ibrutinib plus venetoclax versus FCR for previously untreated patients as other trials with similar treatment design have shown there were improved outcomes for patients who got ibrutinib plus venetoclax over chemoimmunotherapy FCR.

The next presentation was a seven-year update on a combined Phase II, so no comparisons, just all the patients received the same treatment, which was ibrutinib, venetoclax, and obinutuzumab (Gazyva). This was an early cohort of patients treated at the Ohio State University, and this demonstrated long-term remissions with that non-chemotherapy combination of treatment for patients with CLL.

Now, there's work being done with venetoclax that continues and large randomized trials looking at venetoclax and particularly venetoclax in combinations. There are other BCL-2 inhibitors that work similar to venetoclax that are currently in development. So, that next abstract of zanubrutinib (Brukinsa) plus venetoclax was a cohort from a large trial that included the analysis and report was related to what's referred to as arm D.

That was a cohort of patients who had 17p deletion who were untreated and demonstrated efficacy of that combination efficacy, meaning remissions that were reasonably durable, although the follow-up was short with this combination of zanubrutinib plus venetoclax, particularly for patients with 17p deletion.

I'm sure we'll hear more about that. That cohort was expanded subsequently to include patients who didn't have 17p deletion. As I mentioned, there are many Phase III trials that are ongoing with venetoclax-based combinations and evaluating the efficacy of various combinations of drugs with venetoclax, for example, in this case zanubrutinib. Acalabrutinib (Calquence) is another example, and then triplets are being studied.

Speaking of triplets, the next presentation was by our group at MD Anderson that Dr. Jain made, which was a trial that we're doing right now with pirtobrutinib (Jaypirca), which is a new BTK inhibitor plus venetoclax and obinutuzumab, and we're seeing very promising results with a very high percentage of patients an undetectable MRD remissions. So, we're excited about that.

The next presentation was one that I made, which was an analysis

of factors that correlated with response, either overall response or complete response, in patients who had received liso-cel (Breyanzi), the CD19 CAR T-cell therapy. We learned that patients who did better tended to be patients who were less heavily pre-treated and who had less bulky disease, smaller lymph nodes, etcetera. Those are the patients who were more likely to achieve remission with treatment.

BTK, as we know, is a very important protein in CLL cells. We have a number of BTK inhibitors that target and inhibit BTK, for example, ibrutinib, acalabrutinib, zanubrutinib. There's a new category or class of drugs that are in development referred to as "degraders." These are small molecules that bind to BTK, the protein BTK, and rather than blocking the function, they accelerate degradation of the protein and elimination of the protein from CLL cells.

So, the next abstract was an update of data related to a BTK degrader that's under development by BeiGene, the BGB-16673. As I mentioned, there are other BCL-2 inhibitors in development. So, there was a Phase I experience looking at sonrotoclax, which is the new BCL-2 inhibitor that works similar to venetoclax but is different than venetoclax, combined with zanubrutinib for previously treated patients with CLL.

That combination was well-tolerated and did achieve a reasonably high degree of remission and undetectable MRD with that treatment. Finally, epcoritamab-bysp (Epkinly), which is a bispecific anybody, works to recruit immune cells, T cells, to attack against tumor cells.

Epcoritamab has been evaluated in relapse and refractory CLL and also in Richter transformation. So, we saw an early report of activity of epcoritamab in treating patients with Richter transformation, which appears to be promising. I'm sure we'll be hearing additional updates from that experience, so a lot of data at EHA, probably more than we usually see at EHA. What we're looking forward to are a couple of meetings that are coming up.

There's an ERIC meeting, which is the European Research Initiative on CLL. That's a meeting at the end of this month in Barcelona. So, we'll hear some data and discussion at that meeting. Our most important meeting of the year is the American Society of Hematology, which is the ASH meeting, and that will be occurring in San Diego this year at the beginning of December. That's where we hear about all the new data and exciting stuff.

With that, I will hand it back to you, Jeff.

Jeff Folloder: Thank you so much, Dr. Wierda. I now have a new term that I have to put in my CLL vocabulary. That would be "degrader." This is a new thing, and I'm excited to hear about it. I'm not going to lie, I'm a little bit less than excited to hear two words come out of your mouth. We're going to explore those two words a little bit more. Those words are "Richter's transformation."

When CLL patients and their caregivers first start learning about CLL, they often hear these two words, and they get really, really scared really, really fast. So, again, thank you, Dr. Wierda. But, Dr. Parry, you're up next. I understand that some of your recent research with CLL Global focuses on Richter's transformation. Can you tell us about that work?

Dr. Erin Parry: Of course, and thank you again for having me today. So, today, I'm going to be talking about this event of histologic transformation.

This is something that, while I'm going to be talking about it in CLL today, and it's obviously the focus here – it's actually something that we see across many different cancers. It's how cancer cells evolve or actually change their underlying cell type. So, this is something that you may also hear in other settings, although we're talking, like I said, about it, particularly, in the setting of CLL today.

When this happens in CLL, the cells usually become a large B-cell type lymphoma or an aggressive lymphoma. We call that a Richter's transformation or a Richter's syndrome. This is something that we see even in the era of our exciting new treatments. But, hopefully, I can also share with you today that there's a lot of new hope and a lot of new research coming together in this area.

So, this is one of the slides that I like to highlight when we talk about transformation. The exciting part, I think, about this slide is that we're beginning to decipher many different angles or layers of sort of the underlying biology and why transformation occurs, looking at the genetics, looking at model organisms that allow us to study the process in depth, understanding epigenetic and genetic determinants, so different ways that the DNA can be impacted that contribute to this process, and then also how the immune system and immune systems surrounding CLL cells may influence or shape this process.

If you look at the dates on these different studies, the majority of them happened just in the last couple of years. So, I think our science is really starting to catch up. Hopefully, that's going to lead to more knowledge and new ways of tackling this together.

So, one question that I sometimes get is – if we're in this era of amazing genetic medicine and biology and unparalleled knowledge, why do we have so many questions remaining about transformation, and why are many of these studies only occurring in recent years? I think that's because transformation has traditionally a little difficult to study for a couple of reasons.

The first one here, I think, is really thinking about, in order to properly be able to study it, we have to capture the CLL cells before transformation and then have a sample at the time of transformation to really understand what's changing and what's going on. That requires samples that have been stored properly and biobanks.

Also, this is a really rare thing in CLL. So, because of that, this isn't something that can be studied by one person in isolation but really has to be studied by groups coming together. The other issue that has complicated things, I think, is this issue of sample admixture. If we're looking and trying to decipher DNA or molecular changes, how do you know which cells they're coming from?

This is because the transformation biopsies are usually a mixture of normal cells in addition to CLL cells in addition to immune cells and the Richter's cells themselves. So, it really required us to build and innovate and create unique computational pipelines and tools that could be able to look when things are all jumbled up together to really understand what's going on in which cell.

Also, now, as we're moving forward as a scientific field, we have a lot of new technologies, and we can actually now look at a single cell level and ask what the single cell molecular changes are in a way that we couldn't even five or 10 years ago. So, this is really helping accelerate our understanding in this area. I would also say that this has been a nice area to work in and really exciting as a physician/scientist/investigator because this is not something that can really be studied in isolation.

So, the studies that have gone on in this area have been really

highly collaborative bringing together physicians and scientists and investigators, not only across the U.S. – it's one way that I've gotten top work with Dr. Wierda, which has been a really wonderful experience – but also doctors in Europe and many other different places, as we all try to understand this together.

Then, also, sample banking efforts. So, I think, also, immensely grateful to patients with CLL in transformation that have participated in research studies that have allowed these samples to be collected so that people can begin to apply these new tools; and together, as a community, we can begin to understand this better.

So, I think now that we're gaining this knowledge, one of the exciting questions that we continually can ask each other is – how can we take some of our advanced knowledge and better scientific understanding to make a difference for our patients with CLL? So, some of the questions that I've particularly tried to target with my CLL Global Research project have to do with – is there a way to improve diagnosis or recognition of Richter's?

Is there a way to identify transformation risk? Because we know that the majority of CLL patients never have this happen. If there was a way to identify those few cases where we may want to keep a closer eye on people or if we knew that it was coming, could we someday stop it from happening? So, as you can see on this graphic here or cartoon, we know that this evolution happens over time. As we can begin to understand it better, we can hopefully get at some of those questions.

So, my CLL Global project has taken two new sensitive approaches for trying to detect transformation. The first is looking at these single cells, which I alluded to, with these novel technologies that allow us to pick up single molecular changes of DNA or RNA or genes that are in these individual cells and understand exactly everything that is happening on that process of evolution so that someday we might be able to detect it better and intercept it.

The other aspect is looking at cell-free DNA changes, so little pieces of DNA that actually belong to the Richter cells are actually shed into the blood. Sometimes, we can pick them up in the blood without doing an invasive biopsy. If we could do a simple blood test to be able to also sort some of these things out, that could help us maybe apply therapies better or do screening in the future.

So, thank you so much, again, for your support. I'm very

appreciative to the CLL Global [Research] Foundation and all my colleagues in the field and many others who have really contributed.

Jeff Folloder: Richter's transformation, Richter's syndrome, it is a very important topic. I suspect that's not all that you're studying through CLL Global. What else is capturing your attention?

Dr. Erin Parry: So, a lot of my research has really been focused on the process of transformation but many different aspects.

One of the things that was studied in collaboration with Dr. Wierda is also trying to understand things that impact immune response both in CLL and in Richter's. So, I'm also very interested in trying to understand things that motivate the immune system to respond to cells, and how can we really harness the power of the immune system better. So, that's another area that I'm very interested in.

I think also one of the things that's coming on the horizon is being able to, again, continue collaborative efforts to really put together large sets of data and learn what we can so, hopefully, a lot to come that we can all contribute.

Jeff Folloder: One of the things that I'm sensing from you and from Dr. Wierda and from, frankly, all the CLL investigators that I interact with, the tone has become much more optimistic, much more confident.

So, this is a great development for me. Dr. Wierda, is there something that you'd like to add to this before we get into several dozen questions?

Dr. William Wierda: No, maybe just a couple things I would touch on that Erin didn't mention. One is my impression has been that the number of cases of Richter's transformation is decreasing. I think we still see Richter transformation, but we don't have nearly as many cases as we used to when we were using chemotherapy to treat CLL. So, I'm glad to see that the incidence appears to be decreasing. I think it's because we're not using chemotherapy. Patients now are just getting just targeted therapy, and the risk for transformation is lower.

The other thing that I would mention is a phenomena that happens relatively infrequently but can be an important point, and that is most of the cases of Richter transformation occur because the leukemia cells, the CLL cells, have transformed into something

more aggressive. It's the same cell, but it's transitioned into a more aggressive form. That's the most common scenario.

But there is a less common scenario where it's not arisen, the Richter transformation, those large cells have not arisen from the CLL but are an independent process that have come about independent of the CLL. That's something that we call clonally unrelated. Those cases tend to be more sensitive to treatment, and we can potentially cure those types of Richter's with chemotherapy, whereas the Richter's that arise from the CLL, what's referred to as clonally related, is a lot more difficult to treat.

It's really resistant to chemotherapy and the most successful strategies have been immune-based allogeneic stem cell transplant, possibly CAR T-cell therapy. There's some data with these checkpoint inhibitors that are immune modulators. So, we're most excited about immune-based strategies for Richter transformation.

Jeff Folloder: Good. Thank you very much. Again, it's something that concerns a lot of CLL patients, especially people who have been recently diagnosed. So, this has been a lot of really good information. I'd like to mention to our viewers that if you missed anything or if you think you missed anything presented by the panelists today, I can assure that the slides and a replay of this town hall will be made available on the CLL Global website at cllglobal.org within just a few days.

I said that we have a bunch of questions, and I do. And I know that questions are coming in. When I say a couple of dozen, it's more than a couple of dozen. So, we're going todive into those questions. Like I said, we've received a bunch in advance. We're going to try to get to as many as we can. And we're going to try to get to the questions that you're sending in at the last minute.

If you'd like to send in a question at the last minute, please send it to production@thehccollective.com. Let's start with this one. It's on everybody's mind. It's not going away. What are the current COVID recommendations for CLL patients? Is one booster preferred over the other? Dr. Wierda, I'm starting with you.

Dr. William Wierda: Well, the easy answer is the second question, which – is there one vaccination that's preferred over another.

My answer to that would be not really. The Moderna versus the Pfizer are similarly active. There's a new one that's a new version

that's coming out that captures the current strains that people can consider as a booster. If it's not available already, it will be available momentarily and can be given with a flu shot. If patients haven't had a booster within the last year and they haven't had COVID within the last year, then I tend to recommend a booster now.

Now, there are now hard and fast rules about this. I have seen patients who have had flares in their CLL as a result of getting boosters. I know that the CDC has recommendations that may be a bit different than what I'm doing in the clinic.

I'm a little bit more comfortable with being flexible about it, particularly because we have nirmatrelvir/ritonavir (Paxlovid) and we have remdesivir (Veklury), and the strains that we're seeing are less aggressive. So, they don't cause as severe of symptoms in patients. Many patients have had an infection previously and, as a result, have some immunity to it.

So, it's very different than it was in 2020 in terms of being relatively aggressive about vaccinating and boosting, etcetera, for those reasons. Like I said, my practice generally has been if somebody hasn't had COVID within the last year or a booster, then I will recommend a booster now, i.e., this fall. If they've had a reaction, a flare from a prior booster, then I would say, okay, maybe you could just avoid heavily boosting, particularly if you've had a recent COVID infection that has cleared.

I do recommend that people get the flu shot annually. Now is the time to be thinking about that. We have recommended RSV vaccination for patients but less emphatic about that because that typically is not a life-threatening infection with the RSV. It can be complicated, and patients can have to be admitted with RSV infections, particularly those who are heavily immunosuppressed. So, I'm not as strong about that recommendation. I am for some patients. But RSV is another vaccination to think about. That's just a one-time vaccination.

Jeff Folloder: That's really, really good information. Thank you, Dr. Wierda. John has a great question. CLL is not treated like other cancers. We have a situation where the community politely calls it "watch and wait."

The patients call it "watch and worry." More enlightened types call it "mindful surveillance." The thing is a lot of us are going to wait a long time until we get to that first treatment. So, John is

interested in current first treatment therapies. He's had CLL since 2007 and is just now getting close to treatment time. Secondly, what are the treatment sequencing recommendations? Dr. Parry, this one's for you.

Dr. Erin Parry: So, I think as a lot of the people on the call are aware that we have some great approved therapies for CLL and the sort of upfront choice that we discuss with people in general is whether we're going to go the route of a BTK inhibitor, which is a more continuous therapy for something time-limited like the venetoclax and obinutuzumab as a combination.

A lot of that takes into account the individual patient preferences, and we talk about pros and cons of each approach. We're in a position where I think we have an excellent choice. I think the other great option that we have to consider is clinical trials.

Sometimes, clinical trials offer an advantage because they're looking at combinations. You heard about, I think, some of those clinical trials when Dr. Wierda was giving the updates. Those are things that we also present to patients as we often have those available. They may offer an option to get time-limited therapy with a different combination or something that might offer another third option to our approved agents.

Jeff Folloder: Sounds great. I had a question that has come in from R. Richard. I'm not going to lie. This is a chance for both you and Dr. Wierda to shine. Where is the most advanced CLL research being carried out, and how is it funded?

Dr. William Wierda: Well, maybe I'll start. It's being conducted at Dana-Farber Cancer Institute in MD Anderson. There are a few centers in the U.S. that have dedicated programs in CLL. So, Dana-Farber is one of them. They have a very active program clinically and laboratory-wise. We have also a very active program at MD Anderson. The Ohio State University has a very active program with Jennifer Woyach leading that group.

The Memorial Sloan Kettering group has been very active. So, there are a number. Mayo Clinic has been another one. I hate to start naming them because I'm sure I will miss one, but there are a lot of good programs in CLL research that cover pretty much most of the U.S. So, you can likely go some place that's relatively close by and not have to travel a long ways to see a CLL expert.

Some of this work is funded, and the research is funded by

pharmaceutical companies when they're developing new drugs and new treatments. Some of it is funded by the federal government to do research that is important to understand particularly the basic science and translational science behind the disease and developing therapies. The CLL Global Research Foundation is a nonprofit organization that provides research funding, and we have provided grants over the years in the order of $40 million to do research.

So, The Leukemia & Lymphoma Society is another organization that provides funding. So, there are various places that we look to for supporting our research and that are all important to supporting the research, as I mentioned, from the federal government to pharmaceutical companies to nonprofit organizations like the CLL Global Research Foundation.

Jeff Folloder: So, in other words, we need to write some more checks because we need to fund more research, right?

Dr. William Wierda: Research is extremely important because without research, we have no progress, and we're stuck where we are if we don't have any research or progress. We won't have development of new treatments and cure for the disease without continued research, laboratory research, and clinical trials and clinical trial participation with very courageous patients.

So, that's my plug for research. I'm a very passionate person about that. It's extremely important, and we're extremely grateful for the support, engagement, and involvement we have from our courageous patient population.

Jeff Folloder: Thank you. Dr. Parry, we have spoken at basically two ends of the extremes.

We've talked about "watch and wait" and people considering frontline treatment, and we've talked about when things go very wrong with Richter's. There is a middle ground, the relapsed and refractory patients. Some of them never need treatment again. Some of them do need treatment again. Some of them exhaust treatment options. So, after exhausting BTK and BCL-2 drugs, what's the next best treatment going in clinical trials? They want to specifically exclude CAR T-cell therapy from your answer.

Dr. Erin Parry: Of course, I'll try to highlight a few. I think one of the things that's emerging from some of the studies that have been done too that if someone has been treated with maybe time-limited therapy, there

may be opportunities where the therapy may work again.

So, there are actually studies that are looking at people that have been treated with BCL-2 in particular and time-limited therapies and whether that may be an option that may be revisited, especially if the CLL has a nice long remission that comes back later. So, those studies are ongoing.

Then I think some of the new things you've heard about in some of those studies that were highlighted too, I think, were interested in this class of degraders. We know that this BTK protein and inhibiting it has been very helpful for our patients with these BTK inhibitor drugs. So, it's figuring out other ways, even if resistance occurs, if that pathway can still be targeted. So, I think that's another class of drugs that we're very excited about.

I think another class of drugs that is being looked at that we're excited about that you also heard about is thinking of our immune-based therapies. So, there's a new class of drugs called bispecific antibodies that help grab onto the abnormal B cells but also grab onto your immune system killer cells or your T cells. These we've already seen approved in other types of lymphoma where they're showing really great efficacy.

There's been some exciting data presented at some of our recent conferences looking at those as well. So, those are a couple that I'm paying attention to, and I'm sure Dr. Wierda has some to add as well.

Jeff Folloder: This is your opportunity.

Dr. William Wierda: No, I would agree. Those are all the ones that are on our radar screen. There are also some other molecules that are being targeted with small molecule inhibitors. BCL-XL, etcetera, those are in development. There's another one that's targeting protein kinase C-beta. There are several agents that are in development, and we're all excited and interested to see results. There's probably more activity and new drug development in CLL than we have patients.

Now that's a good thing for our patients, because they're doing very well with our current trials and our current treatments with combined targeted therapy. It does make it a little bit challenging, because we have a lot of opportunities and clinical trials that we're interested in evaluating new drugs and a more limited number of patients to participate in those trials.

Jeff Folloder: Interesting, very interesting. I know that one of the most common questions a CLL patient asks is why or how. How did I get CLL? Why did CLL show up? Many of them get told, "We don't know." Paul has a question for you, Dr. Wierda. He's been a plumber since 1980 and a CLL survivor since 2009. He wants to know if your environment can make you sick. Can your environment make you well? Do you use different environments as data points in your study trials?

Dr. William Wierda: So, environment is important. The main connection with CLL and environment has been with exposure to herbicides and chemicals like Agent Orange. So, there are risk factors for developing CLL. The one that has been really highlighted and there's the most compelling connection is with the herbicides, people who live and work on farms or people who have been in the military and exposed to Agent Orange. So, that is a service-connected exposure to CLL in regards to coverage by the VA.

There aren't other things that we say, "Yeah, that's a clear connection," like radiation therapy where you can see connection to other cancers or other types of leukemia. Benzene exposure is not a risk for CLL, but it is a risk for other types of leukemia like AML.

The main connection has been with herbicides. I do think that your environment is important. What you eat is important, and being aware of exposure is important and trying to minimize things that may potentially be bad for you. Roundup has been another compound, which is an herbicide, which has been connected with B-cell malignancies, including CLL, myeloma, etcetera.

Jeff Folloder: I see. Dr. Parry, you've had the spotlight with Richter's transformation. What exactly are the signs of Richter's transformation?

What tests are needed to determine if someone has actually gone down that path?

Dr. Erin Parry: I usually tell people that there's not necessarily a particular symptom that they should be aware of or looking for, but if they're feeling unwell or something's changing, they should be talking to their doctor. So, if someone gets sick really suddenly, that does get our attention because that can sometimes be a sign. Or if we notice rapid growth of lymph nodes, particularly if it's a certain subset of lymph nodes, those will sometimes raise our threshold or

suspicion.

When we're thinking about that, the first step is meeting with your doctor who will do an exam and talk with you, and then we often get a PET scan when there's concern for a transformation, because that can sometimes help us figure out where the area is that we should narrow in on and how we should go about getting a biopsy sample, because right now we still rely on biopsies to make that diagnosis.

Jeff Folloder: Gotcha. I knew this question or something like it was going to come in. Kim listened to you very carefully, Dr. Wierda. She heard you say that there are rare cases that the COVID booster has caused a flare in CLL. I'd like to make one point and then give her question to you. You said that the booster caused a flare in CLL. You did not say that the booster caused CLL, is that correct?

Dr. William Wierda: Correct.

Jeff Folloder: I just wanted to make sure. So, since that booster can cause a flare, are there any other vaccines, like the shingles vaccine, tetanus – are there any other vaccines that can cause a CLL flare?

Dr. William Wierda: So, let me just clarify a little bit by what I mean with flare and what we've seen with COVID and COVID vaccination and flare.

As you say, the vaccination, we have not seen any cases of CLL as a result of getting a COVID vaccination. When I say a flare, it means that the vaccination in some way activates the CLL, which results in enlargement of the lymph nodes or a rise in the white blood cell count, more so than you would expect if nothing was done to the patient, more so than what their standard rise in the white count is.

So, these usually happen relatively quickly. A lot of times, they'll be in the same arm that is vaccinated. Typically, they are what we refer to as self-limited. They subside over a few weeks. It's probably the result of the immune system getting activated and the interaction between T cells and normal B cells and the CLL cells and the immune environment that stimulates the CLL cells to divide and become activated.

Like I said, most of the time, this flare subsides over time, over weeks. In the past, I have occasionally needed to give steroids to quiet the immune reaction down because it isn't subsiding, and that has been successful. There have been rarer numbers of cases

where despite giving steroids, the symptoms have not subsided and patients have needed to go onto treatment. That hasn't been real common, but I have seen that.

So, that kind of describes the flare that we've seen. There are other vaccinations that I have seen this happen with, not so much the flu shot. I have seen it with other vaccinations though.

Again, I don't think it's necessarily the vaccination doing something that's terrible and activating and causing the disease to grow. It's more activating the immune system. We know that there's an interaction between the immune system, normal immune cells in patients with CLL and their CLL cells, where you can trigger growth of the CLL by stimulating the immune system.

Most of the time in those other cases of a flare with vaccination, it is, again, self-limited and subsides over time. The COVID vaccination is, as you all know, a new vaccine, which is an RNA-based vaccination and is something different than we've had to give patients previously. So, we do watch carefully for these things because of the fact that it's a new vaccination. We don't have long-term safety data with this vaccination.

So, that's another thing that we think about a lot and monitor for.

Jeff Folloder: Fantastic. I love getting questions from caregivers, not just the patients. The caregivers often have a wonderful perspective on what needs to be done and how to do it. So, Dr. Parry, Matthew wants to know, when should a caregiver worry about treatment side effects? How does one differentiate between normal side effects and those requiring intervention? This is a wonderful "shades of gray" discussion.

Dr. Erin Parry: It is and, I think, a really good question, because I think this is something on people's minds a lot. I think that when we go to start someone on a treatment, we do talk about what side effects are normal and common, and there are some that we expect and often are mild and self-limited and will get better with time.

But I think if something is making someone very uncomfortable or there's uncertainty around it, it's always good to check in with your team to know if that is something that is expected to get better on its own or if that is something that is more cause for concern.

Jeff Folloder: I'm going to give you a redirect. How do they know that it's a side effect if the answer's always, "I'm fine"? What should the

caregivers be looking for?

Dr. Erin Parry: Oh, dear, another great question. I think that in terms of thinking of side effects, I would say that when you're on therapy, something that is new or different, especially something that's an uncontrolled symptom, is something that should raise flags and worthy of discussion. Does that help?

Jeff Folloder: I think it helps a lot. It's an important distinction. I know that this is an over-generalization, but guys tend to say I'm fine all the time when the truth is usually not even close to that.

So, if you're not able to say I'm fine, someone needs a good eye to see what's not fine. At least, that's my take on it. We have a fantastic question from Jessie for Dr. Wierda. This to me was one of my "aha" moments in my CLL journey. What are the risks of secondary cancers of CLL?

Dr. William Wierda: So, when we talk about other cancers or second cancers, there is an increased risk for second cancers in patients with CLL. We've reported on that from our data set and others have. We think that it's because the immune system doesn't function normally. So, this surveillance and protection against developing cancers that usually occurs because of a normal immune system is deficient.

So, patients have an increased risk for other cancers developing in addition to the CLL. Those tend to be skin cancers. That's the predominant one, non-melanoma skin cancers. We do see melanoma also in patients with CLL. Then other solid tumors can be higher risk. So, we recommend that patients are diligent about screening for other cancers.

Now we don't recommend excessive screening, but we do recommend that patients stick to screening that they should be doing anyways and to be diligent about it. Now, skin cancer screening – so, maybe for a 50-year-old you wouldn't recommend annual visits to the dermatologist unless they had a family history of skin cancer, etcetera. But we recommend at least a once-a-year visit with a dermatologist, but some dermatologists would like to see patients with CLL even more frequently than once a year.

But somebody should be looking at their skin at least once a year or more frequently, depending on what the dermatologist recommends. For men, PSA, annual check for prostate, and then colonoscopy every five to 10 years depending on what they see when they do the colonoscopy. For women, annual mammography

and also a colonoscopy and Pap smear.

Some patients, women, will come me to in their 70s or 80s even and say, "Well, my doctor said I don't really need a mammogram. Breast cancer's not going to kill me. So, I'm not going to be doing it." I'll say, "Well, you don't want to get breast cancer. If you do mammograms annually, there is a chance that they will pick up something. If they pick up something, it's early detection, which is very easily eliminated and addressed and taken care of."

"Whereas if you don't, you're more likely to present because you've found a lump, and then it's a much more difficult and challenging problem to deal with than it would be if it was found early and could be surgically eliminated."

Jeff Folloder: As a patient at your facility, I see the dermatologist every year. I see the gastroenterologist on a regular basis. Literally, my only complaint is the rooms are very cold. That's it.

Dr. William Wierda: Absolutely.

Jeff Folloder: So, get it done.

Dr. William Wierda: I have a number of patients – it surprises me – who say, "Well, I'm not going to get a colonoscopy. I don't want that." I wonder to myself – they are at increased risk for other cancers. It is an uncomfortable procedure. It's not comfortable.

I've had more than one myself, but it's something that's so relatively easy to do that's preventive. They can remove polyps. They can identify cancers early. You fix the problem, as opposed to waiting until it becomes so advanced that you may need to have part of your colon removed or have a colostomy placed.

It just is so common sense to me to do that screening, and it surprises me sometimes how opposed some people are to doing it. It's not just CLL patients. I think it's in general. We come across people who say, "Nope, I'm not going to do it. It's an uncomfortable procedure, and I'm not going to do it."

Jeff Folloder: So, we just talked about the uncomfortable procedure. I have one what may be the most uncomfortable question of the afternoon for your, Dr. Parry. This comes in from Bear.

How important is it to not drink any alcohol if you have CLL? I'm listening to this, because we may or may not be able to be friends

after you answer.

Dr. Erin Parry: We don't have any evidence that in moderation that alcohol consumption impacts things. Obviously, if you're on treatment, talk to your doctor because there may be special considerations there. But I do not tell people that they cannot have the occasional drink.

Jeff Folloder: Good. I'm taking a deep breath, because I have a collection of whiskey that was going to be unlocked.

Dr. Erin Parry: I think like everything, all the things that your primary care doctor would tell you, making sure that nothing is in excess and that you're taking care of your overall health are things that apply.

Jeff Folloder: Indeed. So, Kevin would like to know – how will treatments evolve over the next 10 years? Are there signs that AI could speed treatment development? I'm asking both of you to use your crystal ball.

Dr. Erin Parry: I think one think one thing that has come up increasingly as all these advancing technologies exist with all the different sequencing platforms is we're in an era of big data. With big data, I think we do need ways of analyzing that big data. Some of that is through computational experts, and maybe that AI has roles at picking up different patterns.

I haven't seen AI necessarily directly make an impact on research, but it'll be interesting to see how things evolve, I think, with us getting increasing amounts of data. Certainly, computational modeling and different things will be important, as we try to look for even more things in the future.

Jeff Folloder: More data, more power takes more stuff to get it done, and that's the foundation of research. I'd like to thank all of you that submitted your questions. We're heading towards wrapping up this town hall.

You two are truly medical experts. I'd like to give you a moment to let us know what's on your mind. Dr. Parry, you've explained where we stand with CLL research. How do you feel about how it's evolving? What do you think we're going to see as your patients?

Dr. Erin Parry: I think that as far as things that I'm excited to see in the next five years that, I think, from research that's going on, I think we're

going to learn a lot more about the immune micro-environment and how we can maybe better target the immune system. I think a lot of that is from these novel technologies that are allowing us to better understand things. So, I'm excited to see what that brings and hope that that will bring new avenues for treatment.

Jeff Folloder: Fantastic. Dr. Wierda, I know that we need about another hour—and-a-half to get out all the information to everyone. What's on your mind?

Well, I think more and more about cure, and I spend a lot of my time thinking about how do we cure patients with CLL? We are on the brink of cure for most patients, I think. So, to Erin's point, I think we need to work a little bit more diligently on understanding the immune system and how to optimize our immune-based treatments and with that, also, will come strategies to restore the immune system for our patients so that they're not at high risk for second cancers and for infections.

So, we're going to hear a lot about trials' readout in the next three to five years of combination targeted therapies. I think we have a dedicated program at [MD] Anderson to look at immune restorative strategies and understanding the immune system.

I spend a lot of time now focused on that aspect and thinking about ways that we can eliminate CLL for good.

Jeff Folloder: You spoke my favorite word, "cure." I hope that all of us are throwing that word around with reckless abandon very, very soon, especially for me. I might as well be greedy. I would like to be cured.

I'd like to thank both of you for taking the time to join us today. It's really, really important that we connect with the CLL community. You guys have given your time. You've given of your research. Dr. Wierda, I'm going to give you props for channeling Dr. Keating at the end there. Yes, we want to use that word "cure" for our patients.

Don't forget to fill out the survey, each and every one of you. Please, take a few moments to fill out that survey.

The more answers we get, the better the answers we get, the better our programming is for you. Stay tuned. We're planning out our next town hall, which will be held early next year. We hope that each of you can join us. I've got one parting wish for each of you.

I challenge each and every one of you to not live well but to live very well.

Dr. William Wierda: Can I make one quick comment – two? So, I would like to say, personally, thank you, Jeff, for your dedication and advocacy for the patient community, and your work is highly appreciated. We're very graceful for it. Also, a shout-out and special thanks also to Sam Pace who is our administrative person for the foundation who helps makes all of these programs happen.

Jeff Folloder: It's a wonderful thing. Again, thanks to both of you for participating. Thanks to our audience for spending time with us. Thanks for all the wonderful questions.

We're going to see you next year.