Jeff: Welcome and thank you for joining us for the first CLL Global Research Foundation virtual town hall of 2023. Happy New Year. Today we are going to hear about the latest research from a panel of CLL experts, including news from the recent American Society of Hematology meeting. You'll also hear an update on emerging CLL research and clinical trials, including those supported by the CLL Global Research Foundation.

My name is Jeff Folloder. I'm going to be your host for today's event. I'm currently a relapsed CLL patient, heading into year 13 of my journey with CLL. And I've got to tell you, I'm living well – no, I'm living great with CLL. I'm a patient advocate and a passionate one. And my goal is to make sure that you can live as well as I do.

Before we get started, let me cover just a few housekeeping items. Many of you submitted questions for our expert panel when you registered, and we're going to do our very best to answer them all. If you have questions during the town hall, please submit them via email to townhall@cllglobal.org. Remember, we cannot answer questions about your specific medical treatment. Those should be discussed with your own healthcare team.

Now, let's learn just a little bit about our expert panel. We're gonna start with Dr. Michael Keating. More than 17 years ago, Dr. Keating founded CLL Global to create a collaboration between patients, their loved ones, and a community of CLL researchers, all with the goal of finding a cure for CLL. Dr. Keating, thank you for joining us today. Many of our audience members have been asking about you. Could you please share an update about how you've been doing and what you've been focusing on from a CLL perspective?

Dr. Keating: I'm doing very well. For those of you who don't know, I celebrated my fourth anniversary of a stroke, and I've completed my physical and other aspects of therapy. So, now I have more time that I can just think about CLL and do it. So, presently, I am planning to set up a grant proposal to CPRIT, which is the Cancer Prevention and Research Initiative of Texas, called Curing CLL: The Texas Challenge. So, it will be based on educating not only patients and their families but also educating their local physicians on where we are and what should be done at different decision points in the now, long, long course of CLL, because patients are now getting out close to 25 years of remissions.

Jeff: That sounds fantastic. Thank you, Dr. Keating. It's really great to see and hear from you. Also here with us is Dr. William Wierda. Dr. Wierda is the President and CEO of CLL Global. He's the Executive Medical Director at the University of Texas MD Anderson Cancer Center, where he is also the Jane and John Justin Distinguished Chair in Leukemia Research in honor of Dr. Justin. Dr. Wierda, welcome. Would you like to say a few words to our audience?

Dr. Wierda: Sure, thank you, Jeff. I share in Dr. Keating's enthusiasm about where we have been, where we have come from, and where we are now in terms of therapies for CLL, and the excitement about developing curative therapies for our patients. It's been a remarkable many recent years and very gratifying in terms of the work that we've done and the improvements – improvement in qualities of life that our patients have experienced.

Jeff: Outstanding. Also joining us today is Dr. Nitin Jain, who is an Associate Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center. Dr. Jain treats CLL patients but is also a dedicated CLL researcher. Dr. Jain, please tell us a little bit about yourself and your work in CLL.

Dr. Jain: Thank you, Jeff, and thank you Dr. Keating and Dr. Wierda, for this opportunity to talk to you all today in this form. So, I'm a faculty member in the Department of Leukemia. I treat patients with CLL and other leukemias as well as do clinical trials, which will – some of that we'll talk in the next one hour or so. I'm also super excited about the field of CLL from how we have moved in the last ten years. From chemotherapy which was the best treatment at that time to now largely non-chemotherapy approaches with new drugs which, you know, we'll talk in the next half-an-hour, 45 minutes. So, excited to be here and looking forward to the discussion and question-answers.

Jeff: The world of CLL is certainly anything but calm at this point. Now that we've met our panelists, let's move on to research news. Last month, the annual American Society of Hematology or ASH. The meeting was held in New Orleans. The conference focuses specifically on hematology and is attended by researchers from around the world. Dr. Wierda, you're on deck. Can you share research highlights from that meeting?

Dr. Wierda: So, as Jeff, you mentioned, ASH is our big meeting of the year. It happens the first week in December each year. It's where we hear about the updates and the progress and advances in treatments for patients with CLL as well as other hematologic and malignancies and non-malignant hematologic disorders. The other big meeting that we have is ASCO, which is in June, and then the European Hematology Association meeting which also is around that time, May/June.

So, I'm gonna – in the next two slides, I'm gonna summarize the information that was – some of the information that was reported at ASH. Two slides. The first slide will be in terms of first-line treatment or treatment for patients who were previously untreated. The second slide will be for patients – trials and clinical work for patients who have previously received treatment, which is predominantly new drug development.

So, let's go to the first slide. Many of the abstracts that were presented at ASH this year in terms of first-line therapy focused on targeted therapy and focused on fixturation combination targeted therapy. So, there are three bullet points here, but that summarizes several reports or abstracts. So, you can see the first bullet there is there are four trials that have evaluated ibrutinib plus venetoclax in previously untreated patients. There is one trial that was also reported, as you'll see in the next slide, for previously treated patients with that combination.

We have heard data for all four of these trials. The MD Anderson trial – which I'm sure Dr. Jain will talk about – the CAPTIVATE trail, the GLOW trial, and the FLAIR trial. We've heard about those trials previously at other meetings and this was an update for the outcomes for those trials. And also, a report on what correlated with response to treatment and the durability of the responses.

So, the update in terms of the outcomes for patients treated on those trials with that combination of ibrutinib and venetoclax can be summarized basically by saying we're seeing very deep remissions with very long remission duration for that combination across all of these trials. So, the majority of patients achieve an undetectable MRD status at best response to treatment. The trials evaluated treatment periods of one to three years of treatment with that combination and those responses and remissions are lasting a long time. We don't have a lot of patients who have

needed a next treatment for those trials at this point.

The next bullet you can see there is a point or factor that has been identified across several of these trials, and that is that patients who have an unmutated immunoglobulin gene have a higher rate of undetectable MRD at the end or at best response to treatment with these combinations, which was unanticipated. Usually, patients who have a mutated immunoglobulin gene perform better, particularly with chemoimmunotherapy – but in this case and with these treatments, we're seeing improved undetectable MRD rate for patients who have an unmutated immunoglobulin gene.

And then the third bullet there I think is sort of an indirect summary point, and that is that we still don't know what the best duration of treatment is for this combination in the front-line setting or in the relapse setting. We see patients responding. The early responders tend to do better in terms of having longer remissions, but there are patients who continue to respond beyond one year and even beyond two years of continued treatment. Where they were undetectable for example at the end of two years of treatment, and more than half of those patients, if they continue on treatment, will convert to undetectable with an additional year of treatment. So, we're still working on the optimal duration of treatment with that combination.

The next bullet there is sort of a summary. There are two trials that were presented an update – or updated at ASH. Those were with a triplet: BTK plus venetoclax plus obinutuzumab. So, one was with ibrutinib as the BTK inhibitor, the other was with acalabrutinib as the BTK inhibitor. We're seeing very high rates of undetectable MRD status for those trials, and the responses are durable. And so one of the questions that we're discussing now is what is the contribution of the CD20 antibody in that combination. For example, do you need a CD20 antibody? Do you need it for everybody, etc.? So, we're excited about that triplet and very high percentage of undetectable MRD rate with that combination.

And then the third bullet there you can see is two abstracts combined that both studied either the triplet of BTK plus venetoclax plus obinutuzumab, or venetoclax plus a CD20 antibody. And the important point here is making correlations between response and also with the duration of response. So,

essentially, all patients respond equally well with a venetoclax-based therapy, whether they have a 17p deletion or an unmutated immunoglobulin gene, etc. So, we see a similarly high response rate across those subgroups.

The patients who are identified as higher risk for shorter remission are highlighted there. Those are patients with an unmutated immunoglobulin gene, patients with NOTCH1 mutation, BRAF, NRAS or KRAS mutations, patients who have a complex karyotype, or patients who have chromosome translocations pre-treatment. So those are, I think, patient populations that we will be looking at more closely, particularly with the BTK plus venetoclax combination, and what the outcomes and – perhaps maybe for those patients it would be a better strategy to include a BTK inhibitor with a venetoclax-based therapy based on what I just mentioned about ibrutinib, venetoclax.

So, if you go to the next slide, that summarizes several of the abstracts that included patients that were previously treated. So, like with the front-line setting, with ibrutinib and venetoclax, the CLARITY trial studied that combination in previously treated patients. A very high complete remission rate, undetectable MRD status, and long remissions even in previously treated patients who received the ibrutinib plus venetoclax on that trial. That was a 50-patient trial, and that trial continues to evaluate patients in follow-up.

The next bullet is an abstract that we presented from the MD Anderson group. That trial aims to clarify if there's benefit for patients who are already on a BTK inhibitor – ibrutinib or acalabrutinib – if there's benefit with adding venetoclax to get them into a deeper remission and to get them off treatment. And so we reported that more than 50% of the patients can achieve undetectable MRD status when we add venetoclax to the BTK inhibitor and patients receive one to two years of treatment. So, there is potential clinical benefit with that, and we continue to study that combination.

Pirtobrutinib is a new drug. It's not yet approved by the FDA for any indication, but we do anticipate mantle cell lymphoma it will be approved for and hopefully soon also, will be approved for CLL. It's a reversible inhibitor of BTK. It blocks BTK differently than the drugs that we have available, and there was an update reported at ASH,

with pirtobrutinib in previously treated patients who all had received a prior BTK inhibitor – ibrutinib, acalabrutinib, or zanubrutinib.

And that trial showed activity including among those patients who had developed resistance to the BTK inhibitor that they had been on previously and patients who have the mutation associated with resistance to those agents, the so-called C481 mutation.

The next abstract is a new drug; it's a new drug category. It's referred to as a BTK degrader. It has a number; it doesn't have a name yet – NX21-27. This is a small molecule oral drug that binds to BTK and causes the cells to degrade BTK. And so that's a way, not of blocking the protein, but of eliminating the protein in the leukemia cells. And so that drug is in early development. There is some indication of activity with that drug, and we continue to work on that drug in terms of clinical evaluation.

The next bullet there is two abstracts with two different BCL-2 Inhibitors. So, venetoclax is an oral BCL-2 Inhibitor. There are others in development, and the ones that were reported at ASH this year are BGB-11417 and the other compound – which I have a little bit of trouble pronouncing – lisaftoclax. And both of those drugs have activity. They're both being studied as a single agent as well as in combination with a BTK inhibitor and/or a CD20 antibody. So, we look forward to more updates in terms of that work, and potentially we'll have other BCL-2 Inhibitors available in addition to venetoclax at some point in the future.

And then, finally, the last bullet there is a new drug that's targeting a different protein that is in the B-cell receptor signaling pathway like BTK or PI3-Kinase. This protein targeted is protein kinase C beta. So, it's a signaling protein that a small molecule inhibitor has been developed against called MS-553, and the clinical trial is a Phase 1 clinical trial evaluating the toxicity profile and the activity of MS-553 in previously treated patients. And they are demonstrating activity and tolerability, and that drug's being studied by itself as well as in combinations.

So, that summarizes the data that was presented at ASH. There's a lot of activity; there's a lot of new drug development. There are exciting drugs that work by different mechanisms of action. We're seeing activity in patients in the front-line setting with our

combinations. We're seeing activity with these new compounds that have activity in patients who are no longer responding to our standard treatment options. So, we continue to be excited by all of the therapeutic developments that are ongoing in CLL.

Jeff: That all sounds promising – actually, that sounds exciting. Thank you for sharing this update and your perspective. Now let's hear from Dr. Jain. Dr. Jain, your research on fixed duration abribnib plus venetoclax is supported by the CLL Global Research Foundation. Can you talk to us about this study and tell us a bit more about your CLL research?

Dr. Jain: Sure, yeah, so, you know – One of the studies Dr. Wierda mentioned in his presentation was this combination of ibrutinib plus venetoclax. At the ASH meeting, there was one entire session dedicated to this combination because it is now being studied by many other groups in the U.S. and elsewhere. So, as part of the funding from the CLL Global Foundation, we have been fortunate to get that funding and to be able to run this clinical trial at MD Anderson which is combining ibrutinib plus venetoclax. As many of you know, both ibrutinib and venetoclax are FDA approved. They are both oral drugs.

So, back in 2013, 2014, there was a pretty cool work done by Dr. Varsha Gandhi and many others suggesting that combining these drugs in the lab were synergistic. And based on that work, we developed this clinical trial which started back in 2016 of combining these two drugs together for patients of CLL. We had patients with previously untreated CLL, and then also patients with axial fracturing CLL. But this data I'm going to show you is patients who had no prior therapy for CLL, and this combination was their first therapy.

So, I have several slides to kind of go through it and then I will kind of summarize some of the trials we have at MD Anderson just kind of give you a flavor of the clinical trials that we're currently working on at MD Anderson. Next slide.

So, just kind of as a background for everyone in the group, and Dr. Wierda kind of alluded vaguely to new developments in the field of CLL. But, you know, the story really started many decades ago – I guess it was at least two or three decades ago – when Dr. Keating kind of building on FCR as a regimen for patients with CLL, and that

kind of became really the de facto standard for young patients with CLL, that CLL regimen.

And then about ten years ago, or back in 2014, was ibrutinib approved for CLL and then several other drugs were approved for CLL. BTK inhibitors, PI3K inhibitors, BCL-2 inhibitors which is venetoclax, and also monoclonal C20 antibodies such as obinutuzumab. And then, you know, 2023 and beyond, as Dr. Wierda mentioned, we are going to have a couple other drugs that are likely to be FDA approved, including zanubrutinib and maybe pirtobrutinib as well. And there are some other trials happening in the field of CAR T and other strategies.

So really the field has moved from chemotherapy, which we were doing up until a few years ago, to really 100% looking at non-chemotherapy approaches for our patients with CLL. So in that context you know – with that context in mind, let me talk to you about this trial we did of combining all of that together with ibrutinib and venetoclax. Next slide.

So, as I mentioned, this is a large trial. Just focus on the last bullet point on the slide here. We treated a total of 120 patients at MD Anderson. These patients were enrolled in the study from 2016 up until 2019, and it's quite possible many of you – or some of you listening – may be enrolled in this trial as well. And then we have followed these patients after treatment, and now almost four-and-a-half years, on an average, have gone by from the start of treatment for these 120 patients we have treated at MD Anderson. Next slide.

You know, this is a trial which we designed for patients who had high-risk genetics. So, what that means is patients had to have deletion 17p, which can be assessed by FISH testing, or Deletion 11q, mutation of TP53 for which we need a myonuclear sequencing test, or unmutated B gene which again is a myonuclear test. We did it all patients who are 65 years and older because at that time those patients we were not really using chemotherapy and we felt this might be the best strategy for that group of patients as well. Next slide.

So, how many of these trials are done with these ibrutinib, venetoclax combinations, not just by us but many other groups, is kind of where patients start with ibrutinib first, for maybe two or

three months – in this trial, it was three months. And that way you are able to debulk the tumor, a lot of tumor goes down a few degrees in size. And then you add venetoclax, then continue ibrutinib and add venetoclax. And in this study, we did the two drugs together for about two years, with an option of adding a third year for a specific subgroup of patients.

Some of the trials have done one year of combination of ibrutinib plus venetoclax as well. There's a large study called CAPTIVATE Study which did that, as well as CLL GLOW Study. But the thinking is the same. You start with ibrutinib first for a few months and then you add venetoclax to the mix. Next slide.

So, what I wanted to show you, and there are too many numbers here but just focus on the extreme right graph, which it says the best response at the bottom. So, if you take 120 patients and we did bone marrow on these patients and checked for what is called MRD testing to look for one cancer cell in 10,000 normal cells. So, when we did that by flow cytometry, and among 120 patients, 72% of the patients were MRD negative. So, when we did a bone marrow as a best response, their bone marrow had zero MRD, or MRD was undetectable. So that's a high rate of MRD remission to be achieved for patients with those two oral drugs together without the need for CD20 antibody. Next slide.

And just maybe last slide, second to last slide for this trial – and when we follow these patients, you know the patients were treated for two years, and obviously we follow these patients afterward every six months, and we see how many patients are progressing or what's happening. So, so far, among 120 patients, we had two patients who had CLL progression, and two patients with victor's progression, and one patient who had a rare progression of what is called BPL progression. So, overall, when you look at the four-year mark, upwards of 90% of the patients were still in remission on this trial. Next slide.

And when we talk about high-risk features, and Dr. Wierda mentioned some of this, like okay, we have a high-risk feature of IGHV status, mutated versus unmutated, or RBF2 status. And when you look at the general subgroups of these patients, it doesn't really matter if you have a generally high-risk subgroup or not, everyone seems to be equally benefiting from this treatment. Next slide.

So, our conclusion from this work, again, as I said, this work was funded by CLL Global, was that this regimen of two oral drugs is a highly effective regimen for patients with CLL. And then it generates high levels of remissions, as I mentioned, 72% of the patients achieved, not just the bone marrow remission but this is a deep myonuclear remission, MRD remission by flow cytometry. And then a four-year what is called progression-free survival – or basically asking the question: how many patients are without progression at four years – was 94%.

And then you know, many of these patients who did one year of therapy and then the second, third year of therapy, patients were MRD positive. When we continued the second and third year of therapy, several of those patients were able to become MRD negative. So, so far in this trial, we have still a majority of the patients in follow-up, they're coming to the clinic at MD Anderson almost every six months or so. We check their blood counts, physical examination, and check for their MRD in the blood. And we hope that the majority of the patients will stay in remission for a long time to come.

So, I think after that is my last slide which is a slide which talks about our current CLL trials at MD Anderson. I just tabulated here in a way for patients with CLL. So, if you look at the top left we talk about the first-line CLL trials – so these are patients who have no prior therapy for CLL – and we have several of the trials available. They're all non-chemotherapy-based trials, looking at different – answering a different question in the field of CLL.

For example, the first trial – acalabrutinib venetoclax plus obinutuzumab – answers the question of whether you need the antibody or not. And so, similarly, we are trying to answer some of the questions in the field with these trial designs. We have trials with patients who are already on ibrutinib, and we can add venetoclax as a consolidation strategy. Then on the right side of the slide you see on the top, the patients with relapse/refractory CLL, we have many trials. And some of them which were already mentioned by Dr. Wierda were quoted at the ASH meeting.

And then RT or Richter's Transformation, which is still an unmet medical need, and our group as you can see has a multitude – several trials right now we are running related to RT

transformation. Using checkpoint inhibitors, some targeting, some strategy, also some new strategies with specific antibodies. So that's kind of a landscape that stands as of today, but it's a moving target and sometimes things change. Some new trials come along and some old trials we never fully accrue. So that's where we are at MD Anderson. Obviously, I'll be happy to take any questions in the Q&A session. Thank you.

Jeff: Thank you very much for that update, Dr. Jain. Again, it sounds exciting. Things are moving really, really fast. I want to mention that if you miss anything presented by the panelists today, their slides and a complete replay of this town hall will be made available on the CLL Global website within just a few days. You'll find them at cllglobal.org under the Upcoming Events tab.

And now comes the part of the presentation that I think the panelists enjoy the most – they get to answer the questions that are posed by the participants on this event. So, we have a bunch of questions already in hand. The first question comes from Esther. She would like to know when will CAR T be a viable option for CLL patients, if ever? I'm gonna tee that one up to you, Dr. Wierda.

Dr. Wierda: So, I'm optimistic that CAR T will eventually be a viable option as a standard of care. We're not quite there yet. The trial that we have done that has completed enrollment is the trial called TRANSCEND. That was where we studied two different dose levels of liso-cel, or the CD19 CAR T-cell, for patients with CLL with or without ibrutinib. So that trial has completed and that trial results I believe will be submitted to the FDA for review for accelerated approval. They will need to do subsequently a confirmatory trial that demonstrates clearly activity with the combination. And that process of submission, review, and approval is probably gonna take a year or so.

So, I believe it's coming but it's a slow process and it's a process that requires collection of all the data, doing the follow-up, reviewing the data with the FDA, and identifying and addressing any safety concerns that may arise in the trials.

Jeff: Sounds good. As some of you may have heard, we are still dealing with COVID, and it's very much top-of-mind for many of the people in the CLL community. Susan has this to tee up: My husband has responded well to treatment and has received all the COVID

vaccines and boosters. An initial antigen test result taken just two weeks after his bivalent booster in late September was 327. The second antigen test, taken six weeks later, showed no antigens. Is it even necessary for him to receive them if his body is producing little to no antigens? Dr. Jain?

Dr. Jain: Well, you know, I think this is a tough situation and I think it's where we don't have much medical – I mean we have some medical data in the context of CLL patients, but we know from the very beginning – this has now been going on for three years – the pandemic, that patients with CLL, especially patients who are on treatment such as ibrutinib or CD20 antibody, or for that matter venetoclax as well, that they do not respond well to immunization, the COVID vaccination. It's not that it's zero, like no one responds. The rates of response were from 20-30% in patients with ibrutinib.

So, I think a recommendation at least at my clinic, especially when the vaccinations came about over the last years, is for you to be fully vaccinated because you may get some benefit out of it and we do not know who may or may not respond to the vaccination. So, I think, but you're absolutely right, as the person who asked the question, certainly there are patients who do not respond to vaccination despite multiple doses of boosters.

Previously up until recently we had Evusheld, which is now off the market, but it was available, and I don't know if something similar to Evusheld, which is the antibody's itself, what has been planned for the new strains of the virus going around. But up until a few weeks ago or a few months ago we were slowly asking patients to take Evusheld. As I said, that is off the market right now, because the new strain of the virus is not covered by the Evusheld antibodies.

Jeff: So, along those lines, Dr. Wierda, what is the best way to treat COVID, flu, and even the common cold at onset? Craig is dying to know.

Dr. Wierda: So, I'll just make a couple other additional comments about the vaccinee.

Jeff: Sure.

Dr. Wierda: We heard about quantitative test for antibodies, I believe. You said

antigen but it was probably antibodies and the person who was asking the question was probably meaning to say antibody levels that were tested for and identified. Remember, the immune system has two main arms: the humoral arm or the antibody arm, and the cell arm. And the cell arm – and they are interrelated but they are separate, so you do get responses, although we don't measure those, in terms of cellular immunity, and that can be helpful and important in clearing viral infections. Very important in fact.

We don't talk a lot about cell responses and what's the meaning of that. I do think that you get benefit from a vaccine even if you're not seeing an antibody response. So, I would not discourage any patient from getting a booster, particularly one of the newer boosters with the bivalent strains – or the bivalent vaccine. I think the other thing to emphasize is that now we have some antiviral agents that we didn't have before. One is called Paxlovid, the other is called Remdesivir.

Paxlovid is an oral drug, it can be administered as an outpatient. It's indicated for patients who are not sick enough to be in the hospital but are at risk for developing more severe symptoms. Remdesivir is usually reserved for more severe patients, hospitalized – treatment for patients who are hospitalized for their COVID. But the point is that we do have antivirals that we can use that are more effective if they're used earlier in an infection.

You can get a home antigen test now that you can take at your leisure at your home that's distributed by our pharmacies, so I would encourage everyone to have one of those tests on hand. If they develop symptoms, get tested. If they test positive for the antigen, call your doctor and tell them you test positive and that you may need an antiviral. It's a five-day course of a drug and that has been effective at reducing the severity of symptoms and reducing the requirement for hospitalization, particularly for Paxlovid. Patients can have a recurrence of their or a flair of their infection after they finish their course of Paxlovid.

Some patients, and even people who don't have a hematologic malignancy, have required a second course of Paxlovid. I think the one thing with COVID you can count on is things will be changing, and what we do today is different than probably what we're gonna be doing in six months. So stay alert and stay informed about it.

Jeff: Sounds like excellent advice. Dr. Jain, this is a great question that came in from Irv. How does being treated for CLL affect a person's ability to fight COVID?

Dr. Jain: Well, I mean, I think that at the end of the day it's your immune system which plays a major part in our ability to fight COVID, or for that matter any other infections we are dealing with. So patients who have relapsed CLL or patients who had prior therapy for CLL, and depending on which therapy they have received – and if they received chemoimmunotherapy, which again is only becoming less and less as a choice for patients to use. Patients can get low blood counts and things like that which can certainly influence on getting higher severity of COVID if their immunoglobin is low.

At the same time as we were just discussing, patients who are on active treatment for their CLL or who have had multiple therapies for their CLL, including maybe ibrutinib or venetoclax – many times only their immunoglobins may be low, their hemoglobin which are in the blood. And we know that patients with CLL – who have long-standing CLL – though they may have normal T-cell lumbar, their T-cells don't function very properly. So, their immune cells are dysfunctional.

If you get COVID in that situation where your immune cells are dysfunctional, maybe your neutrophil count is on the low side, maybe your immunoglobin levels are on the low side, so there might be multiple aspects of immune systems is not working properly, you are more likely to get a more severe aspect of COVID if you were to catch COVID. So, I think, for patients with CLL, I think it is especially an important aspect, especially because, as we discussed, we know the common therapies for patients with CLL, at least in the past we know with vaccinations they were not responding to vaccinations as well.
So, I think we have seen some tough, aggressive forms of COVID, or patients requiring ICU and things like that when they develop COVID, and they have multiple relapsing/refracting CLL.

Jeff: Thank you for clearing that up. I'm gonna go over to Dr. Wierda. At the beginning of your presentation, you talked about old school chemo being the standard of care and how we're moving past that. But there are an awful lot of patients out there who did go through the FCR protocol. Nick would like to know what are the main issues

facing long-term CLL patients who did an FCR protocol?

Dr. Wierda: You know, I think probably the biggest risk is their disease coming back and needing to be retreated. That happens more often and is predictable in patients who have an unmutated immunoglobin gene. Work that Dr. Keating did and others here demonstrated that about half the patients who have a mutated immunoglobin gene who receive standard FCR treatment will remain in remission more than 10 years. And so that's the subgroup of patients who are doing very well with FCR treatment. And it's the unmutated cases that are at risk for relapse of their disease and ultimately developing resistance even to the targeted therapies.

I think, the other thing that we worry about is other cancers that can be caused by exposure of the bone marrow to the chemotherapy that you get with FCR. Those are AML, acute myeloid leukemia, or plastic syndrome. That happens – in our long-term follow-up that Dr. Thompson is summarizing now, that happens about six percent of the time overall for all patients that we treated here for FCR100 trial. About six percent. With the long twenty years of follow-up, we have developed MDS or AML. So, it's a small number, but it's not insignificant. It is a risk with that treatment and I think that that's what most of us worry about with that exposure.

Jeff: Got you. Kim has a question for Dr. Jain. She would like to know if you have identified why some patients are slower responders than others in the ibrutinib plus venetoclax trial.

Dr. Jain: Yes, so you know, we were addressing this very specific question as part of the analysis we presented at ASH to see if we can invite patients up front who may respond better to treatment or less well to treatment. And so, we looked at two different ways. One we looked at patients who become MRD negative soon, within six or twelve months – or any time they become MRD negative – and we looked at patient's deletion 17p, their mutation status, and age of the patient, complex karyotype, and beta 2 microglobulin, and including IGHV mutation status. And the only thing we seem to have predicted is that patients who are IGHV unmutated, they have high rates of MRD negativity compared to patients who are IGHV unmutated.

And that was also shown, Dr. Wierda mentioned, in the slide with

other groups as well at the ASH meeting. But none of the other traditional prognostic markers – 17p, mutation status, beta 2 microglobulin, and others were not predictive. And then we looked at – the other aspect we looked at the progression through survival, which is how many patients actually progress on treatment down the line, and then none of the factors, including IGHV status, predicted for that. So, in general this treatment seems to work I guess equally well across the board and we haven't been able to figure out any group which is less likely to respond than the other.

Jeff: Thank you. Dr. Wierda, Matt would like to know do CLL active cells become stronger with each treatment, effectively making them harder to treat?

Dr. Wierda: That's a great question. If we only had chemoimmunotherapy to talk about, I would say yes. We have a lot of historical data that demonstrates that each remission is shorter than the prior remission, and the likelihood of achieving a complete remission with retreatment with chemoimmunotherapy is lower than it was with the first treatment. So if we're talking about chemo – chemoimmunotherapy, that is definitely the case. With targeted therapy – and when I talk about targeted therapy, we're talking about BTK inhibitors, we're talking about venetoclax or BCL-2 inhibitors, that's not quite as clear.

I think what happens with the chemotherapy and exposure to chemotherapy is that you select for the more aggressive cells that divide more quickly. The chemotherapy may also itself be causing some damage to the cells that allows them to grow more rapidly. That's not as clear with targeted therapy. We see patients responding with venetoclax-based therapy. There's not enough data to really clearly make a strong statement to answer that question with targeted therapy, even with venetoclax-based therapy. Because we haven't treated enough patients, I don't believe – or retreated patients with venetoclax-based therapy, after they've had first line venetoclax.

Now the BTK inhibitor is a bit different because you give that treatment until regression, or until it doesn't work any longer, so it's – that concept may not apply as directly as it does to the venetoclax fixturation treatment. Essentially, with targeted therapy, I really don't believe we have enough data yet to make a clear, concrete statement about that. With chemo, yes. But it's

looking like it may be less of a situation with the targeted therapy.

Jeff: That's very encouraging. I have a question for Dr. Jain. You and Dr. Wierda and Dr. Keating, you're all CLL specialists, and many of us are fortunate enough to be able to be seen by CLL specialists. How would you recommend someone who doesn't have access to a CLL specialist who's working with a local hematologist/oncologist – how does that type of doctor work with a CLL specialist?

Dr. Jain: Well, I mean, I think, I was only advised that you should see a CLL specialist maybe at least for initial consultation. You know, many of the patients who may be listening maybe are in the early stage of the disease where it's just watch and wait, and they're just being monitored every three months or every six months. And in that situation I think, you know, it's still maybe a good idea to go to a center – a CLL-specific center, like our center, and there are many of them in the United States – and at least get initial advice in what kind of genomic markers you have and then what kind of treatments are available when you need treatment.

But I think it especially becomes important when the time for treatment has arrived. And if your local oncologist has recommended some kind of a treatment, I strongly recommend at that time to at least go to a CLL center, whether you're not maybe wanting to relocate there or move there to do the treatment, but at least be advised to see what is the best available therapy – FDA approved therapy – which your local doctor, your community doctor can give to you, versus what clinical trials the center may have available. I think it's certainly worth a visit when you're deciding on starting a treatment.

Whether it's the first treatment for the disease or you had a prior therapy and now your disease is coming back, and your doctor is recommending a second or subsequent line of therapy. But we are very open, and we work very closely with local physicians just in our practice. We see patients from all over the U.S., so we work very closely with local physicians in terms of correspondence back and forth. Most of the local physicians are very appreciative of our involvement and kind of helping the patients out.

Jeff: Outstanding. Dr. Keating, I bet you thought we had forgotten about you, but I've actually especially been saving a very important question that I know is on everyone's mind right now. As a matter

of fact, it's probably at the top of the CLL community's list: Is there a hope for a cure for CLL?

Dr. Keating: Well, I think it's very difficult because to say that you've cured it means that the patient never gets a recurrence of the disease until they die. But no one wants to have that as an end point. So, I think we just need to say to define a surrogate. And I think probably a patient still continuing in complete remission for more than 10 years and the disease doesn't recur when you take them off treatment – I think that's an effective treatment because the patients are living a normal life by and large, and that's what they're very interested in.

From the point of view of what Dr. Jain was talking about before with the local physicians, I think it's very important than institution such as MD Anderson plays a pivotal role in educating the local physicians, because there are confusions as to what is the best BTK inhibitor, and eventually it'll be which is the best BCL-2 inhibitor. So that I think one of the things that I want to institute through CLL Global is a very wide-spread education program for patients so that they understand what needs to be done.

Many patients for example don't want to have a marrow done, so we have to demonstrate to them that we get additional information from the marrow that's going to tell us the best way to treat them. And I think there are so many different clinical trials that are published in journals that the average local oncologist doesn't read, so I think it's important for us to have things like this for patients about a general approach to CLL and advice to them as patients early on. They'll have different decisions they have to be making with their local doctor and the academic centers over a period of 15-20 years now, so we have to develop relationships with the community physicians.

You know, believe it or not, CLL is a disease of older people. They don't like to travel to big cities, and many of them are on fixed incomes and they can't afford to stay in nice hotels and go to restaurants when they come down here, so that we have to – when Dr. Jain was putting up the list of priorities, I'm sure the vast majority of people in even our own department of leukemia who are not specializing in CLL would know what to recommend.

So, we really do need to get a glossary of terms. What does MRD

mean, you know – some of the terms like even "the mutation status", that's not something that's easily explained, but I think we can explain it to patients in ways that they understand. So, I want to see if the CLL Global can mount a program such as this because, you know, Sam doesn't have enough to do – they just cancelled all our leave and arranged for us to come in earlier and leave later. So I think if we just had scheduled things, like MD Anderson Talks to Patients with CLL and other series. MD Anderson Speaks to Local Physicians About CLL.

I think education of the emerging treatments and carrying the sense to the patients and the community physicians that patients are being effectively treated and we have to make this accessible to the whole state of Texas. And that's what I'm going to do with my spare time over the next five years or so.

Jeff: That sounds great, Dr. Keating. I guess I can put a very sharp point on this. It sounds to me like we are continuing to make progress and we're getting closer to that cure that is at the heart of your CLL Global mission. So, thank you from one of your former patients.

Dr. Keating: You know, we don't have time to cover all the things that CLL Global does, but we don't just support MD Anderson. We've given away $31 million dollars' worth of grants since we were formed to people around the United States and overseas, and I think we're one of the most influential bodies in CLL research. And you can be very proud that we can very efficiently, from a financial point of view, use donations. So that I would encourage you to give as freely as you can, and if you want to have specific directed donations that would be okay as well. So, let's see if we can get to the point where the state of Texas is leading the world in how we can cure CLL, because we already are and we'll just do it better. Thank you.

Jeff: Great. Dr. Jain, you've shared a lot of promising research. I've got a pointed question for you too: Are you hopeful?

Dr. Jain: Yeah, I mean I'm really, really, very hopeful, and I think I share the enthusiasm which Dr. Keating and Dr. Wierda kind of mentioned about patients with CLL. And I think I'm very comfortable these days when I'm seeing new patients with CLL who are newly diagnosed coming for a second opinion that I think with the therapies that we have today and the therapies that we'll have tomorrow, I think we expect that the majority if not all of the

patients will have a normal life expectancy. I mean I really think we have the drugs – the tools available, right, we have all these drugs we talked about. Dr. Wierda mentioned about the CAR T-cell therapies, there are other therapies coming along.

So, I'm really hopeful that patients who are diagnosed today, who are living today, I think for a majority of the patients they can have a normal life expectancy. I think whether we cure they CLL, whether they get their CLL in deep remission, or they may still have some CLL present but as long as they have a normal lifespan and no other side effects from the drugs they're using, I think that would be a win-win situation. I'm personally very excited about the field where we are, and I think some of the new strategies and trials we are about to do – as a field in general, not just here, as the CLL field in general – things are very exciting for the field.

Jeff: Excellent. Dr. Wierda, I've got one question that we need to get in and then I want you to give us some closing comments. What is next generation sequencing, and should it be done for CLL patients before treatment?

Dr. Wierda: So, next generation sequencing is a method that's used to sequence genes in the CLL cells, and it will tell us if there are mutations in particular genes or no mutations. We have a panel at MD Anderson that is called the End Lymphoma Panel. It has 163 different genes included on that panel, and the method that we use to sequence those genes is called next generation sequencing, or NGS. It is an important test to do because we really need to know, like FISH, whether TP53 is mutated. With FISH you can detect if it's been deleted. With the NGS gene sequencing, you can tell if it's mutated or not.

And that's an important feature to know about in patients, that is, if TP53 is mutated before they go on treatment. And that's with first treatment or with subsequent treatments. I think it will also become more relevant as we move forward with our BTK inhibitor-based therapies because BTK sequencing, which is routinely done by NGS, is important or will be more important, as well as sequencing for PLC gamma 2 which is another molecule associated with resistance to the BTK inhibitors. So NGS, or next generation sequencing, refers to a method to do sequencing, and it's essentially to determine whether or not particular genes are mutated.

Jeff: And your final thoughts?

Dr. Wierda: Final thoughts. I wouldn't agree – I couldn't agree more with Dr. Keating and Dr. Jain about the optimism with where we're going from a therapeutic perspective. I think the other thing that we didn't talk about or mention is work that we're doing and need to focus on in terms of the immune dysfunction that we see in patients. We see that patients, even those who are undetected – who have undetectable MRD status as their best response – have low antibody levels, are still at risk for infections.

So, correcting the immune system is also another significant area for research that's really just beginning for us and is very critically important for our patients, because we can control their disease very effectively. What we would like to do is make sure they don't have bad infections, pneumonias, and second or other cancers. And so that's another area of research. There are a number of areas that we can identify for CLL patients that are needing research, needing advances, needing understanding, and so our work is not done. We are very optimistic about where we are and where we're going.

We still need support; we need patients to participate in clinical trials. We work towards getting funds and funding for our research, and we really support – we really appreciate the support of the patient community, the knowledge base of the patient community, and our peers and colleagues. And then finally I'd like thank you, Jeff, personally, for all of your hard work with the foundation, with your willingness to moderate these meetings, and that's done without any financial renumeration. So that's a volunteer activity that you do, and I really appreciate all the advocacy work that you do with patients and with us, and so thank you.

Jeff: Well, thank you. And thanks to all of our panelists for taking time out of their busy schedules today to share their perspectives. We really appreciate your optimism and dedication to moving CLL research forward. And thank you to our audience for your participation as well. We hope this program helped you understand CLL research and answered your questions, although I know we didn't get to quite all of them.

Don't forget, if you missed anything or want to watch the town hall

again, there will be a replay available soon. And please don't forget to take the survey that is going to be following up immediately after this program. We use your feedback to plan our next town hall which is going to be held later this year. We hope you can join us. Like I said at the beginning of this program, my goal is to live a great life with CLL, and I want you to do the same. So, thank you.