Andrew Schorr: Greetings, it's Andrew Schorr from Patient Power. Thank you so much for being with us. I'm joining from Southern California, but we're going to skip all across the country, particularly to the East, as we have our experts. This program, of course, is a reflection on living with CLL in 2020 and looking ahead to 2021 in the new year. And hopefully, it will be a better new year for all of us.

I want to thank our sponsors AbbVie and Genentech for supporting this program. Of course, like all Patient Power programs, they have no editorial control. If you have a question, hit the Q&A button at the bottom of your screen, we have a lot of questions, and we'll get to as many as we can, but I have a partner in crime if you will, or partner in CLL, I've been living with CLL since 1996. There's Michele Nadeem-Baker joining us from Boston. Hi Michele.

Michele Nadeem-Baker: Hi Andrew. What a year it's been, huh? 2021 will be so much better, hopefully, we'll keep our fingers crossed.

Andrew Schorr: Right. You've kind of really been locked in your house in Boston. Haven't you?

Michele Nadeem-Baker: I have. I have since March 13th when the COVID rules happened because I am immunocompromised and not everyone else is as careful, of course. And I just want to make sure I don't catch COVID because the statistics are rather frightening for us as CLL patients.

Andrew Schorr: Right. And I'll mention that Michele did a whole round table with CLL experts that's posted on the Patient Power website from the American Society of Hematology meeting, virtual. And so all that's there now, a number of other interviews. I'm even interviewing today, Dr. Woyach from Ohio State on some specific trials, but Michele, why don't you introduce our experts who are with us today? One of whom is your doctor.

Michele Nadeem-Baker: Yes, I am so excited to have my oncologist here with Dr. Jennifer Brown. She is the Director of CLL at Dana-Farber Cancer Institute. And we also have Dr. Nicole Lamanna, who's joining us from Columbia University Medical Center, where she is a CLL expert. Welcome.

Andrew Schorr: Okay. All right. Hi ladies. Thank you so much for being with us. So we're going to have lots of questions for you. Let's get started, and maybe we'll start with Nicole. Nicole, this has been like a bummer of a year with worries from all of us patients and you, of course, in New York, but also in Boston, you got hit hard with COVID at the beginning. So what has your experience been with looking back with your CLL patients? You made a comment to me earlier. Maybe you could repeat it here.

Dr. Lamanna: I mean, obviously, it's been a tough year for all. Thanks for everybody hanging in there. Hopefully, 2021 will be a brighter year for sure. But 2020 was very difficult. We had a lot of patients who succumb to COVID in general, and for sure, there were some publications and some of us who got involved in looking at our CLL patient population. And there was no doubt that at least in the early series, hopefully again, this will be something we'll be following very closely. But there was no doubt there was an increased mortality that we saw in our CLL patient population.

And again, this is just us putting data retrospectively together, and we'll have to follow and learn more about what our CLL patients, given your immune systems how they will be, and certainly, now I'm sure we're going to talk about the vaccine. But certainly, it was a hard year. And so I think for everybody, even in 2021, I think for a while, everybody still needs to be very cautious and wearing masks and protection because it's going to take a while to roll the vaccine out.

And so, I think it's still this year we're happy obviously because we're going to be looking forward to a new year with a vaccine, but there's some data to suggest that you guys are certainly more at risk for complications [inaudible] as well.

Andrew Schorr: So, Dr. Brown - BTK inhibitors. Are they helpful at all? There was some early buzz about that where they're helpful either in treating, or is there any research that can help lower the risk?

Dr. Brown: So, I think that that's still an open question. There were some early reports with case series of patients treated with BTK inhibitors who were very critically ill from COVID, who recovered, but they were not controlled studies. And so, it's really hard to tell what would have happened if the patients hadn't received the BTK inhibitors. They might've recovered anyway. And so there are multiple ongoing what we call randomized trials, where patients with COVID are randomly assigned to receive a BTK inhibitor or not. And to look at the impact of that on outcome. And I think we've learned from some of the other drugs that have been studied early on with COVID that we really need those randomized trials to help us understand whether the drugs are beneficial or not.

When we put together an opinion piece about whether people on BTK inhibitors who developed COVID should stay on BTK inhibitors, we ended up recommending that people should, as long as they're not critically ill, but that then if people become critically ill, most of us felt we would hold the drug. And that was a little bit of an evolution from our original position of holding all therapy if someone got COVID, but that was based on the favorable reports early on.

Michele Nadeem-Baker: To carry on with COVID. I would love to know, Dr. Brown, what your opinion is of your patients receiving the vaccine?

Dr. Brown: I'm definitely in favor of all my patients receiving the vaccine. I think what I've been counseling people, though, is that we know that vaccine response tends to be less in our patients with CLL, even untreated patients with CLL, compared to the general population. And so I think that we need to be aware of the fact that it's likely important to maintain all the precautions, the masks, and the social distancing and quarantining at home, even after getting the vaccine until the pandemic quiets down, just because we won't be sure how much benefit all of our CLL patients may have received from the vaccine, unfortunately, and that is something that, of course, we want to study, but it's going to take a little while to get that data.

Andrew Schorr: Nicole, what are you telling your patients?

Dr. Lamanna: Yeah, similarly, the good news is it's not a live vaccine. I want my folks to get it as well. But for sure, I think that just like we know with other vaccines, again, the goal is to try to be preventative and, or to try to decrease the severity of the infection if they should get COVID. So, it's not a guarantee that if you get the vaccine, you cannot get COVID. But the point is to really try to decrease the severity of an infection in our CLL patients.

So. if it helps, again, we won't know what kind of benefit they will have compared to patients without CLL. That's data as Dr. Brown too, just so that we're obviously going to try to eventually get, but certainly, if it helps at all that certainly better than nothing. So I think we're all obviously wanting our patients to get vaccinated if possible.

Michele Nadeem-Baker: Now, what about patients who are on treatment right now? And they would probably be going to their primary care I would think for the vaccine, should they be instead getting it through their CLL specialist so that they know their history when it comes to treatment?

Dr. Lamanna: Dr. Brown, do you want me to take that, or you want to take that?

Dr. Brown: Okay. So, I'm encouraging people that they can come to us, although we don't have the vaccine yet, but institutionally we've actually decided that regardless of therapy, everyone can get the vaccine as long as they're not in the immediate post-transplant period. And again, this is because of the potential for benefit for everyone, even though we don't know that the benefit will be as great as it might be if people weren't on treatment, but still, there's some potential for benefit. And so, we want to make sure that everyone has that opportunity to get that benefit. There's no risk for anyone on any type.

Dr. Lamanna: It just depends on where the vaccine, I think, how it rolls out and what the availability is. Certainly, I'm sure the major hospitals and institutions may have more of it, it depends on how much stash, supply, and demand there will be, including at local places. So I think it depends on what the availability of the vaccine is whether they're going to be in primary care offices because remember, some of the vaccines, like the Pfizer vaccine, requires a specialized holding and specialized freezers. So that may not be available everywhere. So the likelihood is I suspect that a lot of our CLL patients might be getting that with us, with their primary docs, but it could be that they might be getting it locally as well.

So as long as they keep their hematologists' oncologists in the loop about where if they get the vaccine, I think that's important, but many of them might be getting them with their primary physician.

Andrew Schorr: But let's talk about the year independent of COVID for a minute. So first I'll go to you, Jennifer Brown. So, we've had progress. I mean, you have lots of trials, but also we have more experience with venetoclax (Venclexta) in combination, people may be on time-limited therapy, and we have more experience with people on BTK inhibitors, like acalabrutinib (Calquence) or ibrutinib (Imbruvica). So, the news is positive there, isn't it? And what we've been learning with these novel therapies. Am I right?

Dr. Brown: Oh, very exciting. We're definitely getting longer follow up with our venetoclax combinations. And we're seeing very long, nice durations of response in the relapse setting and in the frontline setting, even despite stopping therapy after the two years in the relapse or one year in the frontline setting. So that's very exciting.

And with the BTK inhibitors, we've had some encouraging data suggesting that our highest risk patients with 17p deletion can still derive quite durable benefit from frontline BTK inhibitors. I

think perhaps more durable than any of us almost expected or hoped. And so that was really exciting. And we also have new drugs coming along as well.

Andrew Schorr: We're going to get to that. Of course, you've been studying in 2020. We're going to get to how that may continue in 2021. So, Nicole Lamanna, what about you? How do you feel about what you're seeing from your patients who've either been on time-limited therapy with venetoclax, maybe with obinutuzumab Gazyva, frontline, as you say, or if they've relapsed at some point with rituximab (Rituxan), how are they doing? Let's talk about that first.

Dr. Lamanna: Yeah absolutely. We participated in many of the studies that were presented at ASH, and we're really seeing a nice long-term response in some of these combination studies with venetoclax and a monoclonal antibody, as Dr. Brown suggested, whether in untreated patients or in the relapse setting, which is great. So, patients, I think now that there's definitely more choices for our patients and very good choices. So, people can be on BTK inhibitors and do very well as some data that was presented at ASH showing these nice long time remissions, or I should say durability long-term responses in patients who are taking BTK is even in some of our tougher patients who have 17P deletion, but then patients can also have time limited approaches. And we have updated data at ASH really showing some nice durable responses where patients can be off therapy for several years.

And so, I think that there are many options that are available to our patients, and now we can be a little bit more selective based on comorbidities ability to depending upon patient's social support. So there's lots of options for our patients and really, this ASH, I think, really highlighted a lot of the durability and nice responses that we're seeing with these novel agents.

Michele Nadeem-Baker: Dr. Brown, regarding the novel agents and BTKs, there are new generations of BTK that have been coming out and more that we'll be continuing to begin research next year. Are any of those showing any promise winning combination or on their own of more of a limited duration treatment? I know that we were just discussing, for example, venetoclax and another drug, but what about the venetoclax, Imbruvica trial as an example?

Dr. Brown: Right. So very encouraging data from Imbruvica combined with venetoclax we have actually several frontline trials and a relapse trial of that combination. And we see very high response rates, very high rates of eradication of disease, which is really great. And that allows the potential stopping of therapy. And as Nicole was saying, to get a number of years off therapy, hopefully before having to go back on.

What we don't know yet is whether that combination is if there are particular patients who would really benefit from that combination compared to, say, venetoclax with the antibody or the continuous BTK inhibitor alone. I feel like that that is really a huge question in our field right now. And because we don't have that comparative data, we take into account a whole variety of different factors with our patients, including how they feel about time-limited versus continuous therapy, what type of therapy they want, what their goals are.

Andrew Schorr: Well, both Nicole and I had FCR. And you had that, Nicole, right? Not Nicole. Sorry, Nicole didn't have it. Michele, I have all these wonderful women with me. Michele, you had FCR, right?

Michele Nadeem-Baker: I did in combination with ibrutinib.

Andrew Schorr: Right. I'm trying to understand these combinations. But the idea was, could you do that and stop? And so that's the whole question is can we have, like I had FCR in 2000 in the phase two trial, and I did it for six months, and then I had a 17-year remission, it's pretty good. So I'm really delighted. Well, so then I had four and a half years of watch and wait. Michele, how long was your watch and wait or watch and worry period? How long was that?

Michele Nadeem-Baker: Three and a half years. And Dr. Brown can assure you, it was worrying in that time.

Andrew Schorr: We all have anxiety. It's front and center. So Nicole Lamanna, let me ask you this, is anything changing about whether people should be on extended watch and wait?

Dr. Lamanna: Well, I think if you're asking the question, let me rephrase that. If you're getting at whether or not you think should we be treating people sooner? I think watch and wait, and I hate the term watch and worry as you both know, I really like active observation because during that period where some patients are being monitored as you two both did for a while prior to needing therapy, all these clinical trials and learning more about the biology of the disease, and hopefully coming up with better strategies for therapies can be an advantage for those who are on active observation.

So, I like to look at it a little differently. So I like to tell my patients that they should view it as a time where they can be on the sidelines, and they can get to sort of watch along with their physician what is going on in the field as we've been changing things so dramatically and have developed all these wonderful therapies to treat patients. So I'd like to take the worry out of that, although it's understandable that people are worried, but in terms of moving therapy upfront, I don't think we have enough data to say that that's the right thing to do yet because there is still a subset of patients. I wish that if we could do a blood test on patients to know that there are about a quarter of patients who may never need treatment for their CLL.

And if we knew that they had a blood test that told us who those were, that would be great and wonderful. We could tell those folks that they don't have to worry and be done completely. But we don't. And so, until we can prove that starting patients early, or we have definitive curative therapy that starting patients at diagnosis would eradicate the disease completely from everybody, I think that would be different. But we haven't done that yet. So even though we have these wonderful therapies, I think I'd be hard-pressed to say that we should be moving them until, without data, until we know that moving them early, it would make a significant difference.

Andrew Schorr: And one last thing for Jennifer Brown about that. So is there any evidence that we pay a penalty for waiting to start treatment?

Dr. Brown: No, I don't think so. No. There have been randomized trials that have shown no overall difference, but more toxicity in people treated sooner. And then some of the newer randomized trials, we don't really have long enough follow-up to know if there's really any difference. And many of them haven't really had the best endpoint. So we really don't have new data. And I have to say that I worry that we mostly see the evolution of the CLL, the changes in the CLL under the influence of treatment. And so, if patients are stable and doing well prior to treatment or in-between treatment, I don't like the idea of interfering with that because that may encourage the CLL to evolve.

Andrew Schorr: Oh, you don't want to open a Pandora's box for sure.

Dr. Brown: Exactly.

Andrew Schorr: Okay. Michele, I'm just going to pose this one question that a lot of people are asking because they want to come back to COVID. So there were some reports in the news that people with certain allergies shouldn't get the vaccine. So you're both generally saying you want your patients to be protected, right? Get the vaccine. That's what I been hearing for sure what about this related to, would it be contra-indicated, let's start with you, Jennifer Brown. Have you heard anything about that? Or any people you'd say, "Ah, let's not do it."

Dr. Brown: What I've heard is that it's mostly confined to a history of allergies related to the components of the vaccine, which is a little more specific than what's been in the news reports. But I think this is probably something that's continuously evolving, and so I'm not sure I have the most recent data on that.

Andrew Schorr: Nicole Lamanna, maybe the same from you.

Dr. Lamanna: Yeah, absolutely. I've heard similar things. I think in-patients who already have had issues with, let's say, the flu vaccine or other vaccines where they may have certain food allergies. I think that obviously, I would discuss with your physician about ways that you might mitigate a reaction because we all might have little strategies about what we do with our own patients about how, to sometimes we'll say, well, let's maybe we'll give you an antihistamine or we may try to prophylaxis a little bit, depending upon your history of allergies, to try to see if we can prevent a significant reaction to the COVID vaccine. But I think Dr. Brown's right, I think we don't have enough information yet.

And as you've heard, they're rolling this out to medical staff, and that's not just - that's the medical team, everybody. So, from physicians, nurses to people who take care of the staff at the hospitals, so on and so forth. So we'll get, I think, a better sense over in the next month what the adverse events, in terms of reactions to the vaccine going, how high those reactions may occur. And if there's similar more to the anaphylactic reactions that we might see rarely with a flu shot and things like that.

So, I think we need to wait and get a little bit more data, but for sure, if you're a person who's got food allergies or a history of allergies to vaccines, talk about it with your physician. As we roll this out, it'll be a little bit of time I think before they get it to everybody. So we'll get a little bit more data as more people get vaccinated.

Michele Nadeem-Baker: Dr. Brown, we've been getting a few questions regarding COVID, and if people in their family who've already had it, should that person be tested - the patient, the CLL patient, to see if they have antibodies because people around them have had COVID, and if so, does that mean that they will not get it?

Dr. Brown: So that's a little bit complicated because CLL patients actually don't always make antibodies. So it's possible they might've had the infection but not actually made antibodies. One can check. I am aware of at least some CLL patients who have had positive antibody test. So sometimes they will make antibodies. And as of now, I think that the recommendation is still to get the vaccine, even if you've had the disease, as far as I'm aware.

Michele Nadeem-Baker: And does that mean everyone in someone's family should be getting the vaccine if they're going to be safe? Was that the way to be safest?

Dr. Brown: That would be the way to be safest, especially again, if the family members are likely to have, say, the 95% response rate that's been described in the Pfizer and Moderna studies, and we're not as sure that the CLL patient may have quite as good of a response, it will provide additional protection to make sure that everyone around the patient is vaccinated as well. And that's a similar strategy that we use for flu or any other disease in the past.

Andrew Schorr: Let's talk about how things have changed also in the way you interact with us as our physicians in 2020. And I just did one today, a video visit. So my doctor, first of all, wants to do video visits whenever we can, but I know that she's not poking my spleen. She's not listening to my heart. But I did get a blood test, and we each have the data to look at.

So, first of all, for you, Nicole Lamanna, what's the advantage of a video visit? When's the downside? Where does this fit in? Because you will each have implemented that, it's been implemented nationally. Where does that fit in with CLL care now so we still get quality care?

Dr. Lamanna: Yeah, absolutely. First, just to go back to the vaccine for a second, I think it's important that… I know the patients are focused on getting the vaccine themselves, which of course is one hurdle, but the second hurdle is making sure everybody else gets vaccinated too. So it is that until everybody is vaccinated to really sort of suppress what is going on nationally and globally, we're still going to be wearing our masks, and people still need to be protected for this year. So even though it's a year to look up to because there's a lot going on, and hopefully, there'll be a better year. I still think that you're going to be quarantining and being cautious. And yes, I think that family members and others should be getting vaccinated as well to protect you because, again, your antibody production may not be as good.

And certainly, if you have symptoms, you should get tested. So the random antibody testing, I think Dr. Brown's right. Some patients may have antibodies and lose them quickly. And so it's time-dependent. We don't know, and some CLL patients may not make antibody. So it's something we're still learning and how effective they are. We're still learning. We don't know what that means.

And then moving on to Andrew, what you suggested is absolutely, depending upon where you live and the amount of COVID, doing tele-med is very convenient because then you're reducing your risk of exposure. And you can get blood work, but certainly, I think that patients who are not well and need to see their physicians and their teams, we're still seeing patients, right? So patients that need to be seen, it is not good to be at home if you're sick or you're ill or the things that need to be addressed, because actually, we're more concerned about what's going on in that sense. And certainly, a phone call can help triage that whether to come in or not come in.

So, depending upon the amount of COVID, but yes, I think telemedicine has made it very convenient to get blood works and do a very nice conversation, and more relaxed, you're in your home, so they don't have to be stressed about coming to the environment, particularly if they're otherwise well and can reduce your risk during these times of where the numbers are rising in the country. So yes, I do think telemedicine is here to stay, particularly for a cohort of our patients.

Michele Nadeem-Baker: So that's all, it's good news for the future, that's we have to keep all thinking of that once the vaccine is in the majority of the population… is the number, what is the number? 75 to 80%, then will we still have to wear a mask as patients? Yes, I can tell that's what you're going to say.

Dr. Lamanna: I think we have to see how things roll out. I think we don't know. I don't think we have that answer yet. I think we have to see how, later in 2021 what the numbers are, where everybody's at, and the amount of illness and hospitalizations, and I think it's too soon for us to say how this is going. So for the near future, I think that the answer is yes.

Andrew Schorr: Eileen said Dr. Brown are there any concerns with the vaccines causing inflammatory effects on the lymph nodes? Because we're always like poking around here. Would that cause any inflammation related to these vaccines?

Dr. Brown: Well, that's something that we see in general with vaccines sometimes in our CLL patients, as well as everyone else, too. The purpose of the vaccine is to generate an immune response, and you need to get an immune response to generate the protection against what you're being vaccinated against. And we do sometimes see that our CLL patients, they get a little bit more exuberant, somewhat worse reaction, both in terms of local arm pain, lymph nodes near the area of the vaccine are pretty common and also potentially systemic symptoms, but the symptoms will regress with time. And it's not a reason not to get the vaccine. It doesn't cause any permanent harm in terms of your disease steps.

Andrew Schorr: So, if you feel that way, lymph nodes, you feel more lymph nodes or your arm's sore, or you're fatigued. Is that like a good thing that my nicked CLL immune system is responding?

Dr. Brown: Yeah. That's an interesting question. I don't know if anyone's ever studied that, but I mean, I think that is how you should sort of view it and put up with it because that means you are responding, your immune system is reacting, and hopefully, you're getting good benefits in the vaccine. And so take it in that light, and it'll go away in a couple of days.

Michele Nadeem-Baker: That's great information to know. So we were talking about testing with COVID, but what about how, let's switch back gears a little here on CLL testing and how far that's been coming and to specify more for more precision medicine for patients? Are we there yet that you can absolutely tell by someone's genomics exactly which treatment and variety of combinations they should be getting? Are we there yet?

Andrew Schorr: Nicole, go ahead.

Dr. Lamanna: I mean, I think there are certain tests that absolutely do help us that we have readily available that help us guide treatments even now. Certainly, I think what you're asking is probably even a deeper question. But for sure, I think that having the cytogenetics or FISH, the chromosomal abnormalities help guide us to tell us which therapies we may say should be avoided and which therapies for sure should be included.

So, I do think that there are some testing that's readily available that most patients should have, and that helps us select what might be better for them. I do think that there is a whole bunch

when we talked a little bit about time-limited therapies, there's still a lot we don't know when we talk about minimal residual disease or how to move the field forward, which we might get to.

Certainly, I think there's a lot more unknowns that we're still trying to evaluate in the clinical trial arena about that. But I think there are some common tests that most local physicians can get on their patients. That's the FISH. And also, IgVH study, the molecular testing, and that may help us say, "We don't think you should, you're a great candidate for chemoimmunotherapy. These options are much more palatable and better for your disease long-term." So there definitely are testing that should be done. We're all, I think, in the CLL land, struggling to make sure that physicians get these tests.

So, we all talk at a level at some of these meetings we're further along and things that we're trying to investigate, but at the basics of the core, there's still a lot of stuff that isn't being done for our patients that we'd like them to be done, because it may help guide their treatment.

Andrew Schorr: Jennifer Brown, let's talk a little more about this. So, first of all, Nicole mentioned this about MRD minimal residual disease testing. So I know there's still discussion among you CLL specialists. Let's say if you have a venetoclax patient in combination with one of the monoclonal antibodies and you say, okay, we can stop, you do an MRD test. I know as a patient, I want to know, have we knocked the CLL way back and how deep or can you find it? So what's your thinking about MRD testing now, and where it fits in?

Dr. Brown: So I think many of us who are CLL specialists do tend to do it on these venetoclax regimens, but it's important to remember that the studies were based on one year or two years of therapy and everyone stopped at that point. There was no decision made related to MRD, and we really don't have the data to say that we should be routinely making these decisions with MRD testing.

And so, I think it's more prognostic or informative, but not yet something that we really should be guiding therapy based on. And it's also important to remember that even if it's slightly positive, that doesn't mean that the CLL wasn't knocked back very, very well because the CLL is usually still knocked back very, very well, even in cases with low levels of MRD.

Michele Nadeem-Baker: Dr. Lamanna, I've been reading a lot about the differences between testing for MRD by blood versus by the dreaded bone marrow biopsy. Could you explain which you feel is better or if, or if the difference is negligible?

Dr. Lamanna: Yeah, that's a really great question. I mean, I think that the many of the trials that we were looking at and evaluating for minimal residual disease, we're trying to look at both peripheral blood and bone marrow to see how concordance or similar they both are. And many of the studies show that they're fairly similar, maybe about a 10% difference in some of the studies, because we're hoping that peripheral blood testing can be done since it's done more readily. And obviously, patients dread the bone marrow procedure. We're hoping that certainly, we can use that as a surrogate for what's going on in the bone marrow so that maybe we can move away from bone marrows. But they're very similar.

I think that as Dr. Brown mentioned, I think that since a lot of the MRD testing… we're still trying to figure out how to utilize that information forward, and it shouldn't yet guide therapy, for the

most part, I think most physicians, particularly will probably be doing currently off peripheral blood. On clinical trials, we tend to still do a lot of both because we're trying to still see how well the concordance is. But hopefully, if it's very close, the goal is to obviously move away from bone marrow testing except when it's really needed. And there are times when it really is. But I think that you can get an inkling off the blood because if you've got a little detectable disease in the blood, you know that the bone marrow likely has some disease as well. So that's another way so you could test off the blood first and then not have to do bone marrow.

But I think we still need a more follow-up data about how to use MRD testing moving forward because there are some patients who may have just a little bit of disease left, as Jennifer noted, but yet still do really well long-term and may not need treatment for a very long time. And I think some of the newer data that was presented at ASH, some of the follow-up, even from the frontline study, suggests there are patients who may still have some MRD, but yet still don't have a growth rate yet, that they're really doing well and just need longer follow-up. So we need more follow-up to see where that goes, but hopefully, we can move more to purple blood testing.

Andrew Schorr: Dr. Brown. We got a question from Gary, Gary's for 24 months, has been on ibrutinib, and he wonders are there some markers that can be looked at where he could stop taking that?

Dr. Brown: So we don't have any data on that. We know that single-agent ibrutinib usually doesn't get rid of MRD the same way as venetoclax, but it doesn't matter. People still have really, really long remissions, even though there may still be a little bit of detectable disease, and that's as long as you stay on the drug. If you stop the drug, then we have a little bit of data that it may be about two years until the MRD kind of starts to percolate and show disease again, and then you wouldn't necessarily not only even the treatment, then there would still be a longer period after that of the watch and wait active observation phase before treatment might be required again.

So, at the present, I generally encourage my patients who are on single-agent BTK inhibitors to stay on them if possible. But if people have a lot of side effects or there are concerns about staying on them related to any other issue, we have a conversation about it because it's likely that if you did stop, you would have a number of years potentially before treatment would be needed again. And there's lots of great options when treatment is needed again. So it's really an individualized decision, I would say, but in general, we plan to continue them indefinitely.

Andrew Schorr: Let's carry that forward in 2021. So, you've been studying a drug called LOXO-305, and my understanding is their new generations being studied of bruton tyrosine kinase inhibitors, BTK inhibitors, which is what acalabrutinib or ibrutinib are. So, where are we headed with that? And where would they fit in? What might be an advantage of those drugs when they develop? Jennifer, go ahead.

Dr. Brown: So, in general, I think of the BTK inhibitors in two categories, the first-generation or early generation ones are, they're what we call covalent. They permanently... Their action is permanent on the cell. And so ibrutinib was the first generation of that. And then acalabrutinib and zanubrutinib (Brukinsa) are a next generation of that but are more specific for BTK and generally, we think have better side effect profiles. We don't have as long follow-up data with them compared to ibrutinib yet, but we're getting more and more data.

Now there's another category of BTK inhibitor, which is called reversible or non-covalent. And those drugs are in part being developed to deal with the type of resistance that we see to the first ibrutinib, acalabrutinib, zanubrutinib group. They have similar kinds of resistance and these reversible ones and work against that type of resistance.

And so LOXO-305 is a drug that is now being tested in quite a few CLL patients for 150. And the follow-up is still relatively short, but the responses have been really great in people who have had prior BTK inhibitors prior to venetoclax. And so it's very exciting that potentially people whose disease has come back on ibrutinib or acalabrutinib could potentially transition to this newer generation of drugs and get a lot more years out of BTK inhibition in particular.

And the other thing about LOXO is the side effect profile so far has been really phenomenal. Like there are almost no side effects, which is pretty remarkable. And so I think if that holds up and the effectiveness holds up, there's also the potential that this drug could even move earlier line in CLL. But that's still for clinical trials that haven't happened yet.

Andrew Schorr: Right. And clinical trials, you've been in one Michele I've been in two, actually one for an unrelated condition. We're big fans. So, work with people like Dr. Lamanna, Dr. Brown, always discuss trials. So, I just wanted to ask about one other area Michele, you, and I know people who have gone through CAR T-cell therapy, chimeric antigen receptor T-cells therapy, experimental not approved for CLL, but being studied.

Nicole Lamanna, what's your take on this? Is this getting close to being ready for prime time? And if not, but still what patients might be considered for? Because we've talked about these drug therapies, the BTKs, venetoclax, obinutuzumab, et cetera, but where does CAR T fit in or where could it fit in?

Dr. Lamanna: Yeah, I mean, as we evaluate any new therapies, we're always looking at them initially when we study many of the new therapies. We're always looking at them in patients who have had prior treatment for their disease. And so they're always more heavily treated, and that goes for drugs like even LOXO, which Dr. Brown and I are evaluating and seeing that many of the patients who've had many prior therapies are doing well on this new agent. And similarly, for CAR T-cells, it always tends to be relegated to patients who have had exhausted multiple lines of therapy and maybe couldn't go onto an allogeneic stem cell transplant. And so they've been placed on CAR T-cells.

Now, obviously, CAR T-cells have been around for actually a very long time now, being evaluated and approved actually in some acute leukemia and for aggressive lymphomas and been evaluated in CLL for many years. And obviously some of the concerns about CAR T-cells, including some of the side effects that go along with it. We've been working on those side effect profiles and sort of figuring out how better to deal with them. And so it has moved along quite nicely over the past several years, and no doubt that the responses have improved as well.

And so, there've been many updated presentations also at this latest meeting, really highlighting the significant responses in a heavily pretreated CLL group. And for sure, there's even some studies that are looking at it in combination with BTK inhibitors. And even in that group showing

that there might be less side effects with cytokine inflammatory reaction that some patients can get. And so there's no doubt it certainly has a significant response rate. It's still right now in the relapse and not approved for CLL, but obviously, the thought being is could a therapy like this be also moved earlier on in the patient's disease course? Or maybe even for some high-risk patients moving it on earlier on, depending on the long, as we follow up long-term data about how durable these responses are because many patients have achieved a complete remission.

So certainly, I do think it is getting closer and certainly a very viable option for many patients with CLL, but it's tricky because obviously, we have all these wonderful therapies for CLL. So we just talked about the BTK inhibitors, and we talked about venetoclax and now non-covalent BTK inhibitors. So it gets tricky because there's lots of, I mean, in a good way, there's a lot of hope because there's so many therapies for our CLL patients. And I think we're all trying to figure out the best sequence of these drugs for our patients. And part of it will be based, I think, as we run more trials and do some comparative analysis of some of these therapies and get a better sense of durability of some of these therapies, or maybe that there are certain types of patients that might be beneficial from more aggressive strategies. And so I think we need to learn, but for sure, I think CAR T-cell is moving along in CLL quite nicely.

Michele Nadeem-Baker: Dr. Brown, a follow-up to that, and since CAR T is not going to be approved probably that quickly, and it's not for everyone. What about the side effects from BTK? Like ibrutinib. I had many, as you know, or even venetoclax side effects. Does one have less side effects? So the other, or is that looked at per patient on these side effects whether to stay on or go off?

Dr. Brown: I do generally evaluate them on an individual patient basis. I have to say that I've shifted my practice largely away from ibrutinib toward acalabrutinib, primarily because of its better side effect profile. We still do see side effects and still do sometimes have to reduce the dose, for example. But in general, I find it to be much easier for patients than ibrutinib, and zanubrutinib is coming along. We're still learning more about that, but we actually already have head-to-head data showing that zanubrutinib is better tolerated from a cardiac standpoint, compared to ibrutinib, and that's in a different disease, but a closely related disease.

So, I think it probably also applies to our CLL patients, although we're actually getting data in CLL as well, head-to-head with both acalabrutinib versus ibrutinib and zanubrutinib versus ibrutinib. So that will be really exciting. And we'll probably actually get the data, the acalabrutinib versus ibrutinib this coming year. So people should keep their eyes out for that.

And then the LOXO-305 also seems to be well tolerated. I have to say comparing venetoclax to ibrutinib, I think venetoclax is generally much better tolerated, and it tends to have fewer side effects. We just have to deal with the tumor license issue at the beginning and get people going on it. It can still have some GI side effects, and there are some issues with low neutrophil counts, but I think that the general malaise, fatigue, joint pains that some people have on ibrutinib all the time is not something that you see with venetoclax, so much.

Andrew Schorr: Okay. I know Nicole has to go because you have all these meetings, and thank you so much. And I think snow is coming in the Northeast too.

Dr. Lamanna: Yeah, Jenny. Yeah.

Michele Nadeem-Baker: Is it already snowing with you, Nicole?

Dr. Lamanna: Just looked out the window. Not yet.

Michele Nadeem-Baker: Not quite yet, okay.

Andrew Schorr: Jennifer Brown will stay with us just a couple more minutes. So Nicole Lamanna, any final comment as you think for 2021. What I heard is get the vaccine, be safe, be careful we are at risk, but anything may be more upbeat you'd say to us living with CLL before you go?

Dr. Lamanna: No, I think that we'll get through. Happy new year everybody, we'll get through another year, stay safe, reach out to your teams. Your doctors and teams are there for you. Although it'll be another trying year, I think it's hopeful that we have a vaccine and then we have lots of wonderful therapies. So the good news is for patients with CLL is all these new therapies that we're evaluating. We're exploring some combinations looking at more about honing on how do we really fine-tune the therapies we have, and also looking at how best to sequence some of these therapies.

So, the good news is there's lots of hope for our CLL patient population. I think that there's a lot available for our patients. And certainly, if you're not tolerating one therapy, there's other therapies available, and you just need to have that open dialogue with your physician because sometimes some of the side effects you have sometimes are something we can deal with it. And so we don't want to necessarily throw away all our eggs. But the point is that intolerable side effects. There are new therapies and more options, and we didn't have that earlier on.

So, I really do think it's a good time for our patients. So stay safe, be well, reach out to your teams. Don't stay home if you're sick. Really call your teams and figure out what you need to do. Okay? Jen, I know I'll be talking to you soon. Andrew thank you, Michelle. Nice to see you again.

Andrew Schorr: Nicole Lamanna from Columbia. Thank you, Nicole.

Dr. Lamanna: Take care, guys. Bye.

Andrew Schorr: Bye. We're very delighted, Michele, to have these experts. So final questions you want to ask your doctor on behalf of the community, Michele.

Michele Nadeem-Baker: Well, other than wanting to be on the vaccine list quickly. For the community, a lot of the questions are still about COVID, and the vaccine and others are asking about well, what do you think in your opinion would be the hottest new developments in 2021? We've spoken a little bit about that, but they're wondering if there's anything we haven't spoken of that's on the horizon in research that perhaps we'll be hearing about a year from now.

Dr. Brown: That's interesting. So we are waiting for some randomized trial data that might come in the coming year, that direct comparison of acalabrutinib to ibrutinib, for example, we might have by then. I'm not sure when the head-to-head trial, looking at ibrutinib venetoclax compared to obinutuzumab chlorambucil (Leukeran) may readout, but I think that's a possibility for next year as well. And that's really designed to register the ibrutinib venetoclax so that it

becomes a therapy that people can actually get that their insurance would potentially pay for. So that's pretty exciting.

There'll be more data on LOXO 305, as we said, which I think is a very promising new drug that we're working on. And there are other drugs coming along in the clinic too. It's sort of hard to tell which one might be the next powerhouse, but other classes of drugs, other targets that are coming along. So we always have a lot of new things in the pipeline along with CAR T. So that's exciting.

Michele Nadeem-Baker: It's very hopeful.

Andrew Schorr: Yeah, it is. I mean, Michele, I was diagnosed in 1996, and we had F and C, well, we had chlorambucil, and then I was in the phase two trial, and then we added R, and that made a big difference for so many people. I know one guy, he's never had any other treatment, but I know some people like me, who with the chemo base did maybe it was going to happen anyway, developed a second cancer years later, I developed myelofibrosis. So chemo seems to be... we haven't been talking about it at all. And we've been talking about all these other approaches. So, Jennifer Brown, I want to thank you for pushing research forward at Dana-Farber and your dedication to us with CLL, and your dedication to Michele. Okay?

Dr. Brown: Thank you, my pleasure.

Andrew Schorr: We'll let you go. And Michele and I just have some final comments. Thank you for all you do. And for being with us today.

Michele Nadeem-Baker: Thank you.

Dr. Brown: Always a pleasure. Happy new year, everyone, and hopefully, 2021 will be better for all of us.

Michele Nadeem-Baker: Happy new year.

Andrew Schorr: Okay. Thanks a lot, Jennifer Brown from Dana-Farber. Thank you. So, Michele, a couple of reminders for people, we didn't talk about the money part of things. So if they talk about combining venetoclax with ibrutinib or something else, those are two can be, depending on your insurance, expensive medicines. So at Patient Power, we're going to do a lot more about the financial issues and the access issues. That's important, right?

Michele Nadeem-Baker: That's very important because when you think about it, each of those drugs per month if you didn't have insurance, what would that be? That'd be over 20,000 combined, probably more like 25,000 a month, right? If you didn't have insurance and with insurance I know that Medicare part D you were sharing that, that would cost almost 1,000 a month alone for one drug.

Andrew Schorr: Michele, you, and I have interviewed a whole bunch of CLL experts that's being posted. There's a lot more on the Patient Power website, right?

Michele Nadeem-Baker: Today was just a synopsis of some of all of the new developments that have been happening in treatments for us. And just the more we speak to each one, the more hopeful I get for our futures that we have choices, and that's a good problem to have.

Andrew Schorr: Right. But they all said, and we've talked to like, what 10 CLL experts across the last week or two, get the vaccine as soon as it's available for you, wear a mask, be careful. Michele is staying really close to home. I go bike riding with Esther. We've got good weather in San Diego, but we don't do it with anybody else. We get our groceries delivered. So, and this going to go on for a while, Michele, right?

Michele Nadeem-Baker: That's right. We built a home gym because, I mean, the gyms here closed again today as an example, in Boston. They were open for a short while, but I still erred on the side of caution. And other than being outside with my husband, we try to sequester from doing things with others.

Andrew Schorr: One other thing I'll mention, I don't know if you guys have thought about it, so the ICU around here has very few beds available, right? And ideally, those would be available for people with a variety of conditions if they needed it, but they are being taken up by COVID patients, which means that we have to really be careful, don't have accidents. Hopefully, we don't have a heart attack. We don't have other things where we need urgent hospital care. So please stay safe, take care of your health, and stay unfortunately close to home. Anything else you want to mention as we end, Michele?

Michele Nadeem-Baker: Well, it's just been a very exciting year. Of course, there have been all of the new circumstances around COVID, but there also have been so many other great things in CLL research that we all have to look forward to the results in the next year and years after. And also, just thank you, Andrew, and I hope you and your family have a very happy holiday season.

Andrew Schorr: Thank you. We wish everybody happy holidays. Thank you so much for being with us, everyone, Michele, I'll let you go. She's lovely and green there. And I'll just say as I always do, I'm Andrew Schorr for me and Michele Nadeem-Baker, California, and Boston, knowledge can be the best medicine of all. Thanks for watching.