Andrew Schorr: Welcome to this CLL *Answers Now* program. I'm Andrew Schorr. I'm joining you from Phoenix, Arizona today. Thank you so much for joining us. We're going to cover a lot of ground today and I'm very excited to do it because it's really such an important issue. You're going to meet three CLL specialists along the way. Joining us in just a few minutes is Dr. Catherine Coombs from my alma mater, University of North Carolina, Chapel Hill. She's a CLL specialist there. And then in New York City, Dr. John Allan. You'll meet them in just a minute.

I just want to describe a couple of things to you. First of all, I want to thank our sponsors, who have no editorial control, AbbVie and Genentech for supporting our series right now. I want to mention just a little bit about myself because I think it is a through line. I've been lucky enough to be living with CLL 24 years and so like many of you, I was in the watch and wait or you may be there now, watch and worry period for four and a half years.

Then I was in the phase two trial for fludarabine (Fludara), cyclophosphamide (Cytoxan) and rituximab (Rituxan) - adding a targeted therapy, rituximab, to chemo. Nobody knew how it was going to turn out, it was ... For those of us who'd never had treatment before. But the option before that was simply Leukeran or chlorambucil, and it wasn't that great. But now, everything has changed. Chemo is really falling by the wayside but we'll hear more what the doctors say, and what are the choices you have.

We're at this crossroads where, do you take pills, non-chemo? Or, do you take some targeted therapy infusion for a brief amount of time and then take pills, again, non-chemo, where you can stop and for how long? So, how do you make those choices? And certainly in this time of insurance woes or worries about insurance, depending on how you're set up, how do you deal with cost and what affects cost? Those are issues as well.

All right. Let's meet our live CLL experts. There is Dr. Catherine Coombs, who joins us from, go Tar Heels, I'm going to say, University of North Carolina where I went to school. Also, Dr. John Allan who joins us from Weill Cornell and New York Presbyterian in New York. I'm in the West, you both are in the East. Dr. Coombs, welcome to Patient Power. You haven't been with us before, so thank you so much for being with us.

Dr. Coombs: You're welcome, and it's great to be able to join today.

Andrew Schorr: Okay, and thank you. And Dr. Allan has been with us before. Dr. Allan, welcome back.

Dr. Allan: Thank you. It's always a pleasure, and looking forward to it.

Andrew Schorr: Dr. Allan, I want to start with you. One of the choices that we have now and we've had for a handful of years is a BTK or Bruton's tyrosine kinase inhibitor, and I believe we have to approved, ibrutinib (Imbruvica) and acalabrutinib (Calquence) or Imbruvica and acalabrutinib and there may be more coming. Do I understand it right that one of the choices is, do you take these pills just ongoing? Is that right?

Dr. Allan: Yeah. BTK inhibitors were the first major drug to impact patients with CLL and were some of the first to get approvals, namely ibrutinib for this specific disease. BTK, or Bruton's tyrosine kinase is a

very important enzyme in the signaling and survival of CLL cells. So we are now able to take a pill, ibrutinib or acalabrutinib and this small molecule inhibitor, which is what this pill is, is able to inhibit this enzyme and therefore shutting off the survival signal for the CLL cells.

And because it was the first on the market, we have really long term follow up of patients taking these pills. They're used continuously, they're really well tolerated and they've shown unprecedented impact on CLL patients, their lives and their outcomes. Were the first hit the market, so they became a mainstay. We have more options nowadays, but yes, there are currently two FDA-approved in CLL indication. There's actually three currently FDA-approved across all disease histologies, but the two specific for CLL are ibrutinib and acalabrutinib.

Andrew Schorr: Okay, Imbruvica or Calquence. Then the third one you mentioned, which you could prescribe as a physician if insurance would pay for would be zanubrutinib (Brukinsa), which has been approved for another blood cancer. Okay, let's go to Dr. Coombs. Doctor, there's another direction somebody could go where they could have a non-chemo approach, some infusion, and then pills with the hope that they could then get to a point where they could stop all therapy. Maybe you could describe what that choice is.

Dr. Coombs: Sure. What you're referring to would be a time limited approach, most typically with the drug venetoclax (Venclexta), which is a BCL-2 inhibitor. BCL-2 is just another protein that's very important in the survival of the CLL cell. It was approved after ibrutinib and originally it was studied as a drug just by itself, but the larger scale studies of venetoclax that have led to its wider use have now combined venetoclax with an anti-CD20 drug. There are two different ways of administering venetoclax in combination with an anti-CD20. These anti-CD20s are IV or infusional therapies.

When we treat patients for CLL for their first treatment, most typically we combine the venetoclax pill with the IV form of an anti-CD20 called obinutuzumab or Gazyva. When we do that, most typically that would be given as a 12-month time limited treatment course. When a patient gets venetoclax in the relapse setting, the most common way to do that would be using the same drug, venetoclax, over a two-year period and combining it with a different type of anti-CD20 drug called rituximab.

Andrew Schorr: Okay. With these infusions, how many ... Let's take for patients who've never had treatment before, how many infusions would they have to have? How frequently? Because nobody likes to be poked, so how long would that go for?

Dr. Coombs: The infusions go typically for a six-month or six-cycle course. With obinutuzumab, the drug is actually usually given on more than one occasion during the first month but after the first month, it's then given every four weeks for cycles two through six. And the cycle is about a month, usually a 28-day period of time. For rituximab, it very similarly is given over a six-month period in six cycles. So, usually it's something that the patients only need to get over the course of about six months. Because these are non-chemotherapies, they don't need to be given by a port. They're safe to be given by a regular IV, provided that the patient is able to get a regular IV placed safely.

Andrew Schorr: Okay. And just to complete that track, time-limited therapy. If somebody let's say had obinutuzumab and venetoclax, taking the pills, and you did it for a year, what experience do we have now in how long somebody must be in remission and not have any treatment at all?

Dr. Coombs: That's a great question. I think the longest follow up ... This is a newer regimen, and so we don't have the length of follow up that we would have for, say ibrutinib for example, where we have now seen patients seven, eight-plus years out. The longest follow up I think is about three years, and so the results at about the three year mark to my recollection show that about 80% of patients are still in remission. That would be one year of therapy, and then two years off therapy, and about only one out of five would then have had their disease relapse. That's a rough estimate, but that is to my recollection. We don't know what happens further out, five years, seven years, and I think further study for that initial set of patients who have gotten this treatment will be really informative to help our future patients know what they're getting into when they start one of these therapies.

Andrew Schorr: All right, Dr. Allan, just one more thing about if people have this time-limited therapy. There's something called MRD testing. I've heard it as minimal residual disease testing or measurable residual disease. Dr. Allan, where does that come in if you and your patients say, "Well, let's go this infusion pill route and see if we can stop." Where does that come in?

Dr. Allan: Yeah. MRD, or minimal residual disease is a measurement of basically how much CLL is left circulating in the blood at the end of a specific treatment. Right now, this is one of the big differences between a BTK inhibitor approach, and/or a venetoclax-based approach for a fixed duration. With the BTK inhibitor approaches, these are pills that we take continuously and we don't typically stop them for patients. So this is one of the big decision trees that patients need to factor in, when they are making a decision about which type of treatment approach to take.

They're very well tolerated. The pros are that we have certainty. We know six, seven, eight years later what the outcomes will be for the patients. Whereas with these fixed duration approaches, as Dr. Coombs was speaking to, we don't have that long follow up to be certain about how to guide patients beyond the three years that we know the data has gone up that far. So, risk aversion. We know certainty, certain disease features, certain features about the patient or characteristics about the patient or disease, help us define whether or not we as physicians might recommend one approach for the other.

But when you talk about this MRD, this is really most relevant for the treatment approach with venetoclax-based therapies, because venetoclax is the one therapy that actually can kill off almost all of these CLL cells to where you cannot find them in the body. We consider MRD as one CLL cancer cell out of 10,000 total cells counted in the blood, and that is the strictest definition that we're using right now. It's somewhat complicated, but that's what it is. We as physicians can use this test to assess if we can find these cells in the blood.

And what we know is that if you can achieve this what's called MRD-negative state, patients are going to do very well. We know that and we can put some certainty in the fact that when we stop, that those patients will continue to do well, the disease won't relapse and the outcomes will be very, very good. That's how we use it. Right now, actually the iwCLL guidelines recommend for physicians not necessarily to use it to make decisions because the data is not really there for us to know if we should change therapies, add on therapies or continue treatment for longer than what's already currently prescribed. Therefore, they've backed off.

Now with that said, physicians that have some inkling and some idea of how they want to use it can test for it, and it can be very prognostically important. It gives us information, it allows us to be making educated guesses and hypotheses for our patients, so there is value to it. There's no doubt that there's value to it. So it can be used, and it's something you can discuss with your physician if you are taking a venetoclax-based approach.

Andrew Schorr: Okay. Folks, keep sending in those questions. We're going to get to them. I'm trying to ask some of the ones that I know you've been asking us at Patient Power for a long time. Dr. Coombs, the BTK inhibitors, I want to talk about that for a minute. All drugs have side effects, and sometimes the side effects show up differently for different people. And all of us, I mean, I'm 70-years-old, some of us may have other conditions. Some of us may have a weak heart, or we may have diabetes, or whatever. So related to the BTK, first of all, are they all like? What side effects do you look for? And, how does that affect what choice you would recommend?

Dr. Coombs: That's a really important question and so I would first answer the easier of the two, which is that I think the drugs are not all like. I think there are important differences between the drugs that are available for CLL. The two FDA-approved agents, of course, as we've mentioned are ibrutinib and acalabrutinib. There is an additional drug, zanubrutinib, that is being studied in CLL but is not yet FDA-approved, and so I won't really focus on that one. But what I'll say about the differences between ibrutinib and acalabrutinib are that ...

I think both drugs work really well. I think they're both highly efficacious. I would say there's likely not a big difference in how well they will be at treating the CLL. I think the big difference will be in what side effects any given patient would see. So when I'm talking to a patient about these options, it's actually very important to me what the patient's other medical conditions are, because that could really help point us more in the direction of one of those drugs compared to the other.

Some of ibrutinib's most common side effects are that it can actually cause high blood pressure and a significant amount of patients. It seems that when we look at patients who get acalabrutinib, that the incidence of high blood pressure may be a little bit less. I'm being deliberately a little bit vague on that because we don't yet have the head to head data where a uniform patient population, half gets one, half gets the other. That's the best way to know, is one of the side effects higher or lower? But, hopefully that'll come out in the next year or two. If a patient already has high blood pressure, being on ibrutinib may in fact, worsen than that, and that may be a patient that I lean a bit more towards acalabrutinib.

One of the other side effects that we know ibrutinib has is that it can cause atrial fibrillation, possibly in around 10% of patients. When we look at acalabrutinib, that incidence may be a bit lower, potentially on the order of around 3% based on what we've seen with the patients that have gotten that drug. Atrial fibrillation is an abnormal heartbeat and so in a patient who has heart disease, that again, may be a reason for me to think more about acalabrutinib.

Acalabrutinib, it's different in other ways. It's a twice-a-day drug. Some patients may say, "Gosh, doc, it's really hard for me to remember to take a pill twice a day." That is very reasonable. Taking a pill twice a day is very hard for people who aren't used to taking medicines, and so ibrutinib has an advantage with

respect to it's only a once-a-day drug. Acalabrutinib also can't be combined with a class of drugs called proton pump inhibitors, which may affect the way that the drug is absorbed into the body and so ibrutinib may be a better option for a patient with very bad gastric reflux that really needs to be on a proton pump inhibitor.

These are all really important considerations that anytime I'm meeting with a patient and talking about the pros and cons of these drugs, that I really try to delve into to decide, which is the best option for this person right in front of me based on their profile and preferences?

Andrew Schorr: That's a great explanation among the BTKs. So, Dr. Allan, if somebody chooses the venetoclax route, what do you need to talk to them about that? Any potential side effects, concerns or not?

Dr. Allan: Yeah, of course. Venetoclax overall, it seems to be potentially a better tolerated agent, though no head-to-head studies have been done. Just based on some of the side effects that we see with BTK inhibitors, they are not present with venetoclax based approach, such as the atrial fibrillation, bleeding, some of these joint aches, so on and so forth. What we do see with venetoclax are cytopenias, so we do see low blood counts, low white blood cell count.

Sometimes you may need an injection of a blood-boosting medicine called Neulasta, or Neupogen or Filgrastim to help rise that white count to keep you out of an infectious period where bacteria can get into the blood. We also see low platelet counts and things usually not so severe that it causes too many problems and we know it's drug related, and we just deal with it. It's okay, it never really causes a problem, you don't need transfusions commonly.

Outside of those, diarrhea is also a common side effect seen with venetoclax. While that is also a side effect seen with BTK inhibitors, it is mild with both drugs. In my experience, the diarrhea with venetoclax seems to always persist, though it's again, very, very mild. It does not really impact patients' lives. And with [inaudible], things like that, you can go about your daily business and life, and not be too affected. Whereas with the BTK inhibitors, that diarrhea honestly typically goes away after about a month or two, just on its own. Your body gets used to it, and it resolves without any further intervention.

The one specific thing that is very special and specific to venetoclax that patients need to be aware of is something called tumor lysis syndrome where, as I was speaking earlier, this drug is so effective at getting rid of these bad cells that they almost do it all at once basically, which is great when we see that, but it can be dangerous sometimes. Especially in patients that have high white blood cell counts, and/or big, bulky lymph nodes or spleen. There is something called tumor lysis syndrome where the tumors lyse and open up, and spill their inside so to speak. These involve certain enzymes and electrolytes that can get out of whack and cause potential danger to the patient.

So, this drug needs to be used very specifically, very cautiously, and your physician needs to be comfortable and able to be able to monitor your blood work. The downside of this is that to get it started, the patient needs to invest some time, some commitment to it because there are frequent visits to your physician. Sometimes you have to hang around the center to get six or eight hour blood draws,

you need to come back the next day for lab work. And while it's all very safe, it's just a little bit time intensive.

And this is for about five weeks as we're starting this drug because we take a baby dose, and each week we ramp it up to a higher dose until at the end of the five weeks of the induction, we get to the full dose, which is 400 milligrams for our CLL patients. That's the one downside, but we're learning how to try to mitigate these and make it easier for patients. And there are clear guidelines on how to manage patients that are in high, intermediate or low risk, and your physician can talk to you about that, whether or not you are in that status and how to manage you specifically and appropriately.

Andrew Schorr: Right. And just to comment, I know my friends who've gone the venetoclax route, you all tell them, "Drink lots of water." You say, "Drink lots of water."

Dr. Allan: Lots of water. Sometimes we give a bag of fluid while you're hanging around the center to infuse the kidneys and make sure we're flushing the blood. We also start you on an extra pill called Allopurinol, which also helps bind up some of these electrolytes that spill out into the blood as the CLL cells disappear and go away.

Andrew Schorr: Okay. Dr. Coombs, people are asking now. The same, "Well okay, if you got these really effective therapies ..." And I was on watch and wait or watch and worry for four and a half years, and many people watching today may be in that situation. Why wait? Why wait?

Dr. Coombs: Very good question, and it's something I talk with my patients about a lot. I think it's really hard for patients because I think what society tells you is that it's better to find a cancer early and treat it early. That is true for a lot of cancers. At least as of 2020, that is not true for CLL. There's a couple of reasons for why early treatment is not beneficial in CLL. One is that it is a disease that can be so slow growing in a proportion of patients, that probably around one in three never need treatment in their lifetime and may just die from something else. Exposing those patients to these drugs that can have some side effects could make them worse off than they would've been had we done nothing.

Second of all is that there have been a number of different studies trying to answer this question, and so far, none of the studies have led to a significant survival advantage. Definitely not with the older drugs that likely were much more toxic, the Leukeran or chlorambucil that you talked about. They are re-addressing this question with these now, newer drugs. There was a study that was done with early ibrutinib therapy. It's not prolonging overall survival, meaning making patients live longer, at least as of now, but they will continue to analyze that data set. That was done through the German CLL group.

There are also other studies looking at this in the context of venetoclax. But as of right now, there's no benefit of treating early. It is counterintuitive to what you hear about cancer, but it is a unique feature of CLL. I think the bottom line is that there are a lot of people that don't need treatment ever and we could hurt people by treating them too early or prematurely.

Andrew Schorr: Thank you for explaining that. Dr. Allan, we get questions, of course, about cost. These are expensive medicines and depending upon your insurance or if you have insurance, this is a big deal for a family where someone is affected by CLL. And if you talk about starting earlier, that starts the meter running earlier, too. I know as physicians, you often don't know what somebody's insurance plan

is, and there are financial counselors often at your medical centers that can help. But, is cost a factor sometimes, Dr. Allan, in deciding with your patient whether they have fixed duration therapy or ongoing therapy?

Dr. Allan: Yeah. Financial toxicity as how we talk about it in the field is always a very real problem. That's not just CLL's problem, that's a problem across all of these oral therapies for cancer because Medicare and Medicaid, the CMS have designated oral therapies differently than they designate IV therapies. Therefore, IV therapies are reimbursed at much higher rates and there's much less out-of-pocket cost to the patient. So because these are oral therapies, there is a little bit more of a burden on the patient and the insurance that they have.

Now, with that said, frequently and fortunately in the United States, Medicare does cover these pretty good rates and private insurance plans typically cover these at very high rates as well. Most commonly, what I have found is that the financial impact is not that huge on our patients in terms of ... To your point, though, I don't ever know how to guide a patient specifically until I say, "We need to run the claim and just see what it is. If the copay is too much, call us back, let us know. We got to figure out how to help you or we then rethink our plan for you going forward." Basically, it's a trial and error many times.

What I do tell our ... Who is most at risk who I've found, are our Medicare patients that don't have very good supplemental insurance and Part D plans. Therefore, they are at risk of that coverage gap or what's called as the doughnut hole, and so many times ... And unfortunately, this is our elderly patient population to where there are reserves to pay for these. Even though that yearly out of cost, cost may only be about $8,000, in a continual therapy over five to 10 years because some patients might be on these drugs for that long, that's a significant amount of money that could go to other family members, retirements and whatever it is. Inheritance, things like that. So, these are problems.

I have had situations where, yes, cost played into my thinking, the patient's thinking on a specific approach where fixed duration was a much more attractive option because there, while the cost is about the same for that first year of treatment, there is the hope and the expectation that after that year, we're going to be off of the drug for a significant period of time, therefore saving these costs in the later years. And for a lot of that reason, it is a very attractive approach using a venetoclax-based therapy. But like I said, there are instances where because of the ramp up, because of the infusion component of this, because of the complicated nature to use this drug, sometimes it is safer and easier to use a BTK inhibitor.

It's not just because of cost that that's it, because many times when you run the claim, I find ... I ask my patients always, "How much was the copay?" And many times they say, "$10," or, "It was free," or, "It's $50," and all of a sudden it's not a big deal, and/or they're getting foundational copay assistance from these specialty pharmacies who are also very good at helping us. Then when there are true financial hardships, the companies have always stepped in, in my experience. Now, it takes a little bit of legwork, but there is always a way to get coverage I have found and get these very phenomenal, exceptional drugs in patients' hands.

Andrew Schorr: Okay, thank you for explaining that. So we're looking at how long you take different therapies, we talked about the side effects, now we've talked about cost. In a minute, folks, we're going

to talk about all of this in the context of COVID. But I want to just look in the rear view mirror for a minute, Dr. Coombs, and that is chemo based therapy. I had FCR. F and C, chemos, adding the R, monoclonal antibody or as you said, a CD20 therapy. Do these combinations ... Some people know about bendamustine (Bendeka or Treanda) and rituximab? Is this all gone in your view, in your practice? What's your thinking?

Dr. Coombs: I wouldn't say it's completely gone. I would say the role has gotten less and less. I still think there are a few rare instances where FCR can be offered. The thing about FCR, it's extremely effective so it works really well to kill the leukemia. There is a small amount of patients who potentially can be in remission for a really long time after they get the FCR, and so that is ... Number one, the patient has to be young and fit enough to receive it because the downside of FCR is that it's so toxic. So one, we have to have a patient that can tolerate it.

But two, we also want a patient who has biologic factors that would suggest their odds of a long-term response are pretty good. That specific profile would be a patient with a mutated immunoglobulin heavy chain, and that's just a specialized test that I send on all my CLL patients. And those patients, over half of them end up still being in remission when we look to see what happens and long term follow up study, so 10 to 15 years later, more than half of patients with that profile can still be in remission.

It actually is something that I discuss with my patients that meet that profile. However, I don't typically have patients take me up on the offer to consider it because I educate them about the potential side effects as well, which can be life-threatening and permanent in some cases. FCR, the downsides of it are that it can induce a second leukemia in a different type of blood cell, in potentially somewhere between two and 8% of patients. The type of blood cancer that it can induce is either a myelodysplastic syndrome, or an acute myeloid leukemia, and those are very serious cancers that often prove to be fatal. When I discuss that possibility, that often scares patients away from that therapy, which I think is very understandable.

The other thing that we know about FCR is that it now has been compared head-to-head to an ibrutinib-containing regimen and the ibrutinib-containing regimen did lead to longer survival. But that was lumping together patients in this really good risk group that may have good responses, and patients who don't have that profile. So I don't think it's completely off the table for a small amount of patients but before signing up for it, I thoroughly educate my patients on what the possible risks are and with those risks, it ends up being something that I have not used in quite some time.

Andrew Schorr: Okay. We're going to move on to a lot of other topics, but just briefly, Dr. Allan, would you agree? Would you say briefly you'd agree with what Dr. Coombs just said?

Dr. Allan: Absolutely agree. You got to educate the patient. There's always a small subset you have to consider it for but with these new options, they're just so attractive and so much less toxic.

Andrew Schorr: Okay. Folks, as we do this program, we're doing it when you turn on the news and we hear about COVID with CLL and we had Dr. Awan on the other day. If you happened to watch him from Dallas, we were talking about the risk to those of us with the nicked B-cell condition. We worry a lot about COVID and the complications of it. There are two aspects to it, Dr. Allan. You've been in New York where now you're at it again, but in the spring, you had a lot of experience with coronavirus.

So, first of all, with any kind of infused therapy, we have come to the clinic. First of all, if we come to New York Presbyterian, do you feel ... And you say, "Well, we're going to do this obinutuzumab, venetoclax combination ..." that our safety is protected? That's the first question. Then I want you to comment about the BTK inhibitors where there was some research about, does it play a role in COVID care? Okay?

Dr. Allan: Yeah, absolutely. To address your first question, I think most centers and physician offices throughout the United States have definitely employed safeguards to keep patients safe. I know patients coming to my center, that they are safe when they are here. We are checking for symptoms, we are screening patients. We unfortunately, do not even let partners or family members into the clinic. We minimize how many people are in the waiting room with them, how many people are interacting with other patients potentially, and so really the patient only is allowed to come for their doctor's visit.

Now, they could be dropped off and things like that but up on our clinic floor and in our practices, it's only the patient. Now, very rare circumstances, obviously cognitively impaired patients or very difficult to understand news, or progression, or treatment decisions, these big ... We can get clarifications for one family member, one key decision maker or caretaker to be involved in that. But outside of that, patients respect it, they understand it and we really minimize that. So I feel safe there. Masks are mandatory. The physicians are all wearing masks, and obviously eye guards and shields, and things. So, everyone in my opinion is pretty well protected. I think coming to the center is relatively safe.

Now, I do live New York to where it's not just coming and once you get here, it's how you get here. Public transportation comes into play and that's a big, big deal. That's where I do have to consider, depending on where we are in the COVID pandemic. When we were in March and April and we were in an exponential phase, everything was shut down. We weren't even messing around with it because the mask mandates weren't out there, people just weren't doing it.

Now, even with that being said, if you're taking public transportation with what we're seeing now as it's increasing and things are shutting down again, it does give me some pause and I think patients need to consider how they're going to get here. If they're taking their own private transport, whatever it is, that may be a little bit of a different story rather than taking the subway or whatever. But, we are now very equipped to do telemedicine, and so on and so forth. So I think coming here, we can still employ how we operated pre all of this.

Now, to your second point, and I'll try to be brief because I know there's other things to get to about BTK inhibitors. There is emerging data that BTK inhibitors can knock down inflammation. One of the reasons why COVID is so deadly is that it causes this overwhelming inflammatory response in the body that floods the lungs, causes organs to dysfunction, causes thrombosis. There's microemboli going throughout the body and patients can get very, very sick, and endure organ damage from that.

BTK inhibitors have proven to decrease this inflammatory cytokine, specifically IL-6, among others, and therefore it can dampen this immune response. Contrary to what we used to believe early on where BTK inhibitors are associated with increased infections, we used to stop them in our patients if they got an

infection, and even early on, even when they had COVID until this emergence started to come out late March, early April. Now we are typically ... If you're on a BTK inhibitor, I am talking about continuing on unless their symptoms continue to worsen over time. Obviously, then we need to rethink what we're doing.

With that said, our treatments for COVID, how we one, mitigate transmission, two, if you do get it, we're much more quick to act with steroids and remdesivir (Veklury). And we do have approved therapies that I do think our outcomes are going to improve than what we were seeing in March in April when one, we didn't know what we're doing. There was a mixed population. Some got steroids, some didn't get steroids, some continued ibrutinib, some didn't continue it. There's this mixed population, and so I do think that we will see better outcomes for our patients.

With that said, our patients are still at very high risk for severe complications, potentially whether you're on treatment or not just from the immunosuppressive component of CLL so you're at risk for these things. But I've also seen many patients of my own on watch and wait, pretty healthy, no infections get it and it was a very mild course. So it's not like just because you have CLL and you can track the illness that you are destined for this very scary poor outcome, and I think we are going to get better at mitigating this for many of these patients. But there is a lot of intrigue and as we are entering this maybe new exponential type phase, it does make me wonder, is a BTK inhibitor potentially better for some of these maybe protective effects? But we have zero data to really tell us that or guide us and right now ...

And I think we hope that COVID is maybe a six-month or a yearlong-thing and then with vaccines, we can put this behind us a little bit. Therefore, should we be so short sighted at starting a patient that may have been a venetoclax-based approach ideal and start them on a BTK inhibitor where it's going to be more complicated to transition them over into the future? I don't know the answer to that, but these are things we struggle with and obviously COVID, there's a lot of uncertainty here. There is hope coming on the way I think, and I think we will finally get back to where we're just making our decisions based on what's best for the patient in front of us.

Andrew Schorr: Thank you for that. We're just going to go a few more minutes. Dr. Coombs, we're getting questions in. We say, "Well, if we've got ..." The BTKs work well and we have venetoclax works well. Let's stick them together. One plus one equals three, and combination therapy is often the name of the game in cancer therapy. I mean, after all there was F, and C, and R. If you look at some other blood cancers, they're even sometimes using four drugs together. So, what about getting a bigger bang combining all this?

Dr. Coombs: I think that is definitely a possibility, but I don't think we know at this time if one plus one will equal three. What we do know about the combination of ibrutinib with venetoclax, it does lead to very high response rates and high degrees of MRD negativity. What we don't know is that, is doing both at the same time better than doing one and then the other once the effect of the first one wears off? I would love to know the answer to that question, but I do think it's going to take some time.

There are a number of clinical trials that are ongoing to look at this combination and see, is the two better than just the one? Or, often they combine both with an anti-CD20 depending on the trial. But, I

think we just don't know the answer if it's better to do both at the same time, than one after the other. I think participating in clinical trials, if that's something that you're open to. They're not a good fit for everyone, but I think that's potentially a great way to be part of the process because we really don't know what's better until we test it, and so there's a lot of trials ongoing. If that's available where you are, I would encourage you to consider it if your doctor thinks it's a good fit for you.

Andrew Schorr: Right. I'm going to put in my plug. As Dr. Coombs was talking about the chemo regimens a little while ago, I said, "That's me." FCR, I was in a phase two trial, previously untreated patient. I got a 17-year remission. I did have side effects, so it wasn't fun. I got a lot of sinus infections afterwards and was at risk of pneumonia, not good. I had to take a lot of pills, antibiotics, and you mentioned Allopurinol. Dr. Allan said to take a whole bunch of that stuff. And, I was in that smaller percentage that did develop a second blood cancer, myelofibrosis, which fortunately I'm doing okay with, but would I have had the 17-year remission without FCR? I think probably not.

But did it maybe set me up in my case for a second cancer? Maybe so. I'm just going to talk about one other area, first with Dr. Allan. People, wherein they said, "Well, what about CAR T-cell investigational therapy where they make a drug out of your T-cells, send it back into you?" For people who may be where these other therapies didn't work or didn't keep working, what about CAR T, Dr. Allan? What's your hope about that?

Dr. Allan: Yeah. CAR T-cells and immunotherapies do have some promise for CLL. They have been coming along nicely for DLBCL, mantle cell lymphoma and have actually achieved FDA approvals in those indications for these CAR T-cells. CLL has lagged a little bit in terms of where they stand in terms of approvals for that. Now, with that said, they can be effective for a small percentage of patients. It seems that the outcomes might be a little bit less than what we've seen in other disease histologies. But, absolutely there are a certain number of patients that have very long term remissions and have had heavily relapsed refractory disease that has responded nicely.

So, I think these therapies are going to come in play. They currently are in clinical trial use only, and specifically in CLL, and obviously they do have some toxicities. But as we start to gain experience and more and more patients have been exposed to BTK inhibitors and venetoclax where our salvage options start to remain limited in terms of new small molecule inhibitors, we need to start to be thinking about immunotherapeutic approaches. Whether that's CAR T-cell, whether that's allogeneic stem cell transplant, whether or not that's still a role that continues to be relegated to later and later lines of therapy because of these good drugs that we have.

But there are patients that now have been exposed to both of these agents and are starting to progress through so we need to be still pushing the envelope. CAR T-cells, bispecific antibodies, NK CAR T-cells. They open a lot of immunotherapeutic approaches for our CLL patients and lymphoma patients in general, and are definitely on the future horizon in terms of next lines of therapy. And then potentially even combining these, and/or using them as options to clean up MRD-positive patients, things like that. So, there's a lot of strategies being tested.

Andrew Schorr: Right. I'll just mention to our audience, look up on the Patient Power site interviews we did with Katy Rezvani, R-E-Z-V-A-N-I, who's one of the heads of cellular therapy at MD Anderson. She's doing CAR-NK research where they take cord blood from newborn babies, cord blood and they're using

it to maybe have a refinement in this immunotherapy approach. Stay tuned, but it's a little bit further out and we'll get into gene editing and all kinds of stuff.

As we're getting close to the end here, Dr. Coombs, many patients have written in and said, "Okay, I keep hearing about COVID vaccines. Two questions for your CLL patients. One is, should a CLL patient be more towards the head of the line after healthcare professionals to get a vaccine? And If they get a vaccine, will their immune response be strong?"

Dr. Coombs: I personally would say that I would like for my patients to be toward the front of the line. Unfortunately, I'm not in charge of this decision tree. But my understanding is that what I've heard, and again, you hear a lot of things. But the priority may be health care workers, and then patients who are more prone to developing complications from these conditions, which is where my CLL patients would fall and so I hope they're near the front of the line. The next question is, would the vaccine work in patients with CLL? What we know, number one is that the COVID vaccine, the ones that I'm aware of that are being developed I believe are non-live vaccines so I think they likely should be safe to give.

But whether they'll be as efficacious in a patient with CLL, I think the answer is that they may not be, but I think any degree of protection is better than no protection. Provided that I'm able to confirm the safety of the drug, or excuse me, of the vaccine for my patients, I would encourage my patients to get it. Because again, even though you may not get the full degree of protection because we know many patients with CLL don't quite have the ability to mount the same degree of an antibody response compared to a person without CLL, I think any protection is better than nothing.

Andrew Schorr: Okay. Well, we've covered a lot of ground so I just want to get a final comment from each of you. So Dr. Allan, at the outset, we talked about the crossroads related to pills, ongoing or some infusion, and then pills, venetoclax-based therapy. Both good choices for many people, and you heard Dr. Sharman at the beginning saying he felt most CLL patients are going to live a long time and live well. Would you echo that? What do you want to leave our audience with when you look at what you have now and maybe what's coming?

Dr. Allan: Yeah, I echo it. You know, I came to treating patients with CLL as these drugs were being approved for frontline therapy. So, I was able to be on the wave of this change and really see how dramatically these have impacted patient lives. And really, I provide a lot of reassurance in my visits with patients that as we're using these drugs frontline and we're removing chemo immunotherapy and the resistance and the damage, and all these things that chemo historically has done, I expect that outcomes will continue to improve and that these relapses will be less aggressive as they relapse off of drug and resistant mechanisms will be ... There's less evolutionary pressure, so on and so forth. As we get to combine these, use these synergies, we're going to see really, really deep responses and I expect many patients to live full life expectancies with this disease.

Andrew Schorr: Amen. And Dr. Coombs, would you echo that?

Dr. Coombs: I would. I became a CLL doctor specifically because I love getting to know my patients and not having to ever say goodbye, so I am lucky to be a CLL doctor. I'm lucky to have patients that live a really long time and we get to develop wonderful relationships, and I'm really just very optimistic for the future. I am at a similar point in my career as Dr. Allan. I've been so impressed with all the new drugs

getting developed. I think the future looks bright and I look forward to long, lovely relationships with my patients and long, long lives for them.

Andrew Schorr: Well, thank you. I want to thank Dr. Catherine Coombs from UNC Chapel Hill for being with us. Thank you for your maiden voyage with Patient Power. We're delighted you could join us today. And Dr. John Allan, thank you for being with us from New York Presbyterian and Weill Cornell. We'll let you go. I know you got busy practices. Thank you so much for your dedication to us.

Dr. Coombs: Thank you and thanks for inviting me. It was a great discussion.

Andrew Schorr: Thank you so much for doing it. I'm really optimistic based on what we heard and I think you have the discussion about the choices with your doctor and you understand them better. Thanks again to Genentech and AbbVie for sponsoring this CLL series. We really appreciate that. Okay, I'm Andrew Schorr. Remember, knowledge is the best medicine of all.