



CLL SOCIETY

Webinar Transcript

A Guide to CLL / SLL Treatment Selection and Sequencing

September 28, 2026

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Hello and welcome to today's webinar

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I am Liza Avruch, Program Director with CLL Society.

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We are dedicated to bringing credible and up-to-date information to the CLL and SLL community because we believe smart patients get smart care.

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As a reminder, you can rewatch all of our educational programs by going to the section of our website called Education on Demand.

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Prior to beginning, we'd like to mention a few pre-event items.

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All attendees in this webinar are muted and the only people on camera are the speakers.

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We ask you to please direct all questions to the Q&A section displayed on your screen.

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Questions will be sent directly to our moderator, speakers, and staff and are not visible to the audience.

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After today's event, you will receive a very brief survey that will help us plan for future events.



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We greatly appreciate your feedback

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This session will be recorded and made available to everyone on our website

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This program was made possible through donor support and grant support from our industry partners.

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At this time, I'd like to welcome our moderator. Thank you.

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Thank you, Liza. I'm Terry Evans, a CLL patient and longtime

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CLL patient advocate. I'm also a member of the CLL Society's Patient Advisory Board and a senior support group advisor for the CLL Society

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I would like to welcome you all to today's event.

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We are joined today by Dr. Jennifer Woyach. Dr. Woyach will provide an overview of the current CLL treatment landscape and the many options available to patients across their care journey.

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Drawing on her extensive expertise and clinical experience, she will discuss commonly used treatments for both first-line and relapse refractory CLL

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Including how treatment approaches have evolved over time

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We will be answering audience questions at the end of this event, so please take advantage of this opportunity to ask your questions in the Q&A box

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Before we begin, I'd like to share a few important disclaimers. The information provided during today's webinar is for educational purposes only and should not be considered medical advice

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For any personal health or treatment questions, please consult with your healthcare team

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Please note that while the CLL Society may have its own opinions and policies, our speakers may offer differing viewpoints, especially regarding the management

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of CLL and its complications

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Now, it's my pleasure to welcome Dr. Jennifer Woyach.

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My name is Jennifer Woyach from the Ohio State University and I'm delighted to be here with you today to discuss treatment of CLL and SLL with selection and sequencing

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So during this talk, I'd like to start by introducing frontline treatment choices in the testing and evaluation that's needed prior to starting treatment. We'll talk a little bit about treatment sequencing

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Spend a little bit of time talking about shared decision-making and clinical trials and end by introducing a few treatments on the horizon. Our goal today is to encourage questions, and so we'll have plenty of time for questions after the presentation.

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So let's start by talking about frontline therapy for CLL

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And first, what information do we need prior to treatment? So we really want to know a little bit about the genetic risk of the CLL prior to therapy. And by this, we include the mutational status of the IGHV



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fish and cytogenetics, as well as mutations that may be present in TP53.

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Your physician will also ask you about other medical problems and medications because that might impact treatment choice, just trying to avoid certain side effects that might be worse with any other medical problems you have, as well as medications that may interact with things that we might prescribe for CLL

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And then we also want to talk about patient goals and preferences of treatment, and this is going to be part of shared decision-making, which we'll spend some time talking about in just a little bit.

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So once we have all that information in place, we start to think about what are the appropriate initial treatment regimens to think about

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And we know that now targeted agents have replaced chemo immunotherapy for the treatment of CLL for almost all patients. There's always a rare instance where somebody might need to have chemotherapy rather than a targeted treatment, but as a general rule, we're sticking to agents

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that target key pathways that are important in the survival of CLL

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And generally, we have paradigms of continuous treatment or fixed duration treatment. Our continuous treatments are Bruton's tyrosine kinase or BTK inhibitors. So these are signaling inhibitors. They block a pathway called the B cell receptor signaling pathway

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They result in very long remissions, but do not completely eliminate residual disease in almost all cases. And because of that, they're given continuously. So we start these treatments with the intention of using them as long as they work, unless somebody has a side effect that would make them come off treatment.

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Our other paradigm is fixed duration regimens. And so these would be combination therapies that all include an inhibitor of a protein called BCL-2. So the BCL-2 inhibitor that we primarily use now is called venetoclax



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These types of drugs block what's known as an anti-apoptotic protein. So apoptosis is a programmed cell death, so something that happens in all normal cells.

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Cancer cells, specifically CLL cells, will produce extra amounts of a protein called BCL-2, which is an anti-Apoptotic protein. So that will keep the cancer cells alive. When we block that, that results in rapid cell death

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And also, when given in combination, will promote very deep remissions where if we look very hard at using CAT scans, potentially bone marrow biopsies, we may not find any evidence of CLL and that allows for treatments that include venetoclax to be fixed duration or time limited

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These BCL-2 inhibitors can be used either with BTK inhibitors or with antibodies that target a protein called CD20, which is on the surface of CLL cells. And so anti-CD20 antibodies are given via IV infusion.

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And those will both directly kill CLL cells, but also engage the immune system to help kill CLL.

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So let's talk a little bit more about mechanism of these drugs. So the BTK inhibitors, and these are drugs like ibrutinib, acalabrutinib, and zanubrutinib, all of these are what are known as covalent BTK inhibitors, which means that they

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bind to the BTK protein using a covalent bond, which you might remember from chemistry Class is irreversible.

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They all bind to the same site on BTK. It's an amino acid called cysteine at position 48.

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And the reason that it's important that all of them bind to that same site is because that means that they will share the same mechanisms of resistance. So, if somebody's CLL is resistant to acalabrutinib, it's unlikely to respond to ibrutinib or zanubrutinib

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And so you may be thinking, why are these drugs different if they all bind to the same site and all inhibit the same protein? And that's because these drugs vary in how selective they are for BTK or whether they might find and inhibit other proteins that are structurally similar to BTK.

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And that actually changes the side effect profile of the drugs more than anything else.

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So venetoclax, I already mentioned to you, will block the anti-apoptotic protein BCL-2. When you block this protein, the cells will die very quickly and are eliminated rapidly. One reason this is important is because

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it causes a risk for something called tumor lysis syndrome, or TLS. And this is where the cells can actually break down so quickly that they release toxins into the bloodstream. So this is something that we always are aware of and try to mitigate risk of when we're using drugs like venetoclax

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So BTK inhibitors, these covalent medicines, ibrutinib, acalabrutinib, and zanubrutinib, are very effective and they're especially effective in frontline CLL medicines are better the earlier in the lines of therapy you give them. So in the front line, they

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tend to work the best.

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Ibrutinib, which was the first drug to inhibit BTK

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has an average remission duration of about 9 years when given as the first treatment. Acalabrutinib and zanubrutinib are known as second-generation BTK inhibitors, so they were designed after ibrutinib, and they were designed to be more selective for the BTK protein

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Which makes them better tolerated. Because these drugs haven't been around as long, we don't know the average remission duration yet, but with acalabrutinib, we have data out to about 6 years, where 62% of people are still alive and free of progression

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With zanubrutinib, we have data out to five years, where 78% of people are alive and free of progression. So all these drugs appear to be fairly similar in terms of how effective they are in the frontline setting, and all are extremely effective.

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Venetoclax is given, in many cases, with the anti-CD20 antibody obinutuzumab, and this is another very established regimen in CLL where we have a lot of data

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These are data from a study called the CLL14 trial, which was led from the German CLL study group, which showed an average remission duration of about six and a half years.

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So that's 1 year of treatment in a little bit over 5 years remission duration for the majority of patients. Importantly, with a fixed duration regimen like venetoclax plus obinutuzumab, it's not just how long their admission lasts that's important, because

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We might see somebody who's white count rises just a little bit, or maybe a CAT scan is done and shows a little bit of elevation in the lymph nodes, but if they have no symptoms and everything is otherwise great, we don't necessarily need to jump into our next treatment

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So there's another metric that's called time to next treatment that's also really important, especially for these fixed duration or time-limited regimens. And so with venetoclax plus obinutuzumab in the frontline setting

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the average time to next treatment is over seven and a half years, so it's about a year for most people between when relapse is detected and when they actually need more treatment.

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So I also mentioned that venetoclax can be given with acalabrutinib, and that's based on a clinical trial that's called Amplify, and I show you the data from that study right here. So the Amplify study

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Evaluated acalabrutinib plus venetoclax or acalabrutinib plus venetoclax plus obinutuzumab, so a three-drug regimen, and compared both of those to chemotherapy

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And it showed that both of those, so acalabrutinib plus venetoclax with or without obinutuzumab, was better than chemotherapy in terms of remission duration.

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The two drug regimen and the three drug regimen are a little bit different where the three drug regimen for people with higher risk CLL seem to be a little bit more effective than the two-drug regimen, but also more toxic. So it's not a regimen that is used all that often in Clinical practice, but certainly can be considered

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With this, these two regimens though, we don't have a lot of follow-up. So you can see kind of on the bottom part of that graph there where it says months from randomization, the average time that we have follow-up for is only three years.

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So if people get a year of treatment, we really only have treatment for an additional two years, it's hard to say how effective these regimens are compared to the venetoclax plus obinutuzumab or BTK inhibitors by themselves, where we have much longer amounts of follow-up in terms of our data to look at.

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So how do we decide this first CLL treatment? So I mentioned these kind of three different types of therapies. We have a continuous BTK inhibitor, we have venetoclax with obinutuzumab, and we have venetoclax with acalabrutinib.

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And so I put some of the pros and cons here. This is by all means not an exhaustive list of pros and cons, but BTK inhibitors given continuously by themselves, they're very easy to start, easy to use, it's all oral.

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It is actually probably our most effective treatment for people who have very high-risk CLL, like those with 17p deletion or TP53 mutation.

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On the other hand, though, continuous treatments can lead to toxicity that can occur at any time during the time period people take the drugs. There's risks of bleeding, there is risks of heart problems with BTK inhibitors that can happen, you know, anytime over that course of 10 years.

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With the fixed duration regimens, these types of regimens limit toxicity, limit costs, limit drug resistance. With the venetoclax plus obinutuzumab, we don't have any of the heart issues or bleeding issues we see with BTK inhibitors.

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But it does involve an IV therapy with the venetoclax plus acalabrutinib. We now have another oral regimen, which can be very helpful for some patients.

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And these are all pros and cons that your doctor will talk to you about when starting these first treatments.

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So what's next after first-line treatment? So, these are going to be some busy slides, and they're not really necessarily something that you need to memorize, but kind of, I wanted to show you what goes through our head when we're thinking about sequencing for any individual patient.

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And to make the point that sequencing starts with the first therapy, because what is chosen for the first therapy, a lot of times will dictate what's going to be possible to use next.

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So we're going to go through a few of these different scenarios, again, not to be exhaustive or have you memorize them, but just to kind of show you how the first-line therapy affects what we do next. So if somebody gets a covalent BTK inhibitors or frontline treatment, and I didn't mention this before, but

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If given acalabrutinib, you could also add obinutuzumab to it, so add that anti-CD20 antibody. You still give the BTK inhibitor continuously.

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So if that's chosen for the first line therapy and the person takes it for a long period of time and then progresses, then you would choose something like a BCL-2 inhibitor or a non-covalent or reversible BTK inhibitor.

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Pirtobrutinib

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If they're taking their treatment and stop because of a side effect and then months or years later, the CLL comes back, you could potentially choose a different covalent BTK inhibitor. So if they had a side effect with acalabrutinib, you could switch to zanubrutinib or vice versa

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Or you could choose to switch to pirtobrutinib in that case, pirtobrutinib is another very selective BTK inhibitor, it's very well tolerated, or you could choose a venetoclax-based regimen at that point

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Then moving on to the next line of therapy if that's needed, if a BCL-2 inhibitor hasn't been chosen yet, you do that. You could then go to a non-covalent BTK inhibitor if that wasn't chosen. And then we have our fourth line treatment, which is kind of the same for everybody here, which would be

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the cellular therapy Liso-cel or CAR-T therapy.

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So let's kind of think about this in a different way. So what if the first treatment was venetoclax given with obinutuzumab?

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So, very rarely people will come off of this due to intolerance and then you might go to a covalent BTK inhibitor at that point. Very rarely you might see people who actually progress while taking this initial treatment. And then again, you'd go to a covalent BTK inhibitor

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Most common scenario here is a complete treatment, have a period of remission, and then have the CLL come back. And so, in this case, like I mentioned, you would observe until an indication for treatment is met.

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Depending on the time, you could consider doing the same thing again. So, if somebody took obinutuzumab for a year and had a 5-year admission duration, they tolerated it well the first time, you might consider doing that again.

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Or you could use a covalent BTK inhibitor in that case. You can kind of flip the orders as needed, then moving on to pirtobrutinib, liso-cel as well.



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And then what about our newest therapies of BTK inhibitor plus venetoclax, so acalabrutinib plus venetoclax with or without obinutuzumab.

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So again,

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If somebody was intolerant to the BCL-2 inhibitor, so couldn't finish the regimen, you might just continue the BTK inhibitor. If someone was intolerant to the BTK inhibitor, you might consider just doing the venetoclax with the obinutuzumab. If they actually progress on that treatment, you'd go to a non-covalent BTK inhibitor.

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If they complete that therapy, then have a period of response, and then the CLL comes back, you again might do the same thing, or you might choose one of the different treatments. And then we get to our next line therapies, which are the same, so pirtobrutinib or liso-cel.

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So that was just, again, not for you to remember, but just to kind of show how we think through these decisions. The other way that we really think about choosing therapy, our patient preferences and goals of treatment. And so this is something that's really important. If there's something that's important for you, it's important to talk about it before therapy starts.

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And so I'm not going to go over every goal that we see, but just a couple that we see most commonly. So some people say, you know, my goal is to not be on therapy as much as possible because I don't take other medicines or I take a lot of other medicines.

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And so being off of CLL therapy is very important to me. This is most applicable for people who have lower or intermediate genetic risk disease where you would think that you're going to do a short-term treatment and then get a long remission duration. But of course, so if that's the goal, you want to start with something that's fixed duration, right? Because it's the only way that you're going to get some time off treatment.

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So in many cases, I would use venetoclax plus obinutuzumab just because we have the longest follow-up there.



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And then, at the time of relapse, you could consider doing that again, or going to venetoclax plus acalabrutinib, so another regimen that will give you time off treatment

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And then you could even consider doing venetoclax plus pirtobrutinib, maybe with rituximab, as we just saw in the CLL-322 study.

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And then maybe if you need another therapy, consider liso-cel at that point. So that would be the CAR-T therapy that hopefully is going to give another long-term remission duration

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You could also start with venetoclax plus acalabrutinib and kind of work your way through these different permutations of venetoclax-containing treatments, too.

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Another goal that we see pretty commonly is decreased visits to clinics. So, you know, this might include people who have decreased mobility, so it's hard to navigate the clinic space. Those who live very far away from the clinic, so it's just very difficult to make that drive back and forth

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or people who have responsibilities at home taking care of children or taking care of older parents or other relatives who really just can't get to the clinic as often. And so with this, you're going to want to choose something that is going to get... that is going to be easier to start, doesn't have a lot of visits associated with it. So, zanubrutinib or acalabrutinib.

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When that stops working at some point, I would consider going to pirtobrutinib. Pirtobrutinib by itself doesn't have such a long remission duration associated with it, but again, it's very easy transition, easy to start, and doesn't require a lot of visits.

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If that stops working at some point, then really your next best option is going to be a venetoclax, and if you really want to limit the visits to Clinic, you could actually give it by itself. It's not as effective when given by itself as it would be in combination with something else

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But can certainly be done. Or, you know, maybe you invest some time with venetoclax plus an antibody, and then hopefully get some time off treatment at that point.

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So let's move on a little bit to discuss shared decision making. So this is something that we talk about a lot and it's talked about a lot in patient forums too. And so I wanted to be sure everybody understood what this meant. So the premise for this is that medicine is best when patients and families are active partners and not just passive recipients of information and decisions.

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So it relies on the beliefs that while your healthcare team is the expert on medical options, evidence, and outcomes, you as the patient are the expert on your own life, your own values, and what matters most to you. And so shared decision-making

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Both of these kinds of expertise together

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So this would be a collaborative process where patients and clinicians and families work together to make decisions that are informed by evidence and formed by your care team's knowledge and experience

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As well as the patient's values, goals, preferences, and circumstances. It's a deliberate departure from the old model, where your doctor might say, this is what we're going to do, and the patient says, okay, I'll figure out how to make that work.

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And so, again.

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It implies that both the patient's lived experience and the clinician's medical knowledge are essential. So, neither one of those alone is enough. So we also don't say that it is the patient's responsibility to make the decision, because they're not the ones who, you know, had a lot of training, who see a lot of CLL patients

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and know objectively what these medicines do.

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And so in addition to the patient, family members, and caregivers are also a very important part of this process.



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So, what is and what isn't shared decision-making? So, it is not giving you a pamphlet on your way out that tells you about a drug. It's not your doctor telling you what to do, and it's not you deciding alone. It is a two-way conversation where you play an active role

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Your provider shares options and trade-offs. So, you know, if you choose this treatment, here is the pros, here's the cons. You sharing what matters most to you. And then with all of those things taken into account, arriving at the best choice for your situation

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So how, as a patient, can you participate most effectively in this? So one thing that's really helpful is if people prepare a little bit for their appointment. So write down questions, concerns, even think about writing down what matters most to you

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So that if, when you get into the situation where you're talking to your provider, your physician, or APP or somebody, in those circumstances, when you start discussing therapy, many patients say, oh gosh.

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I just have all this information and everything I was thinking just flew out of my head. And so writing some of these things down beforehand can be really helpful, so you don't have to rely on your memory during such a stressful time.

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During the appointment, asking questions like, what are my options, what are the trade-offs?

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And then make sure you share your goals, your fears, your daily life priorities, because there's really no way for your care team to know that unless you tell them.

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Bringing a family member or another support person can be super helpful. It'll help you listen, help you remember, or be the one who takes notes during the conversation.

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And it's really important that you understand what is being said to you, and sometimes medical personnel have the habit of, like, switching into medical terminology when they start talking about a drug or a therapy or outcomes and things like that.



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So, it's okay to stop your provider and ask them to use plain language or, you know, check and make sure you understood what they're saying. And it's always okay to say that you need more time to decide. Almost never do these decisions have to be made exactly in that circumstance, and it's okay

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to take your notes, to... and then go home and think about your decision a little bit. Maybe not for months, but, you know, it's okay to think about it for a day or two in most situations.

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So now I want to talk a little bit about clinical trials. So a clinical trial is a carefully designed research study. It tests whether a new treatment is safe and is effective.

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And the big takeaway I want you to have from this is that clinical trials are not a last resort. They're really a genuine care option, especially in CLL where we have these very effective therapies. We use clinical trials to try to optimize these either for specific

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groups of patients, so, you know, groups of patients with a specific genetic abnormality, groups of patients who are a specific age or have a specific other medical problem, or who are taking other specific medications. So it's really a process to try to optimize therapy for CLL, especially in the front and early line settings.

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And then a way to bring new drugs in that may be even more effective than what we're using as standard of care.

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So a clinical trial can do a lot of things. It might test a brand new treatment, it might test a new combination, or it might test, like, a different just way to give drugs. You know, instead of giving all the drugs together at once, maybe we start with one drug

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and add another one later on. So that's something that could be tested in a clinical trial too.

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Another really important point is that every treatment that we use in CLL today, so all these effective treatments that I just mentioned were first proven in clinical trial.



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So why might you seek out a clinical trial? So the big thing is that they can offer access to promising new treatments, new combinations, new therapies entirely, and give you a meaningful role in advancing care, hopefully for yourself, but also for others with CLL in the future.

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It may give you access to targeted therapies that are not yet widely available outside of a clinical trial. You know, one thing that we often forget about when we're discussing clinical trials is they give you close monitoring and expert attention from a specialized team

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Throughout the entire course of your treatment. And one thing that is consistently borne out in data is that people who are on clinical trials do better in part because of this monitoring.

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The steady drug is often covered, so depending on the trial, different things are covered. Sometimes travel is covered. Many times the cost of the drug is covered. Sometimes other things are covered too. So those are things that you can find out for any particular trial.

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AI tells me that there is over 331 active CLL clinical trials that are enrolling patients as of right now. So there's a lot of opportunities for clinical trials.

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And then your participation can help benefit future people with CLL.

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So when we think about clinical trials, we talk a lot about phases of clinical trials, and each of these phases is designed to answer a different question.

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Whether it's, is it safe, or is it better than what we have before? So, the first

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type of trial are phase one clinical trials. These don't tend to include a lot of patients. Many times this is going to be a brand new drug. Sometimes it's not a brand new drug, but just a brand new combination. And it's intended to find safe dosages, identify side effects.



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And... but also identify early signs of effectiveness. So, you know, especially in CLL, like I mentioned, there's so many effective therapies. We generally don't have a lot of phase one trials that we have no idea if they're going to work or not. We go into the phase one

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process with a lot of laboratory data, you know, sometimes even data from other diseases that would really make us think that it's going to work in CLL too.

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Phase 2 is the first type of study that has its primary objective to look at how effective a drug is. So, this may have a few more people in it, and just test whether the treatment actually works for the condition.

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Phase 3 is where we are testing a drug compared to a standard of care, and this is how a new drug gets approved by the FDA, is through... usually through a Phase 3 study where it is being compared to a current standard of care.

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One thing that people often ask about when we talk about Phase 3 or these comparison studies is, am I going to get a placebo? And generally, no. Generally, we don't do a lot of placebo-controlled trials in cancer in general. In CLL, I've honestly never seen a complete placebo-controlled trial. Sometimes you might see like

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If you're testing a combination, like, one drug by itself that we know is effective

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Versus a combination, and you may include a placebo in the arm with the drug by itself so that people don't know if they're getting, they're actually getting one drug or two. That's the only time you really see placebo being used.

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And so phase 3 trials can have a lot of people in them. Sometimes as low as 100, sometimes even up to 1,000.

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Phase 4 trials, we don't hear a lot about. These are actually post-approval or post-marketing studies, which is monitoring for long-term safety and long-term effectiveness of real-world use



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So what happens when you join a Clinical trial? And this is a very prescribed step-by-step process. An important thing to know is you can stop participating in a trial at any point in time

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So the first part is just talking with your doctor and asking whether a specific trial fits your diagnosis, fits your personal goals. Hopefully, it's something that your doctor has mentioned to you, that this trial might be appropriate. Then if you're interested in participating, you would undergo a screening process

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Where the team reviews some of your health records, test results, and probably does a few more tests to confirm that you'd actually be eligible to participate in the study.

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And then usually before the screening, we'll do an informed consent, where you can see everything that's going to happen during the trial itself.

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Then when the challenge starts, then you'll receive a study treatment with regular check-ins, that will continue until the treatment ends, and often far beyond that.

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So what are your rights as a clinical trial participant? Do you have the right to full information, so you should be told about every risk, benefit, and alternative before you agree. And then as the study goes along, if the risk and benefits change

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We always have the right to say no or to stop. And your decision to either join a trial or leave a trial does not affect your other medical care.

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There's also a study coordinator that's assigned to every Clinical trial that is just an invaluable resource to answer questions associated with a trial at any point, so you never are without somebody to contact.

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So if you're thinking about a Clinical trial or just want to get some more information, here's some ideas or questions you might ask your care team. So is there a Clinical trial that fits my stage and type of CLL? And we even do Clinical trials in CLL for people who don't require therapy. So something like that might be an option too.



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What phase is this trial, and what's it designed to learn? What are the possible benefits and risks of this trial for my specific situation? An important one is, is this trial available here, or do I need to go someplace else for it?

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And then what happens to my care if I decide to leave the trial, or if it ends early for some reason? And whether are there costs I should plan for, travel, time off work, childcare, or just costs of the therapy or the monitoring itself

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And so if this hasn't convinced you that a trial might be right, here's some reasons why somebody might seek out a Clinical trial. They're interested in receiving novel treatments that might be the standard in the future. If the available treatments that you've been

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offered don't have the desired outcomes or have side effects that are not desirable. If your current stage or current number of, you know, therapies you've had before doesn't have a standard treatment or doesn't require treatment

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And then if you are interested in participating in a semi that might have benefit for other patients in the future.

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So I want to leave you with just a few targets that are of interest in current Clinical trials and future Clinical trials. We're not going to go through any of these in any detail, but just to show you that there's still such a lot of research that is being done right now in CLL

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And while we have great therapies now, we haven't cured CLL for most people, and so the goal is, by doing these Clinical trials, by bringing these novel therapies

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Hopefully one of these is going to be the cure so that people don't have to continue to have multiple lines of treatment for their CLL. So some of the key targets, we have the B cell receptor signaling pathway, so BTK inhibitors, newer ones that are currently in development

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CLL SOCIETY

There are other parts of this pathway that have a potential to be targeted, like the protein SYK inhibitors, IRAK4, and PKC-beta

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I mentioned CD20 monoclonal antibodies. There are also bispecific antibodies, which will both engage the CLL cell and also grab onto a T cell at the same time as they have two different arms to them. So they grab a normal immune cell and a CLL cell, force them together so that the normal T cell

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helps to kill this cell. These are drugs like mosunetuzumab or cpcoritamab, which are currently in clinical trials or surovatamig, which is also in the Clinical trial, and this is CD19 targeting antibody.

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There's other survival pathways in CLL that can be targeted, like PI3 kinase, AKT, and then other ways that you could target the apoptosis pathway, or the cell death pathway, so other inhibitors of BCL.

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Or inhibitors of family members of BCL-2 like BH3.

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So that's where I'd like to end the formal presentation. I'd like to thank you very much, and I'm very excited now to take any questions that you might have.

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Thank you, Dr. Woyach, for that presentation. And we've had quite a bit of questions, quite a number come in during the presentation, and then we had some that were submitted before. We want to thank everybody for submitting those ahead of time

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Because it gives us a chance to take a look at them and put some answers together for you. And I'll go over just some of the ones that might be easy to answer. Repeating your testing before treatment

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Is that always recommended to repeat all the genetic testing

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Just to see where you're at before you get a retreatment of a drug

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CLL SOCIETY

Yeah, that's a great question. So we don't repeat everything every time. So IGHV mutational status does not change during the course of the disease, so that never has to be repeated. In contrast, though, the cytogenetic

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Some fish abnormalities, complexity, and mutations actually can all change with or without treatment, so it's important to repeat those prior to each treatment to make sure they haven't changed and to see whether any changes in them might guide additional therapy.

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Okay. I noticed in one of the slides there was cardiotoxicities mentioned for BTKs. And would that be a major decision point in determining

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Which line of treatment that a patient would get

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Yeah, so the BTK inhibitors all have some cardiac toxicity associated with them, with ibrutinib having the most and as the BTK inhibitors become more and more selective, that cardiac toxicity decreases. Pirtobrutinib in the Clinical trial seems to

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less cardiac toxicity than any of the other approved BTK inhibitors.

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So, it's definitely something that needs to be considered when thinking about a therapy. There's very few times, though, that a BTK inhibitor is absolutely contraindicated because of any heart problem that somebody has, but it's an important thing to think about ahead of time and maybe work with a cardiologist as well

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To make sure that all medications are optimized and that we have any monitoring in place that needs to be

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Okay, we had several questions about this topic, and that's retreatment of a drug once you have had it, you've maybe been without disease for two to three years. And the question is, can you repeat

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the same treatment again and what would be the criteria for maybe not repeating that particular treatment



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So I think that this is still kind of a new field and we don't have a lot of data on retreatment. We know that retreatment is initially work so people can get a response when they're retreated with the same treatment

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What we just don't have long enough follow-up on yet, though, is to know how long that re-treatment is going to last

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We would expect from just other trials done in CLL and other cancers that likely if you retreat with the same drugs, you're going to get a shorter remission duration than you had the first time. And so because of that.

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you know, taking into account how long the first remission was can help decide whether that is a good strategy or not. So if somebody was treated with venetoclax, obinutuzumab and had a 5 or 6-year remission.

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That makes a lot more sense to retreat than somebody who had a one or two-year remission where you might expect that the drugs will work at first, but probably the benefit is going to be relatively short. You know, the REVENGE study, which is looking at

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Venetoclax plus obinutuzumab after initial venetoclax plus obinutuzumab is going to be a really important study because it is actually designed to do just that, look at

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Treatment, do the exact same treatment, and then see how long those remission durations last, and that'll, I think, be helpful for other

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for other drugs as well

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Okay, now here's a question that I think is being looked at now, and it's limited treatment for a BTK inhibitor

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In what cases might you



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Stop treatment with the BTK inhibitor and give the patient a drug break, and is that even possible

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So I think the important thing to remember is that BTK inhibitors are

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meant to be taken continuously when they're given by themselves. So, really, all of the data we have that is prospective, it's kind of our best forms of data, are giving somebody a BTK inhibitor and continuing either as long as it's effective or if there was some side effect that made people stop early.

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There is accumulating data, more of a retrospective nature, so kind of looking at things that already happened to say, well, what if people do stop treatment and then what happens?

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And I think pretty consistently, it seems like if somebody stops a BTK inhibitor because of a toxicity or just because they don't want to be on a BTK inhibitor anymore, they can usually get a couple years additional remission duration before their CLL comes back or before they need treatment again.

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So

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It would indicate that it's probably okay for somebody who needs a break for a reason, so because of a toxicity, you know, for some other reason

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It's okay to take a break and then come back to the medicine later or an alternative medicine later if the drug was stopped for toxicity

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There's no evidence though that can tell us if you're going to get as long of a remission if you do an intermittent approach like that versus if you just take the drug as long as it works. And for that reason, I think most people don't advocate for treatment holidays just because we really don't know if you're going to get as long of a remission if you do that



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But the data that we have suggests that it's not a terrible thing to do if somebody really couldn't or didn't want to take the drug anymore.

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I don't know, as a follow-up to that, what about reducing a dosage of a drug? And let's say you've been on it for a year, especially a BTK, and you remain relatively stable at that point in time

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Then what... would there be a reason, let's say you had some toxicities and would there could there be a scenario where you would reduce the dosage of that drug and maybe even a BCL-2 as well

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Yeah

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With BTK inhibitors, the data is a little bit mixed. So there have been studies that have looked at, you know, kind of holding the drug for procedures and things like that, or going down on the dose. Some show that there's no difference in long-term outcomes if you do that. Some suggest that

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Maybe dose matters a little bit. But I think, you know, especially for somebody who has some toxicities from a medicine, decreasing the dose to allow them to take the medicine longer and have a better quality of life is better than trying to push through with a higher dose

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And then have them stop early because the side effect eventually becomes intolerable. And same thing with BCL-2 inhibitors. My experience has been that there are some side effects, especially the GI side effects, that really get a lot better if you decrease the dose and don't get a lot better with supportive care. So I think same thing with venetoclax or other inhibitors of BCL-2. If you need to go down on the dose in order to get the whole treatment course in, it's probably better to do that.

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So you just open the door for another question about side effects. Side effects in general

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per class of drug, is there anything you can generalize and say you have more issues with GI issues with this drug over that drug or how would you address side effects from these particular classes?

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You know, the side effects are different with each type of drug. So

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You know, the side effects that you get with BTK inhibitors and the side effects that you get with BCL-2 inhibitors are different, which is good because that means that people can choose a Class of drug based on side effect profile, and that usually works out very well

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You know, the things like

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Bruising, bleeding, cardiac toxicities like atrial fibrillation, hypertension, those are things that we see with BTK inhibitors, really don't see with BCL-2 inhibitors. You can see actually

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GI, like stomach or intestinal toxicities with both, they seem to be more common with BCL-2 inhibitors. And then low blood counts, neutropenia, that's more common with the BCL-2 inhibitors.

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This question was raised about what can you do to prepare yourself for treatment? Are there things that you can do that would

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increase your chances of the treatment being more effective

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You know, that's an important question, but there's not much that people can do ahead of time to try to make a treatment work better for themselves. You know, I think the most important things are kind of knowing what other medicines you're taking, making sure that

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That everybody knows, that your doctors know what other medicines you're taking so that there aren't any interactions that we find out later might be making the drugs less effective or increasing the dose and giving you more side effects.



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You know, making sure that you're in the best shape that you can be in terms of like exercising a little bit if possible, or at least being active, having a good diet, things like that. But there's nothing specific to do.

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Okay.

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This one, I think you're going to have to define this for people too, is leukapheresis ever used prior to treatment to prevent TLS

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So leukapheresis is a procedure where somebody will have two, either two IVs placed or a pretty large IV, and it actually is filtering out the white blood cells

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So you kind of, you hook somebody up to a machine where their blood goes out, it goes through a filter that removes the white blood cells and then comes back to their body

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It's something that is used actually more often in acute leukemias than in CLL. We use it very, very rarely in CLL just because the reason for doing so generally is to prevent

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something called leukocytosis, where so many white blood cells can get stuck in, like, the lungs, small vessels in the heart, small vessels in the brain, and cause side effects from there. CLL cells don't tend to be so sticky, so we don't use it for that situation very often.

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The problem with... so, you know, the idea of using it to try to prevent tumor lysis syndrome is a good one, but the problem is you only remove what's in the bloodstream currently, and even if the white blood cell count is very high, the bulk of the CLL cells are still in the lymph nodes and the spleen and in the bone marrow

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So you could transiently reduce the white blood cell count with leukocytosis, but it's just going to go back up. So I don't think that that alone would be that effective in reducing the risk of tumor lysis syndrome.

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Okay, couple questions on this topic, which is a hot topic today, GLP-1s

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Weight loss drugs. And I guess there's two parts to this question. Number one, if you're on treatment, can you take this drug? And two, has there been any talk about using a GLP-1 with therapy

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To have a better result for patients

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Yep, great questions and something that comes up all the time in Clinic now. To the first question, I don't think that there are any interactions with GLP-1 drugs with any of our CLL therapies. Though of course it's something to make sure that your treatment team knows that you're taking, but I'm not aware of any interactions or

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reasons why one wouldn't want to do those 2 drugs together. There is a lot of interest in studying GLP-1s for CLL as an adjuvant for treatment or as an early intervention. To my knowledge, there's not any published data or presented data on it yet, but I'm sure that that will become

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There was a question about liso-cel therapy and can you just in general explain what liso-cel is and

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maybe where the future of it lies right now.

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Yeah, absolutely. So liso-cel is a medication called a CAR T or chimeric antigen receptor T cell therapy. It's also sometimes called a cellular therapy. So it's a method of

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training your immune system to respond to a cancer and the way that it's done is actually similar to the procedure I just mentioned for leukapheresis

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Your blood cells are taken from your body. The normal healthy T cells, so a type of white blood cell, are filtered out, and the rest of your blood is given back to you. The T cells are then taken to a laboratory

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And treated

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in order to, like, genetically modify them so that they are programmed to respond to B cells in general. And liso-cel and most of the other CAR T cells that have been used in CLL are CD19 directed

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So the T cells are programmed to find CD19, which is a protein that's on the surface of the CLL cells

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And then and then kill those cells that have that protein on the surface.

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The T cells are then expanded first in the laboratory, and then they're given to a person after some chemotherapy to deplete the other T cells so they don't kill the new ones

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And then the CAR T cells then are supposed to continue to expand in the person, so kind of creating this little programmed army that's going to go after and kill CLL

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This is actually been used CAR T in general has been tried in CLL for over a decade and actually CLL was the first cancer that CAR T cells were used for. So there actually are people who are

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10 years out after CAR T cells and are doing fantastic. Liso-cel is the product that is currently has accelerated approval for CLL based on the Transcend CLL004 study

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And it's currently in its like an expansion phase of that study to try to get full approval of the drug

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The challenges so far is, you know, it is a pretty intensive therapy, so, you know, it has to really be a discussion of risks and benefits if you're trying to think about that versus like a pill that might not have a lot of side effects

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It's currently approved for people who have had at least 2 prior therapies, including both the BTK inhibitor and a BCL-2 inhibitor.



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And the response rates to liso-cel by itself are unfortunately not that high, so about half of the people will have a remission.

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But only about 20% of people have a complete response, and the people who have complete responses are the ones that we think are going to potentially get those 10-year remissions. So there's a lot of work being done right now to try to optimize cellular therapies for CLL.

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Both look at like new products, but also whether there are drugs that you could take to help the CAR T cells work better. And with liso-cel, there was a study of liso-cel given with ibrutinib because of some laboratory data to suggest that ibrutinib

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makes CAR T cells in the laboratory work better. And in a cohort of patients treated with liso-cel plus ibrutinib, they actually did very, very well. And so that work is being followed up with other clinical trials and

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Just looking at data to see whether BTK inhibitors or potentially other medicines might make liso-cel or other cellular therapies work better.

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This is a great question, and I know it comes up in support group meetings all the time. Are the treatments that you're recommending the same for SLL as it would be for CLL

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Yeah, so SLL, which is just kind of the tissue predominant form of CLL, is treated exactly the same as CLL right now. Most clinical trials will enroll both CLL and SLL, although occasionally there's a rare one that doesn't allow SLL that only allows CLL.

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But in general, like the FDA doesn't discriminate between CLL and SLL for drug approvals, and everything that I have discussed and recommended for CLL, it also would be the case for SLL.

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Are any of the treatments more prone to neutropenia? And maybe explain what neutropenia is first, and then



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comment on the different therapies.

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Yep, so neutropenia is lowering of the neutrophil count, which is a good white blood cell that helps with response to infections. And so, you know, throughout cancer, drugs that decrease the neutrophil count

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tend to predispose people to getting bacterial and also viral, but mostly bacterial infections

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Venetoclax-based treatments have more neutropenia than

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non-venetoclax-based treatments. And specifically venetoclax with obinutuzumab probably has the most neutropenia of any of the frontline regimens or relapsed regimens that we talk about.

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Though even though the rate of neutropenia is pretty high, the rate of infections is actually really low, so it's something to be really aware of and to watch out for, but actually the infection risk is not that high.

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This question had to do with age and in Clinical trials, would there be a cutoff age or is it just based on the patient's profile and what their comorbidities might be as well?

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Yeah, so it's really uncommon to have an actual like upper age limit for a CLL trial because we know that most patients with CLL are older and the goal always is to have a clinical trial work as well in everybody with CLL as it does for the clinical trial participants

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I think it's more common in CLL to actually have a younger age limit and that's because when we allowed trials for everybody

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you tend to see a skew towards younger people, just in general, because they tend to be the ones who are willing to travel for the trials, or maybe, you know, go to these tertiary centers. So sometimes trials are actually designed to limit



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younger people so that the study is more representative for the older patient population

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Okay.

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There's been a lot of questions about this drug and maybe if you could summarize where we're at with sonrotoclax in clinical trials and when you think it might be approved and for what class of patient might that be approved

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Yeah, so sonrotoclax is a newer BCL-2 inhibitor. So it's a drug of the same class as venetoclax

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It has a little shorter half-life than venetoclax does, and that's important because we think that shortening the half-life of BCL-2 inhibitors might make them better tolerated, both reduce the risk for tumor lysis syndrome but also for some of those other toxicities like the low blood counts.

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So sonrotoclax has been approved for mantle cell lymphoma. It has not yet been approved for CLL and

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I think from my knowledge, I believe that the

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The first study that is expected to read out

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That's a registration trial for sonrotoclax is actually the Celestial study, which is looking at zanubrutinib plus sonrotoclax versus venetoclax plus obinutuzumab in frontline CLL.

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That one has been accrued for a while now, and we're just waiting for the data to be presented once the data is mature enough.

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And so that one is looking to try to get approval for some sonrotoclax in combination with zanubrutinib in the frontline, and there are a number of other studies that are ongoing looking at sonrotoclax, primarily with

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zanubrutinib in relapsed CLL as well.

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So do you think possibly by the end of the year, beginning of next year, it might be approved?

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You know, I actually have no real knowledge on this, but I actually would doubt that.

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Okay, okay.

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Let's see.

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There was a question about Rituxan. And in the old days, Rituxan was combined with drugs, you know, chemotherapy drugs especially, and it seems like Rituxan has kind of gone out of favor

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And using, you know, because obinutuzumab is the next generation monoclonal antibody. And do you see cases where Rituxan might still be used or is the transition almost all to Gazyva

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Yeah, so, you know, as you mentioned

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Obinutuzumab or Gazyva and rituximab are both CD20 monoclonal antibodies

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obinuzumab in combinations has looked like it works better in CLL. So, one of the direct measures we have of that was the CLL, I think 11 study, which looked at chlorambucil, rituximab, and chlorambucil plus obinutuzumab

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And chlorambucil plus obinutuzumab was superior to chlorambucil plus rituximab.



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So that was the chemotherapy approach.

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And then the CLL 13 study, which looked at different venetoclax-based combinations compared to chemotherapy, had 1 arm that was venetoclax rituximab and had an arm that was venetoclax obinutuzumab, and then actually another arm that was ibrutinib, venetoclax, obinutuzumab.

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All of those were directly compared to chemotherapy, so they weren't compared to each other, but venetoclax and obinutuzumab was better than chemotherapy, whereas venetoclax, rituximab was not, so kind of indirectly, we can see there that

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Obinutuzumab is better in combination with venetoclax than rituximab is.

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Obinutuzumab is just a more potent antibody in general, but also the way that it's given, you actually give quite a bit more obinutuzumab too. So I'm not sure exactly why it's better. There's probably a few reasons why it's better.

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But I think those data have made us primarily choose obinutuzumab rather than rituximab in these combination approaches. The times that we still use rituximab, one is actually autoimmune conditions in CLL like ITP or immune thrombocytopenia purpura

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or autoimmune hemolytic anemia, so those are conditions where the body breaks down your own red blood cells or your own platelets, and in those situations, rituximab is the one that has been studied in generally what is used.

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I guess the same line of questioning the use of ibrutinib versus the newer drugs, especially acalabrutinib and zanubrutinib, and maybe even pirtobrutinib. And it seems like most of the studies now, especially in combination studies

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are including acalabrutinib or zanubrutinib in the study, and less so for ibrutinib as well

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So is that kind of the direction do you see it going, that ibrutinib is being used less and less

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I think that's definitely the case, and that's because of the head-to-head trials where acalabrutinib was compared to ibrutinib in the Elevate study. So this was high-risk CLL patients with relapsed CLL.

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And acalabrutinib in that study was not inferior to ibrutinib, so that it was as effective as ibrutinib and much safer. So the rates of atrial fibrillation were lower, the rates of hypertension were lower, the rates of bruising were lower.

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And some of those other kind of just annoying side effects, like the heartburn, muscle aches, all those things were better with acalabrutinib. Then the Alpine study, also in relapse CLL compared zanubrutinib to ibrutinib

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And in that study, this was all comers and not just high-risk patients, but zanubrutinib was superior to ibrutinib in terms of progression-free survival, and same thing, lower rates of atrial fibrillation, lower rates of high blood pressure, lower rates of bruising, lower rates of other side effects.

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And because of that, in the US

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both acalabrutinib and zanubrutinib are used much more commonly than ibrutinib, and they're, you know, recommended more highly in the NCCN guidelines, too. Ibrutinib is actually still used in the US and still used in many places throughout the world, but

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And then, in terms of combinations, the safety profile of acalabrutinib and zanubrutinib do make them easier to combine than ibrutinib does.

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I find it interesting that the liso-cel combination included ibrutinib rather than acalabrutinib or zanubrutinib.

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Yeah, so I think that the reason for that is because actually one of the reasons that we thought that



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The BTK inhibitors might be better or ibrutinib might help CAR T cells work better. All the laboratory for data for that was with ibrutinib, and part of it was because

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An off-target of ibrutinib is ITK, which is important in T cell function. So it was actually thought that ibrutinib was going to be like a great combination partner with CAR-T, which it was. The retrospective studies now

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would suggest that maybe, like, pirtobrutinib, which doesn't have that effect, or, like, these other very selective inhibitors are probably also good. So, I think that's... that definitely is something that needs to be teased out further, but that was the reason.

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Speaking of pirtoburininib, can you just quickly describe the difference between how they bind or work compared to, you know, a non-covalent versus a covalent inhibitor

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Yep.

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So the covalent BTK inhibitors, and remember ibrutinib, acalabrutinib, and zanubrutinib are all covalent BTK inhibitors. So if you remember back from chemistry class, they would form a covalent bond with BTK, and so that's an irreversible type of bond. So

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It cannot break until BTK is like regenerated by the cell.

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It has to... those covalent bonds have to be with a cysteine amino acid, and there's one cysteine amino acid that is kind of well-positioned to bind to these drugs, and so all of the drugs have exactly the same binding site

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And that is why the relapses or resistance mechanisms tend to be shared among the three. So if you have a mutation in that binding site, none of those three drugs is going to work.

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So pirtobrutinib is designed a little bit differently, and it forms a non-covalent or reversible bond. And it's actually not bond, it's Bonsai. So when a drug forms reversible bonds, it tends to form a lot of them. So there's multiple areas where pirtobrutinib interacts with BTK, and

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different than where the covalent inhibitors bind. So pirtobrutinib does not bind at that same amino acid, it binds in other places in a similar area on BTK

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And that was why it was originally designed, actually, is so that it wouldn't use that same amino acid. So if

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the cells had become resistant with a mutation there, pirtobrutinib could still go in and bind

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Pierre Grunheim also, like, it kind of locks BTK in a different, like, inactive confirmation

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And pirtobrutinib, when you have a reversible or non-covalent inhibitor, it has to have a longer half-life

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Because you have to have consistent drug in the bloodstream because those bonds like form and unform and form and unform all the time. So with the covalent inhibitors, their half-life is actually very short because it just needs to bind once and then it will stick there forever

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Whereas with Pirtobrutinib, the half-life is longer because it has to, like, form those bonds over and over.

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So

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Yeah.

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I read something recently about drugs and trials that are both covalent and non-covalent. So could you speak to that a little bit? Because that's a whole different method



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Yeah, so there's a really interesting drug, in my opinion, that's in development. It's called rocbrutinib, and it does exactly what you say. It can both bind covalently and non-covalently.

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So if BTK is wild type, so if it's not mutated, it will bind exactly the same way that ibrutinib, acalabrutinib, and zanubrutinib bind

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However, if BTK is mutated, so in somebody who has taken acalabrutinib, zanubrutinib, or ibrutinib, their CLL cells develop a mutation in BTK. Rocbrutinib can actually also bind non-covalently, similar to the way pirtobrutinib would bind, although different sites

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And so because of that, it seems to work in phase one studies at least, after the covalent inhibitor is and also after pirtobrutinib, because the resistant mechanisms for pirtobrutinib

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will still allow rocbrutinib to bind and work

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So I think that's an exciting mechanism because if you think about it, especially if you're using it, like, in frontline CLL, you're

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Inhibiting BTK, but also preventing the most common mechanism of resistance because it's also working in that case too.

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So let's move to the next Class of BTKs that are in trial, the degraders.

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And maybe explain what a degrader is and how it's different from the, the other BTK drugs.

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Sure.

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So all the drugs that we just talked about inhibiting BTK are what are called kinase inhibitors. So they will bind to BTK to block its signaling function. So BTK stays there, but it's just inactive.

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What a degrader does, it is it actually degrades or eliminates the protein entirely. So the way it does this so that a BTK degrader is a drug that has 2 sides to it. One side is

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like, called the hook, and that is what binds BTK. So it'll have, like, a little part to it that's kind of similar to the binding sites of the other BTK inhibitors

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Then there's this linker that combines the two sides, and then the other side of it binds what's called an E3 ligase

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And in the case of the current BTK degraders, that's a protein called cereblon.

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And

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When BTK is bound, the degrader quickly like pulls BTK to the E3 ligase and

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puts these proteins called ubiquitin on it, which targets it for being degraded like any other protein in a cell would get degraded by a part of the cell called the proteasome. So that's, like, the same mechanism by which

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Cells will get rid of proteins that they're not using anymore. They add a bunch of ubiquitin, and then they will, the cell just degrades it

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And so it takes advantage of kind of this machinery that's already ongoing in the cell

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And one of the advantages to something like this is it doesn't really... there's not a lot of mutations that would not allow this, like, such a transient bond to occur.

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So even like the mutations that make people CLL resistant to the covalent and the noncovalent inhibitors, the degraders will still work in that case, because you just need this very weak, very transient bond, and all of a sudden the protein's gone.

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So do you think that there's any possibility these would be used in frontline treatment?

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Yep, so they're certainly going to be investigated in the frontline, and I... in my opinion, if you're thinking about using it as, like, a part of a combination, so something that's going to be a fixed duration strategy, where maybe

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Your treatment course is a year or so. Yeah, sure, that sounds fine. I'm not quite sure what's... why that's better than a kinase inhibitor, but it's still a fine way to do it.

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I do worry about the idea of using it as a continuous therapy in the frontline setting because in the studies that have looked at resistance to the degraders, and there's not many of those so far

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Just because luckily they're working very well and there haven't been a lot of people treated with them. One of the mutations that can happen that makes CLL resistant to the degraders, it's called A428

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It actually will make the CLL cells resistant to all the other kinase inhibitors too, so you probably can't become resistant to a BTK degrader and then go on to like acalabrutinib afterward, and so that's

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going to be important, like, to think about, you know, how sequencing is going to work when moving those drugs up. Now, I said I thought a fixed duration would be fine, and that's because in every study that has looked at fixed durations of, like, a BTK inhibitor with a BCL-2 inhibitor

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When the CLL comes back at some point, we never see those resistant mutations, suggesting that you can use those drugs over and over again, like we talked about. So that is probably a strategy that would work just fine.

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Maybe going back to pirtobrutinib as a first-line treatment. I mean, right now it's being used if you've developed a mutation to either ibrutinib or acalabrutinib or zanubrutinib, and then you might follow that up with pirtobrutinib. But if you use

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BCL2 a first line could you use ibrutinib

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you know, acalabrutinib and zanubrutinib as a second-line treatment

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So that is definitely an unanswered question. And there's a number of mechanisms by which the CLL cells can become resistant to pirtobrutinib that's been shown in the studies in relapse CLL

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And

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It's probably the case that like some BTK inhibitors would work after some of those mutations, but not all of them. So I don't think it's a guarantee that you could go from pirtobrutinib

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to a covalent BTK inhibitor

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That being said, so pirtobrutinib is also being investigated in the frontline setting, and there have been two trials so far that have been published looking at that type of approach

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And the

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The follow-up is very short, so it's only like a couple years of follow-up, but so far pirtobrutinib is looking really great in the frontline setting, and as you know, like the side effect profile is really good with it, so I think we have to see how long those remission durations last in the frontline setting

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Before, before deciding, like, should everybody get this approach? Like, are there certain people that this would work best for? Because



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I think that it's very appealing to think about this as a treatment for somebody who might be in their upper 80s or 90s where they may only get 1 or 2 lines of therapy, and we know that venetoclax does work after pirtobrutinib

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You know, especially if the remission durations are long, it would be a very appealing frontline treatment for people who are older or who have other medical problems or who have side effects or other medical problems where you're concerned about side effects with the covalent BTK inhibitors

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I don't think we have all the data yet that we need to make that decision yet

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Talking about Clinical trials, the question was asked, where do people find out about

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Clinical trials and obviously their medical team

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Couldn't be able to direct them to them, but also Clinicaltrials.gov is a site, and could you just basically maybe explain a little bit what people might search for on Clinicaltrials.gov to find a treatment that they might look at

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Yeah

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Yeah, so on Clinicaltrials.gov, you can filter if you're interested in a particular drug, that's the easiest because you can just type in the name of the drug and the CLL and it'll give you all the studies. Otherwise, I believe that there's a filter where you can say

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You know, frontline treatment or relapsed refractory treatment, and there's also a filter for where you can look to adjust trials that are currently enrolling patients. You don't have to filter through all the ones that are already finished but are still up there

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It can be quite daunting though to look through Clinicaltrials.gov like that. And so yeah, so talking to your treatment team is great, you know, seeking out a second opinion at an



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academic center if you're not at an academic center to talk through like some of the options for trials is a great idea.

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CLL Society, other patient-facing organizations often will have like either navigators or listings of trials that could be helpful too.

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Okay, let's see.

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There was a question about triplet therapy, acalabrutinib, venetoclax, and obinutuzumab, and

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Traditionally, is that a fixed duration treatment and in what case might it not be a fixed duration treatment, and what drugs might you continue, let's say if you don't reach UMRD?

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So in the Amplify study, which was the phase three trial of that triplet, it was fixed duration. So it was a one year treatment with the three. What's in the NCCN guidelines, though, is

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Also, the option to do an MRD-guided, and that's, kind of reserved for people with 17P-deleted CLL or TP53 mutated CLL. I mean, I guess could be considered for other people, but in that case

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I think

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So the obinutuzumab is always only 6 months, and then you could continue, you could continue both the acalabrutinib or the venetoclax or otherwise just continue the acalabrutinib

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If it's not, if it's not MRD undetectable

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Okay.



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Let's see

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Let's see, does sequencing refer to fish and other genetic testing? And

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Where might you learn about what those mean? And I know the CLL Society has

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a number of pages directly related to that topic, but I guess the question is, should those tests always be done at initial consult with your hematologist

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So according to, I think both the NCCN and the iwCLL, you just need to do those prior to treatment

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So they don't have to be done initially. In my practice and our practice at Ohio State, and I think many people are doing this also, we generally do all these tests initially because I think it's helpful to think about

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And for patients to expect, like, is it going to be years before I need treatment, is it more likely to be months, and to start thinking about that rather than feeling like they're surprised the whole time

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So I think that it really just helps with, like, discussions about what to expect if you know those information up front. Sequencing specifically refers to next-generation sequencing, which is a way of looking at DNA for specific mutations

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And there are different panels that can be used. So many centers will have like their own panel that they do or they send it out to a company, in which cases the panels could be different. The gene that is really important to know is TP53 because that is both important in prognosis in terms of time to treatment

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But also might help decide between, like, a continuous treatment and a fixed duration, or BTK inhibitor or not

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But many panels will also include a lot of other CLL associated mutations like Notch1, PLCG2 and things like BTK, BCL-Gamma2.

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might be helpful for prognostication, like, again, like, you know, is it going to be a short time before I need treatment or a long time, but don't have as much data that is, like, helps with deciding on a treatment

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If the gamma mutation significant

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and moving between BTK inhibitors. I know C481S is, you know, directly called out with pirtobrutinib. It doesn't matter if you have that, but what about the gamma mutation

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Yeah, so PLC gamma-2 is the protein that's kind of immediately downstream in the signaling pathway from BTK. So BTK activates PLC gamma-2, which activates, like, the things downstream from there

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And there are a number of mutations that can occur in PLC gamma 2 in people who are taking BTK inhibitors where the BTK inhibitor will still work. So BTK is still inactivated, but a mutation in PLC gamma-2 turns the signaling pathway back on. So it's a way that

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CLL cells can become resistant to at least the covalent inhibitors

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With pirtobrutinib, it's actually just a little bit less clear because the data hasn't really been shown, like, what specific PLC gamma 2 mutations have been seen in the people that are on those trials. There was some

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suggestion that remission durations are a little bit shorter in people with PLC gamma 2 mutations, although I don't think you would think that that

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could be and should be the case, but it's a little bit less clear. With degraders, actually, it looks like people who have PLC gamma 2 mutations can still respond just fine. We're actually looking at that in the laboratory, and I'm sure other people are as well at

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why that's the case.

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Okay.

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This is an interesting question. Clinical trials, when you're, let's say it's a phase 3 and you're comparing 2 different standard, I mean, standard approved therapies versus the new therapy, and

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The question was, will you be told which cohort you're in at the end

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Sometimes you can guess because they add obinutuzumab but not to the other one. And also, let's say that there was a distinct difference between the two

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arms, and the new drug shows a superior response rate

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What are the... what's the availability of the new drug compared to the one you were taking on the trial? And are there crossovers built into trials to allow for patients to move to that new drug?

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So it is actually very rare in CLL to have

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a study that is blinded where you wouldn't know what drugs you're getting. So in most of the randomized trials that are going on, you might not get to choose your treatment arm, but then as soon as the randomization happens, you know which drugs you're going to get. So before you start treatment, you know the medicines you're getting

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There are occasionally

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There are occasionally studies with placebo and actually really not many recently. What I can think of a long time ago was

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And the study that got idelalisib, a PI3 kinase inhibitor, proved it was idelalisib plus rituximab versus rituximab, and that was in the time when rituximab was a pretty fine standard of care. So in that study, you know, everybody got a tablet

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And not everybody's tablet was ideal listen. And so that's how you would run a placebo controlled study. Almost never you're going to get nothing in one arm. And in that case, in those types of trials

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You do find out at some point, and it's just, you know.

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part of the study

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your study is different in terms of, like, when they would tell you, like, if it is when you come off treatment, when the study's over, that's something you would just want to ask up front because it would be different. And whether there's crossover, so crossover can happen in any study, whether or not there's a placebo involved

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So many phase 3 studies where there's a standard of care and then a newer one, there is a crossover design. So if somebody's on a standard arm and it doesn't work or stops working, they could cross over to the other arm. So again, that's study specific, so if you're learning about a study, those are questions you want to ask. Is there a placebo? If so

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When would I find out what drugs I'm getting and is there a crossover? Like, those are all questions that your study team should be able to answer right away

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I guess all the drugs we're talking about, you know, affect the blood in the bloodstream, but what about going deeper into the bone marrow and actually trying to stop

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The mutation as it's happening and what's the direction of that

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Yeah, so that's a great question, and kind of where we want to be is really just eliminating all the CLLs so that there's no



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cells left that can develop mutations and become resistant. Our drugs that we use have variable effectiveness in the bone marrow

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Or, you know.

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We talk about the bone marrow, but really it's like microenvironment niches, so places where CLLs are protected, and that can be in the lymph nodes, that could be in the spleen, that could be in the marrow, and

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And so, you know, that's something that's always investigated with a new drug is like, how well does it clear those different compartments where the disease can be, and drugs that clear them better are ones that can be given in fixed durations, and you can stop treatment

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There's another looking down the road. Do you think that

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Pirtobrutinib might be approved in combination with venetoclax in the future

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So there was a Phase 3 study that was presented and published this summer looking at pirtobrutinib plus venetoclax plus rituximab compared to venetoclax plus rituximab in relapsed CLL

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That was a registration study. I don't know the timing of it, but it was a positive study, so the triplet was better than the doublet in terms of progression-free survival, so we would expect that that combination would get approved at some point. When it is, I don't know

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When that would be.

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Okay, I think we're close to running out of time, unfortunately, and

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I hope we answered most of the questions that you all submitted. We tried to. If you have not gotten your question answered, you can submit it to Ask the Expert@CLLsociety website

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And so,

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I just want to thank Dr. Woyach again for taking the time to be with us and just asking her if she has any closing thoughts.

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Thank you. It was really my pleasure to be here today and ask these wonderful, insightful, and really important questions that I think everybody wants to know the answers for. I think in the closing thoughts I would have is I think we are in a really exciting time in CLL research and Clinical care where there's so many new therapies

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coming forward. And we spend a lot of time talking about sequencing and, you know, what is better than what, and which line of therapy. And I think what I would leave you with is there is not a lot of bad choices here, so we spend a lot of time thinking about pros and cons, but really we're choosing among

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lots of great options, not among bad options, which I think is a really exciting place to be in. And looking forward to the future, I'm really excited to see more of these fixed duration combinations that hopefully will be curing some people with CLL

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And I really expect that in a few years, we're talking more and more about how we're going to get to a cure for CLL rather than how we're going to sequence multiple therapies.

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Well, thank you again for participating today. And I know that

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Without our sponsors, Lillian B1, that this program would not be possible, so I want to thank them for

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the generous donations that they give us to put programs like this on, because I think, you know, an educated patient is a patient that can



CLL SOCIETY

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Help and the decision-making process for treating your CLL so it's extremely important for patients to be educated going in when they talk to their medical team

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We want to thank you. I want to remind you that for those that registered, there will be a post-event survey

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for your feedback, because that's important to us, how we can make these better. And you can also send your unanswered questions to... there's the link, it's called TrustedCare@cllsociety.org.

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And our next virtual meeting will be Understanding Immunity and CLL and that will be on October 8th

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And the CLL Society is invested in your long life. Please invest in the long life of the CLL Society by supporting our work.

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And thank you very much for being with us today.