Virtual Event Transcript
Ask Me Anything: Featuring Dr. Ryan Jacobs and Doreen Zetterlund
March 6, 2026

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This text is based on a computer-generated transcript and has been compiled and edited. However, it will not accurately capture everything that was said on the webinar. The time stamp is approximately 10 minutes off due to editing. The complete recording of this webinar is available on-demand.

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Welcome, everyone. I'm Doreen Zetterlund, CLL, SLL Patient Advocate and member of the CLL Society's Patient Advisory Board. We are live with the CLL Society event Ask Me Anything, where we will spend the next 60 minutes…

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answering your questions with the CLL healthcare expert. We're so lucky to have Dr. Ryan Jacobs joining us today.

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There are no presentations and we encourage you to ask your questions through the Zoom platform Q&A.

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This event is dedicated to your questions, so ask them early and hopefully we can get to them all. Before we begin, I have a few important disclaimers to share. Nothing said today should be taken as medical advice. Any questions about your health and treatment should be discussed with your healthcare provider.

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Without further ado, Dr. Ryan Jacobs, would you please introduce yourself to our audience?

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Yeah, thank you, Doreen. As mentioned, my name is Ryan Jacobs. I direct the Lymphoma Division at the Levine Cancer Institute in Charlotte, which is a part of…

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Wake Forest School of Medicine. Uh, and I've had a particular research focus in CLL since I've started here a little over 10 years ago, and probably a little over half of my patients are CLL. I run all the…

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CLL clinical trials here and I've enjoyed my work with the CLL Society over the years since I've been here after coming from M.D. Anderson.

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Thank you. That's great. We love your dedication and focus on, on our cause. So, let's start with the first question.

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What does a CLL diagnosis mean for life expectancy?

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This is a great one to start off with because what the most recent data tells us, and this has just been published, is that when you look at…

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patients diagnosed and receiving their first line of treatment in this novel era, so this is going to be what the authors of that study classified as the, um,..

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the time period since they sort of marked it when the drug ibrutinib was approved, the Bruton tyrosine kinase inhibitor. That was all the way back in 2014...

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and they followed patients diagnosed in and around that time and having received their first treatment as a novel treatment, you know, as we've sort of…

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moved away from chemotherapy as our trials have shown us, these newer targeted treatments do better than chemotherapy. And these patients that they followed,..

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um, that have received their first line of treatment and beyond in this novel treatment era with these novel treatments, their life expectancy seems to be mirroring what we refer to as the background patient population, you know, the patient population that…

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doesn't specifically have a CLL diagnosis. So, I feel pretty comfortable in 2026 telling my patients newly diagnosed with CLL that really there's no reason to think that this should affect your…

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life expectancy based on the data that we have and the continued progress that we keep making. As I'm sure we'll talk about, I mean, just in the last, you know, we had a new FDA approval two weeks ago, another one before that, at the end of 2025, so it just keeps improving.

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Yeah.

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That's wonderful news. I'm sure everybody's really, really glad to hear that, but I will always remember when ibrutinib was approved, because I happened to be in the oncologist's office. I was in watch and wait. Someone came running down the hall saying, ibrutinib is approved, ibrutinib is approved, so I'll never forget that date.

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All right, we'll go on to the next question. For a generally healthy 60-year-old patient with CLL who is IGHV unmutated and approaching the need for first treatment, how should one think about choosing among the available frontline therapy options?

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Yeah, and this is, you guys probably chose this one to lead to the most discussion. There's, there's probably the most healthy debate, I would say, around this type of patient.

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And, um, and we might get into some of the other scenarios. This patient would fall into what we would call an intermediate prognostic subgroup because of that IGHV unmutated…

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status. So, uh, without going too deep into it, you know, the favorable prognostic subgroup, I mean, it pretty much, I feel like most everyone in every circumstance has its,..

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every patient has its unique circumstances, but in general, most any specialist is going to tell you favorable prognosis really needs to be on time-defined treatment, it’s as a first-line therapy. Indefinite treatment…

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it's not necessary, uh, it's going to work forever, but that's part of the problem, because you're going to be on the drug for forever.

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On the other end of the spectrum, the poor prognostic subgroup patients, um, most characteristically defined by chromosome 17 aberrations,..

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uh, most specialists would advocate that if the interest is to have the longest…

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time free of any progression, that those patients should be on an indefinite treatment with a BTK inhibitor.

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And, uh, in particular, the drug zanubrutinib has a lot of really good data in that particular subgroup, but then you've got this intermediate group that's IGHV unmutated, and there's no right or wrong decision, really, for all of these. I mean, they, there's what specialists would advocate for, but you're choosing between, as I've alluded to in discussing these other two patient groups, time-defined therapy versus treat to progression.

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Historically, time-defined therapy, when you were talking about novel treatments, was only venetoclax for one year, plus an anti-CD20 monoclonal antibody called obinutuzumab.

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So, time-defined therapy historically was a pill plus an IV therapy, and I think what held up a lot of people from pursuing it, whether it was oncologist or the patient or both,..

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is it was a lot of visits, a lot of labs in the first eight weeks, a lot of time in the infusion center, but what I would tell my patients is just hang in there because you get past the two months and the outcomes are excellent, particularly in this favorable subgroup.

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And of course, the treat to progression approach is the single agent BTK inhibitor I mentioned, zanubrutinib, the other newer agent is acalabrutinib. Historically, it was ibrutinib but for new treatment starts these days, we use either acalabrutinib or zanubrutinib...

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um, for, for single agent BTK inhibitor because, um, those agents were shown to be less toxic than ibrutinib.

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So then, you've got this intermediate risk category, um, we know with time-defined treatments, the time that is free of the disease progressing is shorter with unmutated versus mutated, but with indefinite treatments, it doesn't seem to matter. So, whether you're mutated or unmutated, the time…

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free of progression is about the same, it looks like. So, you could really, the difference isn't as large as the chromosome 17 aberration, so you really should feel comfortable with both choices here.

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The big update, though, is, um, two weeks ago, exactly, we have our now first FDA-approved,..
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all oral time-defined treatment options. So, um, I think hopefully more patients will get offered time-defined -therapy, and maybe more patients will be willing to accept it because it's just two pills now. It's acalabrutinib...

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and venetoclax for a year, you lead in with the acalabrutinib for a couple months, and then you take them both together.

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We now really have, kind of, three different options in the frontline setting, two of them time-defined, and then, um, one with IV, one all oral, and then we've got our treat to progression BTK inhibitors with either…

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acalabrutinib or zanubrutinib so long answer, but I tried to kind of paint the picture for the group as a whole to highlight why there's a bit more of a debate with the unmutated…

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group.

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Yeah, that was very comprehensive, and this is probably follows right in with that. How is trisomy 12 and NOTCH1 mutated versus unmutated responding to current targeted therapies, both as individual agents and combination? And sort of what you, if I'm,..

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I was quoting you, were referring correctly, is that everyone is responding well to these new treatments, sort of regardless of markers.

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Yeah. Yeah, so across the board, all of the groups do better with targeted agents than with chemo. Okay, so that's for a little while there we thought, oh, maybe we should still use chemo with the favorable group because they do well with everything, but they do even better with the targeted agents.

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So, no chemo, but in terms of, and the reason why I bring up chemo is trisomy 12 was one of these prognostic markers that historically meant something…

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negative in terms of, uh, how patients should expect to respond to chemotherapy, but it doesn't seem to matter with our novel treatments. Trisomy 12 is no longer necessarily recognized as a…

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uh, prognostic marker that's going to predict a poor response to our novel treatments. Now, some of these things might mean something if you're on active surveillance and have never been treated. You know if you have a trisomy 12,..

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you're probably more likely to progress and need treatment eventually versus somebody with a deletion 13q as a sole abnormality, for example, but for treatment, trisomy 12 is not impacting our decision, and we don't think it's going to…

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have a dramatic impact. You know, NOTCH1 is part of this, um, panel of different markers that, um, that they're checking with next-gen sequencing, it's sort of now maybe working its way into the, like, the NCCN recommendations to check it, which that stands for National Comprehensive Cancer Network Guidelines.

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Um, and it's what we use in the United States as a way for insurance uses it a lot to see what they're going to approve and pay for, and it’s recommendations put together by experts in the area based on evidence.

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Um, that, that next gen panel that includes NOTCH1, among other things, hasn't made its way to the IWCLL official recommendations yet, so it's not, it's not a widespread practice at this point, I would say. And so along with that, we don't have a ton of data to tell us,..

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um, oh, with a NOTCH1 patient, you should do this versus that, and so there's really no specific recommendations at this point with NOTCH1. You might read some information that, oh, these patients have a little bit of a higher risk for…

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Richter's transformation, but again, there's not a specific treatment…

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that's, that's being championed for specifically for NOTCH1 patients.

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Okay, great. Thank you. Next question. What does the current research reveal regarding watch and wait? Specifically, what does it reveal about more frequent treatment sessions even before B symptoms show up? Is the massaging of swollen lymph nodes helpful, harmful, or neither?

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All right, a few questions in there. So, I could spend more than an hour talking about all of the great, you know, breakthroughs that we've had in treating CLL and new approvals and what that means for CLL patients.

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But it would take me, you know, about 30 seconds to give you an update on what's changed in the world of active surveillance, because nothing has changed since I've been an oncologist. The same...

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criteria for treatment have have remained even with all our advances, and it's not for lack of trying. Some in the audience might be aware they did look at taking high risk…

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patients on active surveillance and randomizing them to getting ibrutinib or a placebo and they followed them for a very long time and there was no improvement…

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in long-term, but the long-term outcome I'm referring to is overall survival, so it didn't make patients live longer to start the ibrutinib earlier, and that's really the only reason why you would change the rules of active surveillance is if doing so would make a patient live longer,..

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um, and, and so the answer is no on ibrutinib. There is another study that's open at some institutions that's looking at a similar kind of high-risk patient population based on prognostic workup…

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and giving them obinutuzumab and venetoclax for one year and stopping versus observation, it'll take a long time for that study to read out. I haven't gotten any updates about it at this point, but…

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it'll be interesting to see the results of that, um, and we'll see if that changes anything. But at this time, no changes in the active surveillance recommendations, and we still acknowledge that of the patients that get diagnosed and don't need treatment, about 1/3 are going to never…

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need treatment, so that would be, you know, a shame to treat people that, that may never have needed it in the first place.

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I remember a question about massage worked in there. I have not seen anything to the negative side of…

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of you know data or reports or anything about therapeutic massage, so I would say enjoy yourself, yeah.

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That's good. Are there treatments that work to cure CLL from reputable institutions outside of the USA?

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To cure CLL, so, no, I would say, um, cure is a tough word to use with CLL. We don't necessarily think, you know, in the United States with all the treatments that we have that we're curing CLL when you use the word cure.

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In a traditional sense, meaning, uh, I think when the layperson uses the word cure…

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they are probably thinking of a treatment, maybe akin to, like, an experience with breast cancer or prostate cancer, where there is an intervention done over a finite period of time…

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whether it's surgery or radiation, or chemo, or all of the above, and then the patients have no detectable disease at the end of that treatment and never have their disease come back.

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And there are situations where we get to do that with CLL.

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But we call it, I try to frame that, um, that word a little differently, and, and I talk about the concept of functional cure, and whether that means you start a BTK inhibitor and you're on it,..

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uh, until, within the disease never comes back, and then you live out your normal life expectancy. We were talking about living normal life expectancies. That means you, you know, your end of time, you know, here…

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comes from another issue that wasn't really attributed to your CLL at all. And so, yeah, that patient was still on treatment, but their disease never came back and they lived a pretty normal life. So, I would refer to that as a functional cure. I would refer to somebody that got time to find treatment and was off therapy,..

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you know, and ultimately passed away from another issue as functionally cured. So, I think, um, you know, I don't know country by country what is available. I will say Europe…

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has often had things available that we haven't had, you know, um, for example, ibrutinib plus venetoclax as an all-oral time-defined treatment was available in Europe and Canada and Brazil and other countries,..

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uh, for many years, we're just now getting that option with acalabrutinib venetoclax because the FDA chose not to approve that treatment. So,..

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I think, you know, a lot of these things are available...

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similarly in Europe, but beyond that, I'm not quite sure, you know, what's, what's available…

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outside the US.

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Okay, I'm interested in how doctors use MRD, minimal residual disease measurements, after initiating treatment, particularly time limited treatment.

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Yeah. So, there is no real reason to use MRD for the indefinite treatment…

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approaches with single agent BTK. Um, those agents often don't even produce complete remissions. It's actually uncommon for…

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somebody to get in a complete remission on a drug like acalabrutinib or zanubrutinib as a single agent.

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Those agents, put the CLL to sleep, that's how I explain it to my patients, and it's sort of like…

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you're in a, you're in a room and flip the light switch off. That sort of puts the cancer to sleep and taking the BTK inhibitor every day keeps tape over the light switch so you can't…

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flip it back on. Uh, there's still some detectable CLL there that you can see pretty easy if you do a scan, a lot of these patients will still have a little bit of mildly enlarged lymph nodes. So, you don't need to use MRD to go looking for a deep remission there, but for the treat, for the time-limited therapies...

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what the data has shown us is when you look at…

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one specific treatment, um, like patients getting venetoclax and obinutuzumab,..

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and you compare the patients that get to be undetectable for MRD, and at this point, the official marker is for what is deemed undetectable is below one in 10,000 white blood cells,..

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um, and you can do a couple different tests to look at that. The newer test on the block...

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is next gen sequencing probably the most commercially well-known. It's called ClonoSeq, and that can go down to one in 1,000,000...

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white cells but, and you're starting to see some clinical trials report below 10^{-4} data, so this idea of what actually is MRD undetectable is somewhat of a moving…

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target as we get better technology, but I think colloquially…

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1 in 10,000 is still the most commonly referred to because it has the most data. So, when you take patients that get a similar treatment and you compare those that are undetectable versus detectable,..

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those that are undetectable seem to stay in remission longer…

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without their disease coming back, so the most standardized way to use MRD is after a time-defined therapy to see how well patients respond.

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And that is really the only approach, at this point in time, that's of like a high category recommendation…

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on standard practice guidelines. What the future may hold is using MRD to see, to separate patients out who may need treatment longer and stopping treatment in those without detectable disease after a certain time point, like a year,..

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and continuing treatment on those with detectable diseases. There's been some studies largely involving, the biggest involving ibrutinib and venetoclax that do some complicated stuff with MRD,..

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um, and have had some good outcomes, but as I mentioned, ibrutinib and venetoclax is not approved here in the United States by the FDA. So,..

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there is a study that I put a lot of patients on called the MAGIC trial that is acalabrutinib with venetoclax, and it's going to keep treating patients for an extra year if they're detectable, but they moved the mark to one in 100,000, so they made it even harder...

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and it used ClonoSeq, so we'll see what that shows. That's called using the MRD tool as a predictive tool in personalizing treatment based on it. The one thing I would caution patients on…

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is using MRD from one treatment and thinking it means the same thing as another treatment. Like, patients would get historically, a percentage of patients would get to be MRD undetectable…

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from chemotherapy but there's plenty of data to show that a patient that gets a acalibrutinib and venetoclax for a year, for example, does not get to be MRD undetectable,..

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is still likely to stay in remission a lot longer than patients that got chemotherapy, so you can't use the tool…

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and compare different types of treatments. It's sort of complicated to think about. You would think you could use it in sort of across-the-board compare treatments, but you can't. And of course, I mentioned, like, nobody on…

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indefinite BTK gets to be MRD undetectable, and they do, they do really, really well.

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Great. Thank you. What is the difference between an allergic reaction and an infusion reaction?

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Well, you know, the obvious answer was that you can, you can be allergic to a lot of things that you aren't getting infused with. So, an infusion reaction is a specific type of allergic reaction and…

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it is, you are just having an allergic reaction, quite simply, to something you are getting infused with. And for CLL patients, that's mostly going to be monoclonal antibodies, I've mentioned the drug obinutuzumab.

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About 50-55% of patients will have an infusion reaction to obinutuzumab when it's the lead-in part of the obinutuzumab venetoclax combination.

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So that's something, uh, that you should be aware of. We do a lot of things like steroids and antihistamines to help prevent that, but don't,..

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um, I know they can be significant, but don't get too discouraged. I think in my whole career, I've only ever had one patient that had multiple reactions to obinutuzumab and couldn't continue on it.

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I've had some pretty severe reactions to the first dose, and then, and then it doesn't, doesn't recur.

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Okay. When CLL recurs after first line treatment, how often are the symptoms of the recurrence different from or the same as the initial CLL symptoms?

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I think it depends on the treatment. I think for time-defined treatment. When you recur, the symptoms are going to be most likely to be more similar to, to what your original symptoms were. Where I've noticed a difference is when people start progressing on...

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BTK inhibitors and they're still on them. Um, the progressions will be different sometimes, and I've seen situations specifically where,..

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um, historically, a patient's progression was defined by very high white cell counts, but,..

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like, when they progress on a BTK inhibitor, their white count is, like, still normal, but their lymph nodes are growing, and so I've seen that happen a few times. So, it can always be something new potentially, but that's been my clinical experience.

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Thank you. I had the FISH test done at diagnosis, and I'm untreated. Should I have the FISH test redone before I start treatment? Should I have a biomarker test done? And what is the name of it?

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Um, so FISH, the, like, most kind of basic way to explain the prognostic workup is, you know, the FISH test which tests for a few different aberrations. The IGHV test, which is the next gen sequencing test, and it's only going to look at…

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whether a patient's mutated versus unmutated. And, and then there's a next gen set for a TP53 mutation and then sometimes you'll, you'll get the report of like a complex karyotype. So that's just looking at,..

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like, all the patient's genes and are there more than five, you know, aberrations, sometimes people will say it's complex if it's more than three, but I think the more recent data supports using five as the cutoff for what is truly complex and a negative…

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prognostic factor. So, uh, what you don't have to recheck is the IGHV test. So that's a one time, once you figure that out, you never need to recheck it. It's either mutated or unmutated. And it's just a reminder…

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you don't need a prognostic workup if you're not going to start treatment. It is okay for you to want to hold off on doing that. It's an option I give patients, and historically, I would say most patients want a prognostic workup at diagnosis. Recently, I've had several tell me that they wanted to defer it, but historically, I would say,..

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um, most patients do want the prognostic workup because…

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it can paint a picture of what to expect while on active surveillance, and this is based on, like, large-level population evaluations of CLL patients on active surveillance that had similar markers, you know, so they can quote…

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the average amount of time that certain patients stayed on active surveillance before needing treatment. But to this patient's specific question,..

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you, um, should recheck prior to each line of therapy, a FISH and a TP53, and if your doctor gets a karyotype, that's fine as well. You don't need to recheck the IGHV.

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Um, if I've, like, done an initial FISH test, and then I end up starting a patient on treatment a few months later, I don't need to recheck them, but if it's been multiple years, uh, that you've been on active surveillance, I think it probably is…

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worth rechecking.

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Yeah, and CLL Society has the test before treat section on the website, too, so that's, uh, that can also be helpful in guiding you.

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Mm-hmm.

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Okay, what are the causes and mechanisms of inflammation flare in CLL patients when in the watch and wait stage? What are the symptoms, and what should patients do to prevent the inflammation flares, and how should they be treated?

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That is a, um, you know, that's a phrase I'm actually not familiar with as a CLL specialist, inflammation flare.

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And, uh, you know, the word flare I've seen used associated when patients, like, stop a BTK inhibitor, their disease can sometimes flare up and progress pretty quickly. You know, I've had a lot of patients that have diagnoses of, like,..

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uh, rheumatoid arthritis and such about, like, you know, is there a connection with their CLL and, and, in, in, in, in, and there's not, like, a really well documented connection between CLL and different rheumatoid disorders.

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But I'm not sure if this patient is referring to, like,..

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you know, sometimes we'll see patients on active surveillance and then their white count will, like, jump up to a degree and then it'll level off some or even come back down, and then instead of this like steady progression, there's sort of like flares of…

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progression. I don't think there's any unique symptoms to these events. It's all the same symptoms that we're looking for, you know, for...

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judging who does and doesn't need treatment and just to review with everybody beyond the blood work of…

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hemoglobin less than 10, platelet count less than 100.

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Patients always want to know what their white count is, but that actually is not an indicator for treatment. I've had a patient come in that feels fine. I think my record is like 440 in a patient who felt fine.

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That's not common, but we're really interested in knowing…

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how functional is the bone marrow despite the CLL and if it's making enough red cells and platelets, we don't need to treat even if the white count is very high. Historically, people would quote, oh, well, if my white count doubles within a six month period...

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that's a criteria that we've sort of gotten away from, uh, and don't use it. It's not really encouraged to use that as much anymore, but the symptoms, in terms of what patients feel, that's going to be the rest of the indications:..

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painful lymph nodes, not just noticing lymph nodes, it's whether they are uncomfortable and you want them shrunk down,..

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um, it's, it's recurrent drenching night sweats. You know, I don't see, um, a lot of weight loss or fevers, but every once in a while, I'll see weight loss. I almost never see fevers.

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But, and then finally, you know, a big functional decline. You know, the word people use is fatigue, but that's a difficult one…

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to, um, to know for sure whether it's the CLL. But if we see a big functional decline in somebody's spending half the day or more in bed and can't do what they need to do, and I don't have another good explanation for it, then I'm going to give treatment a try to see if I can help patients.

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Okay. How significant is the immune suppression associated with CLL?

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It's very, it's quite variable, I've found, and I'll have patients that,..

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uh, well, so what the data tells you is a CLL patient,..

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um, that, that is in remission, having previously been treated but not on active treatment now, that that patient's immune system on average…

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is just as functional as somebody without CLL. Now, obviously, that's not going to be true 100% of the time, but that's, overall, what the data has found. Then sort of the next tick down into a bit more…

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immune dysfunctional is going to be a patient with active CLL but not on treatment. And then, you know, most of our treatments have some level of immune suppression. So, patients on treatment…

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will likely have some level of immune suppression, but that's specific to the treatment, you know, the combination of…

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particularly the anti-CD20 agents is quite, is probably the most immune suppressive thing that we do in CLL these days, now that we've gotten away from chemo. So those are going to be the most immune-suppressed patients, patients getting obinutuzumab, for example.

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Another reason why we're, we're kind of excited about the all oral combinations is maybe we can get outcomes that are really good without that significant of immune suppression. The long-term BTK patients, we think, there's probably a period of time earlier on where they're more immune suppressed, but like long-term,..

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when their disease is under good control, there's some data that shows that we've probably improved their immune system...

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being on, on, on treatment. So, the specific issue that can pop up regardless of treatment history, but probably more common in previously treated patients is the low antibody levels, and so that's sort of a…

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field that doesn't have a real standardized approach, but the most common you'll hear is if a patient is having recurrent problems with infection and their antibody level falls below a certain threshold, the one you hear most commonly is 500...

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but some have quoted lower thresholds. And we can use antibody…

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transfusions, usually, you know, once a month to start and then go from there, but we can use antibody transfusions to help those patients.

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We talked a little bit about fatigue. Another question is, what may be done to promote energy? What are your thoughts about coffee, energy drinks, etc.?

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Uh, the best. So the, the hardest situation with the CLL patient outside of like, you know, patients with uncharacteristically, you know, bad disease or things like that, but just in terms of like a common thing that comes up that I find the most challenging…

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is, um, when somebody's got fatigue that's significant enough that it's affecting their quality of life and we're, but their, but their disease burden of their CLL is quite low…

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and, uh, it's really questionable how much their CLL is contributing to their situation, but I don't have another good reason for why they're fatigued, necessarily.

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Before I start treatment in a patient like that, because, you know, sometimes our treatments cause fatigue too, so before I start treatment, I always try to recommend exercise. Exercise, you know, regardless of CLL has...

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the best data. There's not great medicines out there, CLL or not, for fatigue, you know, and exercise has the absolute best data. And it's not just one kind of exercise.

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And it's whatever you find that you like to do and it's not a certain threshold, you know, some activity is better than none.

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Um, so, so whatever you can do, I would recommend and find something that you like to do so you can keep doing it and build a, build a habit. I, um, uh, coffee might be one of the things I love the most in this world, in terms of, uh, like, food and beverage, so I'm never going to tell somebody, um, yeah, yeah, uh, I'm never going to discourage somebody from…

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you know, it's all about, you know, with reasonable limitations, you know, in terms of…

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Yes, yes.

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of how much consumption there is, but there's actually a lot of good health-related data associated with coffee, but I don't want to go down that rabbit hole. Energy drinks, energy drinks usually have a lot of sugar, so, um, that's where you've got to be careful with those. They usually have caffeine plus a lot of sugar, so if you can find, I mean, I'm

not going to begrudge someone caffeine, and if you can find a way to do it without pumping a lot of sugar into yourself, then that's fine, yeah.

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Great, good. Does the presence of CLL modify the risk benefit analysis for statin therapy in patients with high cholesterol and a zero coronary artery calcium score?

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No, I think the cardiologist or primary care physician is free to stick with their standard recommendation there in the CLL diagnosis shouldn't affect that.

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Can I donate blood when I have CLL?

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Unfortunately, no, they do not allow for that.

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Okay. Okay. And you go to…

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live questions here. What are your thoughts on taking probiotics? And for how long? Any specific type? I've been on seven different antibiotics this year.

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Yeah. So that's the type of patient you would really think about probiotics for every time you take antibiotics, you just you've got a lot of healthy gut bacteria in your gastrointestinal tract, particularly your large intestine so...

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you disrupt that when you take antibiotics. It's one of the reasons why I know patients often want antibiotics every time they get ill, and there's certainly times where antibiotics are helpful, but I do,..

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uh, try to not just be too free with the antibiotics if I think it's a virus, for example, for situations like this, and so I don't pretend to know a lot about specific…

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prescription probiotics or even, like, supplements that you find at the, at the store. Um, it's, it's in that field of supplements where...

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you know, um, and it's possible that there are some that are prescription from a doctor, but those I'm not too familiar with. But the ones you're going to find in the store, you know, it falls in the field of supplements that they actually don't have to…

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produce data to substantiate any claims, and sometimes there's additives that you're not aware of. So, I always initially remind people that, you know, something like yogurt is a really good…

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source of natural probiotics, there's other things you could look up on the internet, but yogurt is probably the most widely known. So, if somebody's interested in probiotics, I try to tell them to start with yogurt and see how that helps.

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You know, if you're wanting something beyond that, your primary care physician will probably give you a better answer than I can.

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Okay. Does the use of alcohol have an effect on cancer?

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So there's, um, there's been sort of a change in the dialogue around alcohol recently.

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There was some kind of historical data that has since been a little bit, um, debunked to a degree of, like, alcohol leads to lower cardiovascular events. What is clear is alcohol consumption increases HDL…

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which is like the good cholesterol marker and maybe that has some positive, but the negatives…

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most clearly outweigh the potential positives. I am not a teetotaler, so I'm not sitting here and telling people they can't drink alcohol. I mentioned…

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how I try to frame this conversation is, um, you know, I mentioned sugar earlier, right? So, um, what you're hearing recently is, like, there is no safe level of alcohol. Okay, um, so if we concede that…

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you could say the same thing about ice cream. You know, there is no safe level of ice cream. And I still like to eat ice cream sometimes. So I don't, I have never seen, I mean, there's just certain things that we make a risk-benefit judgment on…

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and think our life would be better with ice cream from time to time, and live with the consequences. And obviously, those consequences would be different for somebody that has, um, weight problems or diabetes…

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versus somebody that doesn't, just like alcohol would be a different consideration of somebody that has a history of alcohol use disorder. So, I think it's a personal decision, but I will reassure everybody on this…

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Mm-hmm.

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call, that there's no connection with CLL, specifically. And, uh, but there are connections with, I think, the most notable one is women in breast cancer. There's some increased risk with breast cancer with alcohol and for smokers,..

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um, the combination of smoking and alcohol, it can really increase the risk of esophageal cancers and such, so there's other cancers to consider, but not CLL.

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Okay. What is the physiology behind having an increased chance of secondary skin cancer with CLL/SLL? Everyone talks about the possibility of skin cancer but no one gives an accounting for why this exists in people with CLL/SLL.

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Great question. And there's some recent along the lines of supplements, there's some recent, I think, actionable potentially data to help with this. So, what the data tells us is…

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that CLL patients have a higher rate of non-melanoma skin cancers, and usually that's going to be squamous cell carcinoma.

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That's part of the reason why, as a CLL doctor, I remind my patients to check in with a dermatologist, particularly if they're over 65, like once a year or so, and the reason why this is happening...

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is CLL. We've been talking about the immune system, right? You know, we didn't necessarily talk about why CLL patients have…

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to a degree dysfunctional immune systems, but if you have a cancer of your immune system and it's not working as good as it should, the medical term is called energy, it's referring to the fact that the immune system cells are just not as active and responsive…

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as they should be. And this this occurs in other areas.

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Uh, sometimes it's medically induced, like in organ transplant patients. We suppress the immune system and we see the same thing: more skin cancers. So, the connection is when you suppress the immune system, whether it's through CLL or another route,..

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you're suppressing the body's mechanism for surveilling against and shutting down,..

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among other things, skin cancers, and specifically more frequently the non-melanoma skin cancers. So that's why we see more of those. There was some connection maybe that BTK inhibitors, more ibrutinib than I've seen with other agents,..

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might increase the risk even more. Um, the, the recent, there's a phase 3 study going on…

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that is looking at a supplement called nicotinamide, and I've started to hear some other specialists talk about this. It's vitamin B3. So, it sounds like nicotine, but it's nicotinamide, but it's just, it's a B vitamin. B as in boy, vitamin B3.

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And there's some suggestion that supplementation with that reduces the rates of squamous cell carcinoma, so I don't know if I'm to the point where I'm telling everybody

to get on that with CLL, but certainly if a patient's had issues with squamous cell carcinomas before, it probably doesn't hurt…

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to get on that. The other supplement that probably many people on this call have heard of, not unique, not specific to skin cancers, though, is the vitamin D supplementation, and that, that might slow progression in patients that are on that...

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active surveillance.

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Okay. Would you talk about the diagnosis of SLL? Is it different than CLL?

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It's different in how it presents. It's not different in how, um, and what drugs are, it's all the same drugs, all the same, all the same approvals are for, for both CLL and SLL. So the...

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name, uh, so of course CLL, chronic lymphocytic leukemia, SLL stands for small lymphocytic lymphoma. So, the word that's missing in SLL is leukemia.

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What leukemia is, is a cancer of the bone marrow, so SLL is defined by enlarged lymph nodes with CLL cells but no…

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significant amount of CLL cells circulating in the blood.

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And, um, if you go looking for the CLL cells in the blood with...

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something like a flow cytometry test, you're probably still going to find them, they're probably still there, but it's just they're not over the threshold of…

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5,000. That's the same threshold that we use, you know, to…

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say whether somebody is a monoclonal B cell lymphocytosis, which is not a cancer versus the…

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CLL when, when you don't have a lymph node diagnosis so, if you're just using blood, that's 5, the 5,000 monoclonal B cells on flow cytometry.

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So, um, for SLL, it's a little bit harder to diagnose because you have to do a lymph node biopsy.

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With CLL, luckily, we don't need an invasive procedure these days to diagnose most people. You can take the peripheral blood and send it for that same test I was telling you about, flow cytometry, and make the diagnosis.

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It's about 15% of cases are SLL versus CLL.

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Um, because, just because you start as SLL doesn't mean you may not end up as CLL at some point. I've followed some patients that were diagnosed as SLL originally, and then ultimately their white count…

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started to come up, so we just changed the label on them to, um, to see a little prognostically, there's not really a recognized difference. It's not necessarily better or worse to have SLL versus CLL.

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Yeah, that was, that was my progression SLL to CLL, and now I'm back in watch and wait after acalabrutinib treatment, and I'm thinking, well, will it manifest again the same as SLL first? So, you know, we sort of discussed that already.

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Yeah. We kind of talked about that earlier. Yeah.

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Yeah, yeah. If there is no evidence of disease progression, where is the CLL residing in the body? How can it continue to impair my immune system even when the blood counts appear stable?

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Well, um, and like I alluded to earlier, if somebody is in remission, there's data out there that their immune system is doing great, like, you know, overall, like patients with CLL in remission, their immune systems…

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in general, are doing, are doing well. I know, again, there probably are, examples where that's not the case. But, but by and large,..

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that's the, uh, that's the situation. So, uh, what, uh, you know, historically, we used, um, what's called that, and it's still referenced in clinical trials, but it's called the iwCLL/Hallek criteria of defining what remission is, and we would do CAT scans, and all the nodes had to be less than 1.5 centimeters, all the lymph nodes, and the spleen had to be under 13 centimeters...

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and, and then the blood work had to be normal and then you do a bone marrow and that had to have no visual evidence of CLL, and that's what we would define as complete remission. We've already talked about MRD. It has been shown…

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that MRD is a more, which can be, tested just in the blood without any invasive testing or scans. The MRD is a more effective…

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prognostic tool than doing scans in a bone marrow and all that other blood work, and it's because it can look deeper and I've talked about how initially we could only detect down to one in 10,000 and then it was one in 100,000. Now it's one in a million.

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So, um, it's not that the CLL is gone, it seems, it's just, like, how deep can we look to detect it? And so, I think that's my best answer I could give to that of, like, where is the disease? Like, we can push it down to very deep remissions...

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but sometimes I think it's our technology that limits, um, being able to see it.

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Okay. Oh, I think we have time for one more question. With your background in research and clinical trials, what are some of the most promising advances you see on the horizon?

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Yeah, I'm really glad we got to this before. So, I am a big fan of…

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time-defined therapy where appropriate. Like, I think if we can keep people off of long-term toxicities and the financial toxicity, too, of being on treatment for years and years, that that's excellent. And the biggest impacts are going to be...

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on first-line treatment because a lot of patients will never need anything after first-line treatment. And so, I think really exciting trials are these different looks at different ways to do time-defined treatment in the frontline setting. I mentioned the MAGIC study. There's another one called Celestial, which is...

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going to be zanubrutinib's approach to trying to do time-defined therapy formally, and it'll be the first time we've seen potentially any improvement on the drug venetoclax. So, the company that makes zanubrutinib is making their own version of venetoclax that they call sonrotoclax.

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On the other end, so talking about, um, uh, you know, patients that are kind of running out of treatment options, I think the approval of BTK degraders is going to be exciting. There's two companies making them, and they're kind of racing to get their drugs approved, but they both look good.

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And, um, they've even worked in patients that have progressed on drugs like ibrutinib, then progressed on pirtobrutinib and these degraders still seem to work, so that's exciting on the other end of that spectrum.

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Well, Dr. Jacobs, this has been great, and I hope you come back and join us again. Before we close the program, do you have any closing thoughts for our audience?

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Yeah, I would just like to emphasize the, I like to end on positive notes, so the high points of…

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you know, we're already at a place where it seems like the CLL diagnosis doesn't affect life expectancy, which is wonderful. This is a common malignancy. It's the most common chronic lymphoma slash leukemia.

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So, we've taken a common malignancy and normalized life expectancy, so it's been such a pleasure to be a part of that research, and so now where we're at is we're developing cool technologies…

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um, that'll help the few that still need something, despite the three or four options that we already have that are pretty good, and they're really good, I should say. But most of, a lot of what we're doing that's going to affect…

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the most patients is taking what we have and finding the safest way to give it in the most effective option. So that's where my enthusiasm is around figuring out the best kind of combination of well-tolerated treatments in the first line setting because it's now, can we dial back a little bit…

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and still give people really amazing, amazing outcomes.

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That's great. Thank you, Doctor. Thank you so much for your time and expertise. We're very grateful for your participation and sharing your wisdom with us. Thank you to everyone who joined us today. We'd also like to thank our generous donors to the CLL Society and grant support from Genentech and Lilly for making this event possible.

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A few brief reminders. Please complete the short event survey shared with everyone. We really want to hear your feedback and appreciate your time in completing the survey. Please join us on May 27th for our next webinar, Shared Decision Making in CLL, Partnering with Your Doctor to Choose the Right Path.

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If your question was not answered today, please send it to our Ask the Expert email service. This is a free service available on the CLL Society website under Programs and Support. Remember to follow CLL Society on social media platforms.

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And lastly, the CLL Society is invested in your long life, and you can invest in the long life of the CLL Society by supporting our work. Thank you.