Webinar Transcript
ASH 2025 Comes to You!
January 14, 2026

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Hello, and welcome to today's webinar. I am Liza Avruch, Program Director with the CLL Society.

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We are dedicated to bringing credible and up-to-date information to the CLL and SLL community…

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because we believe smart patients get smart care. 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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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.

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Thank you, thank you, Liza. I would like to welcome our audience to today's event.

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I'm Dr. Brian Koffman, Co-founder, Chief Medical Officer Emeritus of the CLL Society…

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and we're joined today by my friend, Dr. Adam Kittai,

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Associate Professor, Division of Hematology and Medical Oncology, Assistant Director of Lymphoma Clinical Research,

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CLL Clinical Research Leader, at the Icahn School of Medicine at Mount Sinai Hospital in New York, New York.

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And the two of us will be presenting some important research from ASH, the American Society of Hematology's annual meeting that was held in December in Orlando, that's related to CLL.

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This webinar is going to be advanced, but everyone is welcome to participate and learn.

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The recorded webinar, the associated slide deck and transcript will be available for everyone to view after this event.

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Before we begin, I need to share some important disclaimers.

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The information provided during today's webinar is for educational purposes only...

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and it should not be considered medical advice. For any personal or treatment questions, please consult your healthcare team.

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Please note that the CLL Society may have its own opinions and policies…

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and our speakers may have differing viewpoints, especially regarding the exact management of CLL and its complications.

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We will be answering your questions, which are very important to this webinar, at the end of the event…

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so please take advantage of this opportunity, and ask your questions in the Q&A box.

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Now, Dr. Kittai will share a few updates of the breaking research from ASH…

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2025. Dr. Kittai? Thanks, Brian, for that introduction. I'm really excited to be here as part of the CLL Society's ASH 2025 comes to you. Once again, I'm Dr. Adam Kittai, and so, when I was thinking about…

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what abstracts we should present at this particular lecture. I thought, what might be the three most practice-changing abstracts at ASH this year. And it was a really exciting year for ASH for CLL. We had multiple big presentations, and…

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actually, the biggest presentation of all of ASH is something called the plenary session, and we had the CLL17 study, this top abstract…

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being presented, um, at the plenary session, which was really exciting to see. Um, and the reason why this was so exciting was that this is the first randomized study…

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to challenge our current two main treatment paradigms, which is...

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continuous BTK inhibitor, in this case ibrutinib, versus venetoclax plus obinutuzumab for one year.

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And then also, in this study, was included the combination of ibrutinib plus venetoclax.

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The second study that I will present is the BRUIN CLL-314 study, which is the first study to compare the non-covalent BTK inhibitor pirtobrutinib versus ibrutinib, and last but not least, um, we will present an abstract on Richter transformation showing some really exciting data out of MD Anderson that combines…

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pirtobrutinib plus venetoclax plus obinutuzumab for this very bad disease, and so it was really nice to see some of these really wonderful outcomes of this particular study.

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So, let's start off with the CLL17 study. So once again, this is a randomized Phase 3 study, so what that means is that the patients were randomized to either receiving ibrutinib,..

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ventoclax plus obinutuzumab or ibrutinib plus venetoclax. This study was run out of mainly European countries, um, and was put together by the German CLL group. They are the ones who usually put together the CLL titled trials that you might see around.

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So, to start off, the presenter presented this slide, which...

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basically shows us the two main paradigms for treatment in CLL today. And so,..

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most likely your physician talked to you about being treated with a continuous BTK inhibitor, in this case, in this trial, ibrutinib, or doing time-limited therapy with either venetoclax plus obinutuzumab...

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or ibrutinib plus venetoclax. And the reason why you might be wondering why you haven't heard of the combination of ibrutinib plus venetoclax in the US is because it's actually not approved in the US.

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But it is approved in Europe and has been widely adopted there. And so that's why the ibrutinib plus venetoclax arm was included in this particular study because this study was performed in Europe.

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And, as I said, it was a randomized study where patients received one of the three regimens.

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And up to this point, you know, we didn't know which regimen might work better in the frontline space. Typically, we would use certain criteria to treat somebody with continuous therapy…

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versus time-limited therapy, usually based off of risk of disease, such as TP53 status, or maybe if someone had any comorbidities that would preclude them from getting one of the therapies.

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This was a really large study. It was 976 patients, and they had follow-up of 34.2 months.

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Now, I do want to highlight that for a second, that the follow-up was only around three years so, I'm looking forward to seeing further follow-up for this study because...

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three years is not long enough, really, to be able to show a true difference between any of these three arms. But they were able to show their primary endpoint, which I'll show in a second…

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um, looking at whether one of these arms are more effective than the other.

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So, first off, let's start off with adverse events, because when we think about which…

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treatment to choose for somebody, we really think about the adverse events and what our patient in front of us may or may not be able to tolerate.

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And I highlighted in red, um, the adverse events that I wanted to talk about. So, first off is neutropenia. So, neutropenia is when you have a low neutrophil count…

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and when patients have a low neutrophil count, they're more likely to get infections. And so what's interesting on this study is that,..

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not surprisingly, there were more low neutrophils in patients receiving the venetoclax regimens versus ibrutinib, but if you look at four rows down underneath infections and infestations…

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the actual rate of infection was no different between the arms.

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Additionally, when they looked at cardiac disorders, and you all may have heard about how ibrutinib might induce things like atrial fibrillation and hypertension, you can see that there was a significant…

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decrease in cardiac disorders when patients were treated with venetoclax plus obinutuzumab versus ibrutinib regimens, which was no surprise.

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Last but not least, which caught me off a little bit guard, because I usually, um, tell my patients to watch out for diarrhea with venetoclax plus obinutuzumab, is actually the rate of diarrhea with venetoclax plus obinutuzumab was less than those being treated with ibrutinib.

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Now, one other thing I want to highlight on this slide is that widely in the US, the second-generation BTK inhibitors have overtaken ibrutinib as the...

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primary BTK inhibitor of choice, and that's because of toxicity. So, one limitation of this study is that ibrutinib was used and not acalabrutinib or zanubrutinib.

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So, let's move onto the efficacy. How well did these treatments work?

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And not surprisingly, they all worked about the same. So, this is the iwCLL response criteria.

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And as you can see, the response rates were widely the same across the three arms, but there were more complete responses in the venetoclax arms in the blue and the green.

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And when they looked at overall survival, the lines were overlapping. What this shows is that continuous therapy led to non-inferior overall survival compared to ibrutinib and venetoclax or venetoclax plus obinutuzumab.

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They worked the same. That being said, as I said, this is only three years, and I do want to see how long-term survival plays out over time.

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Let's look at a couple other more interesting things that I found.

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So, first off is high-risk disease. Sometimes we try to avoid treating patients with high-risk disease...

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with time-limited therapies. And as you see here in the blue line, the blue line comes down lower than the other lines.

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It does appear that patients who were treated with venetoclax plus obinutuzumab who had high-risk disease…

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do worse than those who were treated with continuous therapy or those who were treated with ibrutinib plus venetoclax.

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So once again, we need more long-term follow-up, but it does appear that our assumption is true, that patients with high-risk disease should probably be treated with continuous therapy.

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Last but not least, this slide I thought was really interesting, so here they looked at how…

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cumulatively ill somebody was, how many comorbidities did they have.

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And classically, we think about giving continuous BTK inhibitors to patients who may be a little frailer than using the venetoclax…

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plus obinutuzumab regimens. But in fact, here, patients treated with ibrutinib who were unfit, those are the patients in that red dotted line on the bottom, they did the worst.

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And so, that may re-challenge our assumption that we should be avoiding using time limited therapy with new venetoclax regimens in unfit populations. Once again, we have to think about that…

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the second-generation BTK inhibitors, acalabrutinib and zanubrutinib, are certainly better tolerated than ibrutinib, so it's hard to draw conclusions without having these as arms on this trial as well.

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So, in conclusion, this was really nice to see a trial comparing our two main regimens, time-limited versus continuous therapy...

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and not surprisingly, all patients did great on this study. So, my take-home from this is that no matter if your physician chooses to treat you with continuous therapy versus time-limited therapy, you are likely to do very well.

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And I think that when patients and providers look at this study and think about how will this reinforce what they currently do, they'll either look at it and say, okay, I'm a continuous person, I'll continue using continuous therapy, but they'll also look at this and say, okay, I'm a time-limited person, and for time-limited treatment with one year, I'm getting equal outcomes, I'm going to continue using time-limited therapy.

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All in all, this was really exciting to see our regimens finally put up against each other, and I'm excited to see long-term outcomes.

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What do you think, Brian? What do you think about this study?

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Well, first, I think this was a very important study in the German group, I think, is an example of how research can be done…

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because they pulled in from all kinds of countries, it's a long-term study, and they've really revolutionized how CLL should be…

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investigated, so, you know. And the fact that it was the plenary session, and the largest room, and, you know, literally thousands of people in the room listening to that is, I think,..

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gives a sense of how important it is. There's a couple things that I'd just like your take on.

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The sense I had, and maybe you can explain a little bit about this, was…

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IGHV mutation status would often be a determinant about which therapy to use in patients that were a little higher risk, more likely to progress were given the continuous therapy.

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This didn't seem to bear that out to the same extent. Do you think that's because it was only three years or do you think there's something there in the earlier kind of suggestions of that direction are different? Because that seemed to be a determining factor, and it didn't really show up on this.

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That's a great question, Brian. So, what's interesting about IGHV mutated and unmutated disease is that…

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patients who have unmutated disease, which is usually associated with worse outcomes,..

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actually respond better to therapy, they just relapse earlier.

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And so, what's interesting in that analysis, typically, is that the overall response rate does not correlate with progression-free survival. Usually, those two things come hand in hand.

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But interestingly, IGHV unmutated status respond better, but have worse long-term outcomes. So, I do think that we need longer follow-up to look at that particular variable.

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Thank you for that, yeah, very interesting study. What other studies do you have for us?

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Sure, let's move on. So, the next study is the BRUIN CLL-314 study.

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So, this is the study of pirtobrutinib versus ibrutinib. So, for one, there are very rare BTKi versus BTKi studies. This is only the third.

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The first two were comparing ibrutinib versus the second generation acalabrutinib and zanubrutinib…

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but those were all the same class of medication, covalent BTK inhibitors.

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Pirtobrutinib is something different. It is a non-covalent BTK inhibitor. It binds differently to BTK…

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leading to stronger binding and also was developed to work in patients who had...

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resistance mutations to covalent BTK inhibitors. So, this is a really interesting study.

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Additionally, pirtobrutinib in the Phase 1, 2 studies, the earlier studies, looked to be really safe. So, we were really curious to see how pirtobrutinib would stand up versus a different covalent BTK inhibitor such as ibrutinib.

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So, a couple of things, this enrolled both patients who had relapsed disease...

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and also treatment-naive CLL. They could not have received prior BTK inhibitor but prior venetoclax was allowed.

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And the primary endpoint was overall response rate, with a secondary key endpoint of progression-free survival.

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Now, in general, in CLL, we don't care as much about overall response rate, because our patients live for a long time…

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despite having good or bad responses. And so, we really care about PFS. But I do need to know that, you do need to know that the study showed equivalence between the arms…

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meaning that pirtobutinib was non-inferior to ibrutinib, and this was a non-inferior study. So, pirtobrutinib led to the same response rates as ibrutinib, and that's what this chart is showing.

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So, moving forward, I want to show you the Kaplan-Meier curves.

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So, these Kaplan-Meier curves, how, once again, I want you to look at these is that,..

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um, the red line is higher than the black line, so that means that the red line did better than the black line. That's how you should look at it.

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And that the red line had higher survival for our patients than the black line did.

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So, on the left, we have relapsed refractory, and this was, um, about 420 patients, and as you see here, pirtobrutinib did a little bit better than ibrutinib, but, you know, statistically it's about the same.

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So, what I'm looking at there is the hazard ratio, the HR, and the p-value. So, both of those tell me that the arms, although they do look a little bit different where pirtobrutinib might have led to a little bit of a benefit, um, statistically they are the same. So long-term follow-up is needed for that arm.

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Now, for treatment naive, you can see there's a clearer distinction between the lines.

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Pirtobrutinib led to a bigger benefit than compared to ibrutinib…

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and this was seen in the p-value too. So, this study was not powered to study this difference, so that's a little complicated. I can't say...

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with statistical rigor that pirtobrutinib led to a significant improvement in progression-free survival than ibrutinib did, but the arms look like that's the case. And so longer follow-up is definitely needed here.

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Moving forward to safety, as I said, this was a key question on this study. Pirtobrutinib, as you see in the red, led to a significant improvement in atrial fibrillation and flutter compared to ibrutinib…

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and also led to less hypertension. Additionally, it does look like it's a little bit better for infections, but not significantly.

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So, I think when I look at this study, um, one of the major drawbacks, as alluded to in the CLL17 study, is that pirtobrutinib here is being compared to ibrutinib and not acalabrutinib or zanubrutinib so it's difficult to know how pirtobrutinib matches in terms of safety,..

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um, compared to what we're currently using. But I did find it extremely interesting that pirtobrutinib led to an efficacy benefit and it looks like a safety benefit as well.

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So, in conclusion, pirtobrutinib led to a improvement, or I should say was not inferior for overall response rate compared to ibrutinib…

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but it did look like PFS favored pirtobrutinib. So, you know, how is this going to change what we do in practice? I think that pirtobrutinib is looking like a really good drug if we're treating older patients, maybe frailer.

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But there are issues, um, something I did not mention here is that pirtobrutinib sometimes will induce what we call kinase-dead mutations, which makes us unable to use the covalent BTK inhibitors after pirtobrutinib.

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And so, while it's very nice to see that pirtobrutinib might beat ibrutinib from an overall response rate, maybe survival benefit here, I really want to see overall survival and long-term follow-up.

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But it was nice to see that pirtobrutinib does appear to be very safe, at least compared to ibrutinib in this study.

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So, I'll leave it at that. I'm curious to know what, Brian, you thought of this study?

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Well, I was impressed with the safety data like I've been from the beginning with pirtobrutinib, and it seems to be an extremely well-tolerated BTK inhibitor, and blocking BTK has really changed how we treat CLL.

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Uh, and, but I was surprised that its efficacy started to separate on the treatment naive.

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But I wanted to push you a little bit on this issue of using it in the treatment naïve, that means frontline, they haven't had any other therapies,..

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uh, because of what you talked about. We know that, at least in the relapsed refractory setting, that certain…

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mutations develop in some, that render it not able to work anymore, made people refractory, they become resistant to the drug.

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But some of those mutations, it's thought, would also make you resistant to all the BTK inhibitors, like ibrutinib, acalabrutinib and zanubrutinib.

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So, explain to me a little bit more detail the concerns about if we put pirtobrutinib in front…

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do we know whether that's going to make it harder? Right now, the sort of the,..

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the paradigm is, you use one of the covalent, usually, honestly, a second generation, acalabrutinb or zanubrutinib and if that doesn't work, then pirtobrutinib…

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is often an excellent next choice. But could we go in the other order? Do we know? Is that a concern?

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Play that out a little bit for us. Yeah.

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So, um, right now, all of the data that we have for mutations...

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that develop on pirtobrutinib that make acalabrutinib, zanubrutinib and ibrutinib not work...

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is in the relapse setting. Meaning that we don't know how this mutational story is going to play out in the treatment naive setting.

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And in fact, the, first, or some of the first data...

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for the mutational data in the frontline setting was presented at ASH with ibrutinib, and it did look quite different than what we see in the relapse setting...

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meaning that relapsed CLL acts different. It's more likely to develop mutations, it's more likely to act…

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aggressively, especially if someone got chemo and then went on to get a BTK inhibitor.

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And so, I think that there is definitely concern that pirtobrutinib might lead to…

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mutations that lead to our covalent BTK inhibitors from working. Therefore, the sequence of…

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pirtobrutinib to covalent BTK inhibitor might be obscured or unable to happen in the treatment naive setting.

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I question whether or not those mutations are going to occur at a high enough frequency that that will happen.

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Additionally, in the relapse setting, about 30% of patients who progress,..

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don't progress with a BTK mutation. Meaning that there's this element of resistance progression that hasn't even been defined yet.

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And we don't know how pirtobrutinib plays into that story either.

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And so, while we do need to know how these mutations develop for patients who progress on pirtobrutinib and what that looks like and how that might impact overall survival, it's going to be a long time before we find that out.

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And if I scroll back a slide, and I show you this safety profile, showing that patients do quite well on pirtobrutinib with very good risk and...

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safety profile, and then I show you this slide and show you this solid curve...

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on PFS, meaning that patients weren't progressing by three years.

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If this line keeps on going out, showing that pirtobrutinb is truly more efficacious than ibrutinib and leads to an overall survival benefit, which may or may not happen based off of safety and efficacy.

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The argument is that I'm not sure I care so much about what mutation develops on pirtobrutinib. We're seeing an overall survival benefit, meaning that the sequence doesn't really matter.

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So, I think, once again, time will tell, and it's a really good question, and something that we are concerned about, but we just are hypothesizing without having all the information.

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Thank you for that thoughtful answer. I can't wait to hear the next abstract.

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So, this last one is on Richter transformation. Um, as some of you may be aware, um, Richter transformation is my passion. It's something that I study personally and have been trying to make an impact on for years. And so, this study, um, of pirtobrutinib to venetoclax plus obinutuzumab was really exciting for me.

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So, this is a study of Richter transformation to remind the folks, Richter transformation is when CLL turns into an aggressive lymphoma, like diffuse large B cell lymphoma.

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Classically, we use chemoimmunootherapy treatments to treat this disease, but we don't see great outcomes. As you see here listed in the middle, here are some of the new therapies that we use that are not chemotherapy.

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Um, and they led to an overall response rate of about 60% and I wanted you to keep that in mind as I go through these slides.

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And there has been some recent data that showed that pirtobrutinib as a single agent led to decent outcomes for patients who had Richter's transformation that were refractory.

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So, this study combined pirtobrutinib, venetoclax and obinutuzumab and patients got the treatment for at least two years.

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Fifteen patients enrolled, so it was a small group of patients presented,..

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and median follow-up was 16.5 months. And in a disease that has an overall survival that's measured between six months to 24 months,..

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16.5 months is pretty good. So, as you see here, prior lines of therapy, most patients have either gotten a treatment for CLL or a treatment for Richter transformation.

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And most of the patients have been treated with prior BTKi and BCL-2 inhibitor.

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One criticism of this study is that I would have expected, for those patients who had prior CLL or Richter transformation, to have gotten more BTKi and more BCL-2 inhibitor, especially on this particular study, that they're using pirtobrutinib and venetoclax.

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But that's a small gripe because the patients did quite well.

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So here is the overall response rate. Remember how I showed you the three other...

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treatments that led to an overall response rate of 60%?

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Here, in these 15 patients, it was 80%, which is quite high. I don't think I've seen an overall response rate this high in a Richter study...

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which is exciting to see. So, of those 15 patients that enrolled,..

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12 had a response, either a complete or partial response. Three went on to get a transplant, which is typical for Richard's transformation,..

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and nine remain on study and are still alive.

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Here are the progression-free survival and the overall survival curves. Um, as you see here, the 12-month overall survival and progression-free survival were around 80-90%,..

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meaning that 80-90% of patients were alive at 12 months, which is a general improvement compared to what we have previously seen in Richter transformation.

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So, in conclusion, I think that this is really exciting. I think there's some limitations here in that this was only 15 patients.

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Um, pirtobrutinib, venetoclax plus obinutuzumab are drugs that we have access to within CLL and can be recapitulated and used for Richter transformation, so I think that this is something that people can get right off the bat without having waiting long for FDA approval or anything like that.

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So, I think that this combination is an exciting combination for our patients with Richter transformation…

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and may lead to a significant improvement in survival over time.

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So, yeah, really excited about this. What do you think, Brian?

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Well, I was very excited about this too, because pirto was one of the major unmet needs in CLL, and is still a death sentence for most patients, so this is very exciting.

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I'm going to be talking about pirto too, uh, to some extent, so it was kind of the buzz, pirtobutinib, um,..

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uh, but is there something special about it, um, that seems, because there's been other trials with other BTK inhibitors which didn't have as impressive…

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data. So, is there something special about the way it works that might be important in Richter's transformation?

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There is a hypothesis that pirtobrutinib might lead to better synergism with venetoclax compared to the other BTK inhibitors.

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Um, additionally, this study enrolled a lot of treatment-naive Richter transformation patients and also patients who had only received zero lines of therapy for CLL before Richter transformation.

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So, patients who develop Richters who receive no prior therapy for their CLL before developing Richter's do quite well.

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And so, we might see some of that here, and with only 15 patients, it's really hard to parse out whether…

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that had an effect. Um, and additionally, the zanubrutinib as a single-agent study looked actually pretty good, so there's a subset of patients…

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in the zanubrutinib tistlelizumab study, where they got zanubrutinib by itself,..

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and that led to an overall response rate of 50%, 60% alone, kind of like pirtobrutinib as a single agent.

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And so, this is one of the first that combines all three together, the pirto plus the ven plus the obin.

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There's not many other covalent BTKi plus ven plus obin studies out there so I think,..

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considering all of that makes me think that, you know, our hypothesis that combining all three of these for Richter's does likely work.

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Well, thank you so much, and I'll take over in a minute.

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I'm going to cover five abstracts, and I'm going to cover them in a quicker way, uh, to get through them all, because I thought they were all important, and just want to touch on them a little bit.

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Um, and I'm looking forward to Dr. Kittai's comments on them. The five I'm going to cover, um, are liso-cel, which is the only CAR-T that's approved in CLL,..

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and comparing real-world data to research data, which was surprisingly strong.

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Bexobrutideg, which is a BTK degrader, which is being used in relapsed refractory CLL. I'll explain a little bit more about that. Another BTK degrader that doesn't even have a name yet,..

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just a number, BGB-16673, uh, rocbrutinib, which is a very interesting novel, dual-binding BTK inhibitor for dual-exposed CLL, and finally a paper that I was privileged to be the lead author on, which talks about the importance of testing, testing before treatment in CLL.

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So, the first one I'm going to talk about which is this superior real-world outcome,..

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a lisocabtagene maraleucel which is called liso-cel for short, and it's the only CAR-T therapy which, uh, that is approved in CLL, which is a cellular immunotherapy, and…

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the responses in clinical trials for the patients that it works for have been good, but the responses haven't been overwhelming.

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But in the real world, and this is unusual in my take, the responses were better than they were…

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in the clinical trials, 83% of patients responded to treatment, and 60%...

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had no detectable disease. They were uMRD. Now, what was really interesting to me, especially after what we've heard about pirto earlier, is 72% of those whose last prior treatment was pirtobrutinib responded compared to only 28% who did not receive it just before.

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Now, the problem with this study is very similar to the other studies you heard. The average follow-up was very short, only three months,..

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adverse events, the majority of patients did have CRS, cytokine release syndrome, a significant number had neurological toxicities, um, so, the usual kind of adverse events, but these were managed in, and people seemed to do quite well with this.

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So, the results are promising, it's very, very early, but the data was much better than clinical trial data, and that just…

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caught me, and I thought it was important to share. Dr. Kittai, uh, anything that you want to share on this?

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So, the original Lliso-cel data was liso-cel as a single agent…

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and the response rates, if I remember correctly, were about 40-50%, so it was underwhelming.

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Then the ibrutinib plus liso-cel arm of that study was finally presented last year, and the response rates doubled, where the response rate was about 80%.

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And so, what's interesting about CAR-T is two things: number one is that CAR-T…

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is effective in patients who have disease control. Doesn't matter if you have the most high-risk disease with complex karyotype, deletion 17P, IGHV unmutated status.

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It's disease control that matters. And so, when you use pre-pirtobrutinib to get disease control, that's why you're seeing better outcomes.

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Additionally, BTK inhibitors, when used, improve T-cell function, and CAR-T cells are T cells, they're just modified T cells.

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And that's why, also, when you see pirtobrutinib here, likely led to improvement in T cell function.

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Whether that's a direct effect of the drug itself improving T cells or it's because of disease control, because we know disease control, when it goes down, improves T cells…

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is questionable. But I think that this data looks much more similar to the ibrutinib liso-cel arm of that study than the original liso-cel as a single agent, and it's because…

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as Docs, we knew to use BTK inhibitors at this point, which improved the efficacy of the CAR-T itself.

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And so it was, once again, agreed, very different than what was presented at the trials, but the reason is because of the concurrent BTK inhibitor use.

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Well, thank you for that clarification. Let's look on to another dog, bexobrutideg, or NX-5948, which is what I'm going to call it, because that's a little bit easier. And I have this cartoon, uh, to explain what it works, and...

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we've talked a lot about the BTK pathway and how important that is, and how that's revolutionized care in CLL. Well, the BTK inhibitors that we've heard about, pirtobrutinib, acalabrutinib, zanubrutinib...

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and ibrutinib, think of them as a switch that turns off BTK but the BTK is still there.

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What the BTK degrader does, I said, I love this cartoon, is it gobbles it up…

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and the BTK no longer exists, it's no longer in the cell. It's sent to the recycler in the cell. They actually…

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chew it up through constituent proteins and recycle it and use it to build other parts of the cell.

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So, that can be very important for things like…

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how that's, BTK, that enzyme, fits into A pathway into what they call scaffolding, and getting rid of it may have a different effect all around.

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Because we know that eventually, many people relapse from BTKs that block the ability for the BTK inhibitors to bind.

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And if you completely remove them, they can seem to work when patients have relapsed from traditional BTK therapy. So, NX-5948, this is a phase 1, this is the first in human trial, again, very early data, in relapsed refractory, these patients have had other treatments before.

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And you're going to see at the very bottom, I use this line in several of the papers I'm presenting…

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because I'm, we have excellent treatments frontline, but what do we do about this difficult group of patients…

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who have failed multiple therapies. So, this was a tough group to treat almost everyone had had a covalent BTK inhibitor,..

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one out of three, essentially, it had pirtobrutinib or a different non-covalent inhaler inhibitor,..

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the, uh, three out of four had had BCL-2, which would essentially be venetoclax, and almost three out of four had had both the BTK inhibitor and venetoclax, and surprisingly, over 77% had had chemotherapy.

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And some had even had CAR-T, and if we look here, this is a high-risk group of patients who…

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four out of ten, more than four out of ten, had mutations where the BTK inhibitor would no longer bind. One out of ten had a gain of function mutation downstream, turning the BTK back on, and four out of ten had TP53 mutations, which we know,..

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um, even in the presence of using the modern therapies we have still tends to lead to worse outcomes.

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So, what were the results? People responded quickly and the results deepened over time.

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Again, early data. Some patients are on treatment for over a year and a half, and the median has not been resolved, which means that more than...

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half of the patients are still responding. Side effects are quite similar to that that we see with...

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the BTK inhibitors, though there may be less cardiac...

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adverse events. That's a little early to tell. It was well-tolerated.

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And the, so, again, very early data, but the results are promising with rapid and durable responses in difficult-to-treat patients…

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with almost eight out of ten patients responding. Again, overall response rate isn't what the bottom line is for us, but I thought this was encouraging in a difficult group of patients.

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Dr. Kittai, what's your takeaway from this, and any questions you have?

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Yeah, I think definitely encouraging. The BTK degraders are exciting because…

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as we talked about with pirtobrutinib, these drugs should work no matter what mutation mechanism occurs, unless there's some new mutation or resistance mechanism that we haven't identified yet. So, I think that degraders are exciting for that reason and have a unique mechanism of working, and I'm excited to see how they do as they are moved up in earlier lines of therapy.

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Well, I'm going to move on to another, and the reason is that we have two, um, that are in, we have two that are more advanced in the development, and several following, the other…

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is BGB-16673, another degrader, and if you look again, very similar kinds of numbers in terms of prior exposure, high risk,..

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the TP53 here is even higher, the mutation statuses are similar, the PCL-gamma 2 was a little bit higher, another difficult group of patients to treat.

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Again, the adverse events were very similar. People do have adverse events, but they're usually well-tolerated,..

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maybe a little less cardiac adverse events, and again, very strong.

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You can't really compare one overall response rate to another, but again, very strong response rates.

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Eighty-six percent in this difficult, uh, group, difficult to treat a group of patients, and it worked against all the patients, whether they'd had a BTK inhibitor before or they had mutant disease.

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Any thoughts or differences you see between these two degraders, or anything that you wanted to comment on here Dr. Kittai?

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Looks very similar, uh, it looks very similar to the prior one, and so I'm very curious to know how these two get developed in the future, because it's, they both look exciting to me.

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Yeah, I thought they were both great. Uh, rocbrutinib LP-168, this is an interesting one because we've, what it seems to do is…

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work by binding both covalently and non-covalently, like pirtobrutinib binds, and like those first and second generation BTK inhibitors combined. Again, another very difficult…

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group to treat that had multiple prior lines of treatment, multiple...

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mutations, multiple complications and let's look at the results on these patients. The most common side effects were similar to what you see in the BTK inhibitors.

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But there weren't married very much in the way of side effects, maybe a suggestion, a little too early to tell, um, that…

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the heart problems were a little less. Again, generally well-tolerated by patients.

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What's your thought of this unique inhibitor LP-168 seems to have a different mechanism of action of anything else that's out there right now. Any thoughts on it,..

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how it might or might not fit in in the future?

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Yeah, super interesting. Um, you know, as we had alluded to, the problem with the general BTK inhibitors is that…

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when they bind, the CLL can develop a mutation…

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where they bind to make them ineffective. And so, what this one will do is switch back and forth depending on, um, what your resistance mutation might be present. And so, I think from that…

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standpoint, it should work in both patients who have…

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mutations that confer resistance to covalent and non-covalent BTK inhibitors,..

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you know, I think it's super interesting. I think if the side effect profile continues to look great, um, it may be a player as things move up.

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Um, but, you know, it's getting, like, a crowded space, uh, for targeting BTK, so it's a tough, uh, thing to navigate. And I think focusing on side effect profile is going to be key for these new agents coming through because if we can find a…

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better side effect profile drug, um, those are more likely to be moved to earlier lines of therapy based on what we currently have.

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Uh, and here's, uh, I just, uh, a second, uh, a part to this here. We talked a little bit about this, how it binds, this dual action, and the response rates, which look really pretty excellent. Thank you.

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I'm going to talk here about my, um, I'm not saying mine, I say I was privileged to be the lead author on this, the impact of genetic testing, and one of the mantras…

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in, um, CLL Society has been test before treat.

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And this was a study where a large number of patients were looked at, and what we looked at…

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was just before their treatment, if patients were tested for the things that we look for, deletion 17P, TP53 mutation in their IGHV status,..

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because we know that looking at these markers help patients choose their best treatment, avoid treatments that don't work well and predict how their disease will behave. So, they're both what we call predictive and prognostic.

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And what we found is the patients were tested…

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tended to stay on their treatment almost a year longer, had lower risk of progression of their disease…

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and we're more likely to receive the appropriate therapy based on guidelines. In the patients who were not tested,..

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were more likely to start treatment without full information, more likely to get old-school chemotherapy, which has essentially no role in treating CLL, and more concerning had a shorter time before needing their next treatment.

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This is regardless of what the test results showed, whether they showed that you had high-risk disease or low disease.

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Just ordering the test made a difference in terms of how well you did. Um, which is suggesting that this testing is a surrogate marker for the kind of care, getting excellent care.

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Um, so, any thoughts on this? This is a drum that I've been beating for a long time and I just wondered what your take was on this paper here.

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Mine was very similar. I, but that, basically, the, active testing probably is correlated with the physician's familiarity with how to treat CLL and so I think that's what we're seeing here. And also, you know, the test…

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helps us figure out what treatment, in a lot of cases, to give, right? And so, if you don't have the test, you can't really…

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give a great recommendation on what treatment to give, and so I think your conclusions here are spot on.

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Well, thank you, and uh, I think it's time to move on.

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Well, I hope everyone learned something new and useful from, uh,..

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this selection of ASH work. There was certainly a lot to choose from...

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and I learned a lot from it, and I hope everybody else got something about it,..

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from it and learned about it. Dr. Kittai, very clear,..

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helpful explanations of difficult concepts and presenting what I think are important findings.

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I mean, there were several hundred CLL papers. So, I mean, choosing the right ones is always somewhat arbitrary…

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but I thought, um, your, your choices were very important and important because they're going to make a difference, like you said, they're practice changing.

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We're going to try to answer as many questions as we can, and we have almost a full hour to answer questions, which is great.

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But we're not going to get to them all, so if we don't get to them, uh, please, um, you can use other accesses that we have at the CLL Society. We have Ask the Expert.

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You can, and we'll give you that email address afterwards. And so, after the closing slide, you can send that, and please, um, feel free to ask questions and get back to us later. But I'm going to start with some of the questions that people sent in early, um, and, um,..

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and let's go with those, and then we'll go with some of the questions that were presented here, and we'll try to get through them as quickly as we can.

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Let's talk a little bit about this. issue, and I just, and I know that there's not hard answers on this, but I'd like to get your take.

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The controversy about continuous BTKi therapy versus BCL-2, that's, the standard has generally been people start on a BTKi, that's what's happening in the community...

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and then if they relapse, they're going to venetoclax, which is the BCL-2.

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But do you think some of the research may be turning that on its head, that they may be different? How do you, as a CLL expert…

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think about that when a patient comes into you. What are you weighing? I think this is...

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because the reality is, most, at least younger patients, very different with an 80-year-old patient, are going to need more than one therapy.

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So, how do you approach that? What's that discussion like with your patient?

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Yeah, this is the, um, the age-old question with CLL over the last, uh, ten years or so. Um, so I think, you know, if we inherently just look...

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at the efficacy, how well time-limited therapies work, and how well continuous BTK inhibitors work, they look like they work about the same in the frontline setting.

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So that's one thing. The next thing, after we look at efficacy, we typically look at safety, especially if there is a big efficacy difference, we want to make sure that efficacy difference,..

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um, is worth maybe a safety detriment. And in general, the CLL17 study showed us that the safety is about the same, with the concerns that we had always about BTK inhibitors continuously, which is...

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an increased risk of atrial fibrillation. The issue with CLL17 currently is that it was using ibrutinib and not the second-generation BTK inhibitors, and we know that the second-generation BTK inhibitors are safer than ibrutinib and have been widely adopted…

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as our preferred first-line continuous therapy compared to ibrutinib.

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But that being said, you know, looking at this data,..

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I think that besides high-risk disease, which we can talk a little bit about,..

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there's not much of a safety or efficacy reason to pick continuous therapy…

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versus safety. So where does that leave us? How do we help guide our patients? How do we talk about these two regimens?

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How do we choose between the two? First off, it's high-risk disease. I think that's the obvious thing. High-risk disease, I'm defining as somebody who has a deletion 17P or a TP53 aberration…

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or a complex karyotype, and may, maybe, maybe not IGHV unmutated status, depending on who you talk to.

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But if you have high-risk disease, I think all academic doctors will tell you that you should be on a continuous BTK inhibitor as your frontline option, because over and over again we see better outcomes with continuous BTK inhibitors.

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The other thing to consider besides safety, efficacy, and high-risk disease is logistics.

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So, starting a BTK inhibitor is super easy. It's an oral pill, um, I give it to my patients, I advise them of the toxicity to watch out for. I then see them in two weeks, a month later, and then three months later. And 90% of my patients...

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take these meds, tolerate them well, and feel better without having many, much impact on their life.

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Whereas venetoclax plus obinutuzumab or acalabrutinib plus venetoclax, as our option,..

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does require more monitoring when we're starting therapy. So, specifically, the venetoclax plus obinutuzumab patients have to come in weekly for the first two months,..

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uh, to get either their venetoclax ramp up or the obinutuzumab infusion.

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And if they're getting the acalabrutinib plus venetoclax, it's a little bit easier. They get the acalabrutinib for two months but then at the third month, they have to come in weekly for TLS monitoring surrounding the venetoclax.

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And so, in my world, if someone does not have high-risk disease and doesn't have a specific preference,..

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um, it really is based on logistics, and can they come in for those appointments, and do they want to come into those appointments?

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And so, I view this in a very positive light. It gives a lot of options for our patients to choose from.

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And it also makes me feel better that no matter what we pick, the patient is going to have a great outcome,..

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um, as we saw in CLL17.

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And just a follow-up on that, um, uh, because it's great to have these options, what about the option of repeating a limited duration therapy? And the one that is approved in the U.S.…

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is venetoclax and obinutuzumab. Um, the in, second-line therapy, the approved option is venetoclax and rituximab, but I think a lot of experts use venetoclax and obinutuzumab.

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Can you talk about that a little bit, about reusing that in the choice of venetoclax rituximab versus venetoclax obinutuzumab…

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in the relapse setting after patients have done well. How do you make that decision?

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Sure.

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Sure, um, I have something else to add on my prior response, too, I'll get back to that in a second.

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So, if someone's treated with a time-limited venetoclax regimen, um,..

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There are three, two things I look at, um, when they need treatment again.

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So, the first thing I look at is how well do they tolerate that first regimen?

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Did it go really smoothly without having many adverse events? Did the patient tolerate the medication well? And so, if that was the case, checkmark, great, likely to tolerate it again because they already had tolerated it to begin with.

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The next thing I look at is duration of remission. How long from end of treatment until disease progression did the patient have?

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And if the length of remission is short, um,..

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defined as one or two years, then re-treatment with a venetoclax-based regimen likely won't have…

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great outcomes. And so, I typically would switch classes at that point.

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Now, if someone enjoyed a really long remission, certainly retreating with venetoclax, um, I think is totally warranted.

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Um, currently, per the NCCN guidelines,..

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they do recommend the combination of ven obinituzumab versus ven rituximab because there have been multiple studies that have shown that obinutuzumab is superior to rituximab in patients with CLL. So, experts typically will pick obinutuzumab.

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Now, the next question is, um, should you stop after two years of therapy? Because that's how classically ven regimens were studied in the relapse setting. We don't have much data for ven after ven like described…

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but that's where I use MRD as a crux, where patients who have really good responses to the venetoclax regimen in the second line, I am perfectly fine with stopping again. But if they're not having great, deep responses, I might continue that venetoclax…

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as itself, especially if the patient is tolerating it well.

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One thing I just want to add to my original response about picking frontline therapies is that most academic CLL-focused people...

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do favor the venetoclax obinutuzumab or acalabrutinib venetoclax time-limited regimens.

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And the reason that is, is because it's time-limited, and saves resources for both the patient…

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and the hospital, right? So, the patient doesn't have to pay for this expensive drug forever. And then, um, the patient also doesn't have to come into the hospital for these lab checks…

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forever, um, you can maybe space it out for a long time. Um, and the reason why we also favor it is because we are typically just much more familiar and comfortable with the tumor lysis syndrome management.

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Um, and so very frequently, um, for patients, or say, for patients who are seeing Docs who are not academics, not CLL-focused folks,..

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who are interested in time-limited therapy, I will ramp up their venetoclax for them and then hand them back to their local doctor, so that way they don't have to worry about their local doctor's familiarity with the tumor lysis syndrome involved.

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Just one comment, the reason that venetoclax rituximab is approved as a second-line therapy, because that's what was studied.

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But nobody's going to do a study on venetoclax obinituzumab, it's just a better choice, and it can be used, quote, off-label to help patients, and it is a better choice, and I think that's a takeaway.

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Yeah.

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You touched on something there, and there's a number of questions about this, and that's the role of undetectable measurable residual disease.

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So, the language gets thrown out about limit duration versus fixed duration, should uMRD guide it, and I'm hearing you're using uMRD, undetectable measurable residual disease.

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Remind us what that is exactly, and why that might be an important factor in certain cases, where in other cases, it doesn't matter at all.

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Yeah. So, undetectable measurable residual disease is when we cannot detect your CLL using our most modern-day techniques.

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And we can test it either in the peripheral blood or in your bone marrow. However, the...

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concordance between peripheral blood and bone marrow is pretty high, so most of us aren't doing bone marrows on our patients for the MRD testing, we're just using peripheral blood.

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The importance of MRD is that patients who get these deep responses...

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have longer time to next treatment with time-limited therapy.

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And so, there are three scenarios that I consider using MRD.

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One is someone who's getting frontline venetoclax regimens, um, and I will test MRD at the end of treatment, so that's either at cycle 12 with venetoclax plus obinutuzumab...

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or cycle 15 with acalabrutinib plus venetoclax. Um, and I use it just as a way to inform my patients how long I expect them to be in remission.

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Um, it's very rare that somebody does not have a deeper remission after their first line of therapy.

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Um, but it helps me guide them about how long I expect them to be treatment-free. It doesn't necessarily change our management of the patient.

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Now, two scenarios, the two other scenarios that I use it, where it might change management, is A; in that setting I just discussed,..

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uh, using venetoclax in the second line, either after venetoclax or a BTK inhibitor. I will test MRD after treatment's done, and if patients do not have a deep response or remission, I will continue venetoclax as monotherapy.

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That's one way it changes my management. Another way that I haven't used yet, but I do plan on using, I just haven't had the patient come in that fits this bill just yet, because I put patients on clinical trials typicall,..

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is that, um, in younger patients, I do plan on using the combination of acalabrutinib...

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venetoclax obinutuzumab for patients who have high-risk disease who are interested in time-limited therapy.

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And in that scenario, there's a specific regimen where we use what we call MRD-directed therapy, and this is becoming more popular.

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And so what MRD-directed therapy is that MRD is tested at some time point…

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and then a decision of whether to continue therapy is contingent on whether or not MRD is achieved.

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And so, there was a nice study that was put together by Dr. Davids from Dana-Farber, where he used the combination of acal, ven, and obin...

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in patients who had high-risk disease and he tested MRD at cycle 16, and if patients had MRD undetectable disease…

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they were able to stop therapy. And if they did not, they continued therapy for another nine months, and again, MRD was tested with a similar change in therapy paradigm. And so, that's how I might use MRD specifically in high-risk patients…

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who I think could tolerate the triplet, because the triplet can be a little toxic, so that's why I…

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tend to favor younger patients for that regimen.

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The, what I remember with the triplet in that, that data on that triplet was during the COVID pandemic...

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and there was more deaths from infections, because you're taking three drugs that can affect your immune responses, and you already have CLL...

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so it may be a little, uh, different right now.

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Exactly.

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A sophisticated question on the CLL17 trial, um, and I know this is asking you to...

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postulate, which is something experts hate to do, but I'll put you on the spot.

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Do you think this applies? This is a study with ibrutinib. Do you think it applies just as well to acalabrutinib and zanubrutinib and maybe pirtobrutinib…

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um, down the line, or is it specific to ibrutinib?

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So, I think that the efficacy applies. Um, I would be surprised if a second-generation BTK inhibitor worked better in this particular scenario, although I've been wrong about that in the past with the, um, Alpine study, which led to a zanubrutinib efficacy benefit compared to ibrutinib in the second line.

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But I would be, um, I think you can extrapolate this, um, certainly for efficacy.

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I pointed this out during the presentation. I do not think you can extrapolate this in terms of safety. So, in safety, you saw a lot of atrial fibrillation with ibrutinib, which was expected, which we know is decreased with both acalabrutinib and zanubrutinib.

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Now, pirtobrutinib is an entirely different story. So, pirtobrutinib has a different mechanism of action than ibrutinib, acalabrutinib, and zanubrutinib so I don't think we can necessarily extrapolate…

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the data from CLL17 to pirtobrutinib. And what…

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is highlighted by this efficacy, sorry, this, mechanism difference with pirtobrutinib is…

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a study that was performed that we highlighted, um, the pirtobrutinib versus ibrutinib study showed that there was a clear safety benefit in terms of atrial fibrillation and discontinuing the medication for adverse events with pirtobrutinib.

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But interestingly enough, it looks like there might be an efficacy benefit in the front line compared to ibrutinib as well. And so,..

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I think we need more studies, uh, looking at pirtobrutinib and, uh, whether we can extrapolate the data from CLL17 to pirtobrutinib is still a lingering question for sure.

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Well, we could go on on this area forever, but I'll switch to a couple other topics.

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Anything new in CAR-T therapy that you want to discuss, and I'm hoping, elbow, elbow, that you'll talk about in vivo CAR-Ts and maybe touch on that.

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So, um, you highlighted the real-world data, which I was really excited to be a part of,..

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um, and I highlighted during our talk that I think the reason why the real-world data was better was because we were more often using the BTK inhibitors in combination with the liso-cel.

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Um, in terms of future of CAR-T, there's a couple of things playing out. So, for one, the main issue with CAR-T,..

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um, and it's actually not that big of an issue with CLL, is the manufacturing time. It typically takes two to four weeks…

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for the CAR-T cell therapy to be made between them drawing your blood and sending it out to the company. And so that's a big deal when we're talking about aggressive lymphomas,..

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things that, um, move too fast. But in CLL, we can typically get some kind of disease control during that time…

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and what I've been seeing with CAR-T is that there's been new CAR-Ts that are being developed…

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that have a very short manufacturing time, meaning from the time of blood being taken to create the CAR-T until that gets manufactured is just five days.

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So, that's really exciting to see. We're getting very close…

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to it being basically an off-the-shelf product. Um, other things that are exciting in CAR-T is that they are constantly coming up with new targets.

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We are now seeing CD19, CD20 CAR-Ts, CD19-2022 CAR-Ts,..

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those also might lead to better efficacy in CLL. Additionally, as Brian had mentioned, there's two literally off-the-shelf…

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types of CAR-Ts, and what I mean by off-the-shelf is that it's already pre-made. You can kind of just grab it. So, one is what we call, um, allogeneic CAR-T, CAR-Ts coming from somebody else.

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Um, and so those should be able to just give off the shelf to somebody, and they're working out the kinks with that one, too.

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And then, um, as Brian alluded to, we have a lot of these new in vivo T-cell engagers.

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Um, and what it basically is, is it's a vaccine, and so what they're doing is they're giving this CAR-T vaccine, I'm calling it a vaccine, but it's not really a vaccine, it's kind of a vaccine.

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Um, and what it does is it basically programs your own cells to create the CAR-T or bispecific antibody in your own body. Um, so it's really fascinating work. Things are just getting more and more sophisticated, and I'm hopeful that with these advancements…

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we have CAR-Ts that are safer, more efficacious, and we don't have to wait for them to be made.

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Yeah, I'm very excited about this in vivo because it's a quicker, it's just a single shot, it should reduce the costs and sort of democratize it.

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Yeah.

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Um, let's take a step back and remind us…

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about some definitions here, a basic question, what is chemotherapy?

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What is immunotherapy? What is targeted therapy? And I know that they're used a little loosely and there's some overlap, but just explain what those are and maybe what their roles are in CLL now.

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So, in general. We use chemoimmunotherapy exclusively for all lymphomas at this point.

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And the reason that is, is because rituximab and obinutuzumab are both considered immunotherapies.

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So chemotherapy, how chemotherapy works, is it targets…

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fast dividing cells, and all cancer cells are fast dividing cells.

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Um, but you'd imagine that other areas of your body that are fast dividing, like your GI tract…

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can also be affected by chemotherapy. So that's why classic chemotherapy causes a lot of nausea, vomiting, and diarrhea, because you're inside of your GI tract is constantly dividing.

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Immunotherapy, like rituximab and obinutuzumab, are antibodies, so they're immune cells, they're immune agents that we use. And so that's why I say, I know it gets tossed around a lot, but basically everyone with lymphoma is getting treated with chemoimmunotherapy these days because everyone's getting rituximab or obinutuzumab in combination with their chemotherapy.

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The other two main classes of medications are called targeted therapies…

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and then cellular therapy slash T-cell engagers, I'll call them. So, targeted therapies are things like Bruton's tyrosine kinase inhibitors, like ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib, and BCL-2 inhibitors like venetoclax and sonrotoclax, which is likely coming out.

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So, what those drugs do is they target a specific protein that's essential for the cancer to divide.

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Usually have less toxicity than the chemoimmunotherapy does. Last but not least, is the cellular therapies, or the T-cell engagers.

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And so the cellular therapies are agents that activate our own immune system.

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So with CAR-T cell therapy, we're taking patients' T cells...

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and we're manipulating them so that they better attack the cancer, and then we give them back to patients.

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Similarly, bispecific antibodies. are antibodies that…

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attach to T cells and bring them right to the cancer, and then activate the T cells to attack.

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So, these are more cellular therapies because we're using our own cells to attack the cancer.

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Let's focus in on the BTK drugs, um, both the inhibitors and the degraders. And remind us what BTK...

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does. Why blocking it is so important. And there's a question here, and I'm very interested in your answer on this, are some of these side effects, like atrial fibrillation, or the muscle joint pains and things like that,..

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are this because of the role of BTK in normal cells, and how much of it is,..

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in explaining, I'm going to ask you for another step back, what off-target means, you know, when, because some of it isn't because of its effect on BTK, but it also inhibits another enzyme, so it, walk us through that in a patient-friendly way to understand why BTK is important,..

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how pure these drugs are at blocking it, and even when you do just block it, what…

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adverse events could you get?

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Yeah. So, the BTK story is a really interesting one. So, um, BTK stands for Bruton's tyrosine kinase. So, you may ask, who is Bruton? So, Dr. Bruton was actually a pediatrician, and he noticed that males...

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who couldn't fight infections had no antibodies. So basically, these young kids, these young boys,...

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were getting repeat infections and they had no antibodies.

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And so what he did was he was able to tell, based off of genetic studies, that these young boys were missing a protein called...

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BTK. At the time, it wasn't called BTK, he called it and named it BTK, but this lack of BTK led to something called…

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Bruton's agamma globulinemia, which is big scientific word for no antibodies.

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And so, this is when BTK was found to be essential for B cell function. And so, cue in now 70 years later, or 80 years later, um, and we are now dealing with CLL.

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And we've identified CLL as being a B-cell cancer and there were studies that showed that this…

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B-cell cancer upregulated Bruotn's tyrosine kinase showing that it was essential for CLL survival, because it relied on overexpression, overproduction of this specific protein…

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to make sure it divided faster and lived longer than the rest of the cells. So, once they identify that this specific protein was essential for CLL survival,..

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um, smart people, discovered that they can specifically target this Bruton's tyrosine kinase with an inhibitor and so this is where ibrutinib was born. And they found that ibrutinib…

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bound to BTK and made it inactive. And by doing so, basically shut off this survival mechanism for the CLL cells.

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And the CLL cells just then would just die. And so that's how we discovered that BTK inhibitors, because of young boys who had infections,..

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um, were, uh, important for B-cells and CLL survival, so really interesting story.

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Um, so now, whenever we create these inhibitors, these kinase inhibitors, these protein inhibitors, same word, different, um, meaning, but same word,..

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um, we are not perfect at just targeting that protein.

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So there's a lot of overlap in other proteins in our body, because all the proteins in our body, they are, they look similar, but not the same, right?

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And so, therefore, whenever we create one of these inhibitors, we unfortunately not only shut off the BTK protein, but we shut off a number of other proteins in the body.

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And when that happens, unfortunately, we can lead to off-target effects, so that's what off-target effects means.

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Um, and that's what we explain as why ibrutinib likely has more toxicity than acalabrutinib or zanubrutinib or pirtobrutinib. It's because ibrutinib was…

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basically accidentally discovered as a good Bruton's tyrosine kinase inhibitor, um, and unfortunately had all these other kinase effects that were shutting them down,..

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causing and putting people more at risk for atrial fibrillation, bleeding, joint pain, etc. Whereas when acalabrutinib, zanubrutinib, and pirtobrutinib were developed, they had the luxury of ibrutinib's development, they had the luxury of…

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better identifying where in the Bruton's tyrosine kinase might be more specific for that particular kinase.

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And so, they were able to design drugs that had less of those off-target effects.

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And so that's why we see just better toxicity profiles with the Bruton's tyrosine kinase inhibitors that came along later.

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Now, this hypothesis is a great one, and it makes a lot of sense. However, we still see some of that atrial fibrillation with the second degeneration BTK inhibitor, so we didn't make it go away entirel,...

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um, and it's probably because there is other functions of protein tyrosine kinase besides just B-cell function that live in the heart, live in the joints,..

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um, etc. And so, there's really no way to make a pure, um,..

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inhibitor that only targets the CLL's BTK inhibitors, but we can make really good ones that just specifically target BTK without having all those off-target effects. Great question.

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Let's switch to a topic that's this screaming unmet need in CLL Richter's transformation, and where you've dedicated a lot of your research and...

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clinical expertise, um, you talked about, we both talked about some research going on there. Is there anything...

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new or outside of ASH, or that you're working on, or your colleagues are working on...

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that has you excited in terms of Richter's?. Yeah, just give us that sense. Also, somebody asked, how common is Richter's? And I'll throw one more thing at you,..

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NOTCH1, is that something they should worry about if they have NOTCH1? Does that change how you treat a patient, if they have, so tell us what NOTCH1 is, why that's...

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Yeah.

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important for Richter's and what's my risk of getting Richter's? I mean, you're doing such a great job of keeping me alive with CLL that I think all of us in the back of our head are saying, is it going to turn into Richter's? I mean, that's a concern. If we're living longer and longer…

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is Richter's numbers going up? What's happening?

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Yeah. So, um, Richter transformation is when CLL, which is considered an indolent, slow-growing cancer...

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turns into an aggressive cancer, most often diffuse large B-cell lymphoma fast,..

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um, big, big lymph nodes, people don't feel great all the time, requires urgent therapy.

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So, the reason why Richter's transformation remains such a big issue for patients with CLL…

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is that, um, really the big dichotomy between the two diseases, where CLL is known for a slow-growing, patients have a normal life expectancy, but have to get treated periodically, disease…

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whereas diffuse large B-cell lymphoma and Richter transformation significantly can impact someone's life, um, has, you know, associated with poor overall survival and not good therapies.

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Now, one of the reasons why Richter's doesn't act the same as normal diffuse large and is worse is that, in general, as a rule of thumb in cancer, when anything turns into something else, it's never a good sign. And usually what that tells us is that specific patient's cancer is just a more aggressive cancer.

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It's dividing faster and adding on to itself more mutations that make it more resistant and hard to treat over time.

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Now, in terms of risk of Richter transformation, that's something that's...

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actually being re-evaluated. In prior data, it's, like, stuck around 10-15% of patients would get Richter transformation, which is quite high.

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Um, however, we've noticed anecdotally that the risk of Richter transformation appears to be decreasing, um, just by the amount of Richters that we're seeing, um, across our patients with CLL.

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And so, a friend of mine, Dr. Hampel from Mayo, looked at Mayo's experience with Richter transformation over time, and he found that the incidence of Richter's is actually decreasing, at least in the Mayo experience.

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And the hypothesis there is, um, could the prior use of chemotherapy, which we know can lead to mutational changes in the cancer, lead to an increased risk of Richter transformation over time.

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And now that we're predominantly using the BTK inhibitors and the BCL-2 inhibitors, which…

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lead to less mutations, maybe that's the reason why we're seeing less Richter's.

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Um, I'm trying to answer this question in my own studies, and hopefully I'll have more information in about a year from now, but in general, at least per Dr. Hampel's data, the

risk is no longer around 10-15%. It looks more like 1-5% for patients, so that's a nice thing to see.

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Wow, that's a big change.

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Hopefully it plays out, yeah. Um, another worry that we have is that maybe Dr. Hampel and the Mayo data hasn't been following our patients long enough. Maybe we need more time. And maybe what's happening is that the BTK inhibitors and the BCL-2 inhibitors are actually working…

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to treat the Richter's transformation a little bit and just punting the problem down the road.

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Um, I think only time will tell, and we'll see how this happens over time. I think it's a win regardless, um, the longer time that patients don't have to deal with Richter transformation, the better in my book.

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Now, one of the questions that you ask is, what's my personal risk of Richter transformation?

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So, one thing that we found, besides NOTCH1, which I'll get to in a second, um, is that, for the most part, patients…

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develop Richter transformation within one to two years of requiring therapy.

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So, I'm not sure what happens here, but there must be some sort of trigger or just higher likelihood of Richter's…

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when patients turn from watch and wait to needing treatment. Um, during that...

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hard time when therapy starts, typically, the highest risk in Richter's...

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or the time that we find Richter's is within one to two years of starting that new therapy. And it's not because the therapy is inducing Richter's, it's because likely there was underlying Richter's there already that we just didn't identify just yet, okay?

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Um, that's one thing. Number two is the NOTCH1 trisomy 12 CDK2NA/B dilemma.

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So, um, in all cancers. there's this concept of, um, muted genesis over time. Let me explain what this means. So, all cancers rely on the fact that they are dividing faster...

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and living longer than normal cells, okay? And the way that cancer does this is when it divides or a normal cell divides...

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during the replication, there's a mistake that happens, because we're not perfect, our cells are not perfect.

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And one cell brings along with it either too much of the accelerator or not enough of the brake and that mistake is what typically leads…

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to cancer. And so, we found that in a lot of different cancers, there is...

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mutations that code for either accelerators or not enough brakes, um, that we can identify as being...

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associating with the development of that specific cancer. So in patients with CLL, what we've identified, and this is a really small group of patients identified in relapsed CLL,..

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that NOTCH1 combined with trisomy 12, plus-minus that CDKN2A/B, and I'll talk about what these things are in a second, is associated with a higher risk of cancer. I'm sorry, a higher risk of Richter transformation.

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Um, there's no studies out there that suggest that we need to…

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treat patients who have these high-risk features to decrease their risk of Richter's. That's not my approach of it. I think it's…

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that if I see these things, I let my patients know about them and be more concerned with rapidly growing lymph nodes, and it helps me just remember to consider Richter's…

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during that progression event. But there's not so much robust data about specific risk of somebody who carries these specific mutations.

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So, the last thing is, how do we define these mutations? How do we find them? So trisomy 12 we see on FISH testing. So, if you've gotten FISH testing, typically we'll know if you're trisomy 12 or not.

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And by the way, trisomy 12 has to be with the NOTCH1.

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Trisomy 12 by itself is not a high-risk feature for Richter's transformation, and in fact, there's some studies that show that trisomy 12 by itself…

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actually decreases risk of Richter transformation, interestingly enough. And then NOTCH1 and the CDKN2A/B, um, is, done via next generation sequencing, and so, how we test for TP53 mutations, usually that test also includes NOTCH1 and the other one as well. And so, I would say more data is needed about defining specific risk of Richter's in patients with CLL, but certainly for someone who has that trisomy 12 NOTCH1 combination, it's a patient I pay a little bit more attention to.

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So, this wouldn't be a CLL webinar without putting you on the spot to answer this question, and I'm going tothrow a number of things at you.

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But this is a question you hear in your office all the time.

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What can I do? Talk to us about diet.

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Got it.

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Exercise, supplements, people worried is the vitamins feeding the cancer? I'm going to add another twist,..

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probiotics, I'm getting recurrent infections will probiotics help? What can a patient do? And I think what's different now than when I asked this question a few years ago is there's actually some things now that we can do that have shown that may help your CLL.

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Yeah.

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So, um, I'd just like your, put you on the spot and tell you what you tell a patient they can do besides what you're trying to help them with.

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Yeah, you know, this is a difficult question. Um, the answer, unfortunately, is that once you have cancer…

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there is unfortunately not much, things you can do to make the cancer move slower that is within your own power.

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Um, that being said, we do know that patients who are healthier, who go into treatment do better.

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Meaning that, so for instance, um, we know that the BTK inhibitors cause heart issues.

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And so, if before you have to go on therapy, if you've...

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treated yourself well, decreased your cardiac risk enough, you know, your chance of doing better on a BTK inhibitor is higher than somebody who has bad coronary artery disease,..

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congestive heart failure, etc. And so, what I tell my patients is that they should do the no-brainer things, eat a well-balanced diet,..

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um, that is full of non-processed whole foods, um, increase your vegetables intake,..

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um, and stay active, right? The more active we stay, the better our muscles and joints and our ability to tolerate therapy is. And so, those are the kind of no-brainer stuff that, like, doctors have been saying forever, and it's very hard for patients or anybody in society to actually implement.

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And so the healthier you are going into therapy, the generally better you're going to do.

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Now, in terms of specific things, in terms of avoiding infection, is I do recommend all of the vaccines.

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There have been multiple studies now that show that CLL patients, unfortunately, don't respond to the vaccines as well as normal people, but it does help. It does help prevent infections.

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And so, even though our patients with CLL aren't responding as well as they should, they do have a lower risk of infection when they get the vaccines. So, I do recommend a flu shot every year, pneumonia every five years, the shingles shot, the RSV vaccine,..

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as well as, um, the COVID shot as well, every year, or at least whenever a new one comes out.

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Another thing that actually has proven to lead to a longer time in watch and wait is vitamin D supplementation, so I do recommend standard vitamin D supplementation to all of my patients.

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And that's the classic 2,000 units per day, and I tell my patients just to go the cheapest vitamin D they can find.

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Um, there is emerging data about specific diets that have actually improved outcomes in multiple myeloma, and so I do suspect that sometime in the next…

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few years, we might have data regarding lymphoma and CLL in terms of specific diets that might help.

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But, um, until we have that data, it's hard for me to recommend a specific diet. So, I just generally recommend a good, whole Mediterranean food diet to improve heart health, because that's the one that's been shown over and over again, the cardiac studies to lead to better things.

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Um, last is the, um, probiotics. I have no problems with my friend, my friends, my patients, my friends…

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taking probiotics. Um, the only thing that I want you to do is ask your doctor about it, because people do have certain opinions on this. My opinion is that it's fine, especially if you have a normal neutrophil count. So, if for some reason you have a low neutrophil count, probably shouldn't be on probiotics.

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But it's something to talk to your doctor about.

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Thank you, uh, for that. The thing I would add is that there was a, there was a Spanish study that did show that…

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patients who took a Mediterranean diet with their CLL tended to have somewhat better outcome.

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So I, but a Mediterranean diet is what we recommend if you have heart disease, if you have arthritis.

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Yeah.

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If you have diabetes, whatever you have, you should be on a plant-forward Mediterranean diet.

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Yeah. Yeah. And one of the issues with the vitamin D and probably that study as well, is,..

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the question is, it's not necessarily, it may not necessarily be the diet itself, it may be the access to the diet, and the ability to comply with the diet, right? Because unfortunately, um, you know, some people just can't afford to abide by a Mediterranean diet or that vitamin D over-the-counter, right?

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It's something to think about.

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You know, throw a couple quick ones at you, because we only have a few minutes left, and I'm not going to get to them all. Uh, what does fit versus unfit mean? What does that mean to a clinician?

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Uh, you ask ten of us that question, we'll give you ten different answers, but the classic,..

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um, so we, so when you say fit on fit, there's actually a, um, uh, calculation,..

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so, it's called the SERS criteria. It's a comorbidity criteria, and basically what it does is…

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it, um, adds up all of your comorbidities, and based off if you have, um, you know, severe comorbidity or not, that's how we kind of determine fit unfit.

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And so, uh, in the trials that accrued more unfit patients, um, or specifically was designed for unfit patients, it was a specific, um, calculation that was performed.

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Um, so that's how they did it in the trials.

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Um, SLL and CLL are the same disease, different stages...

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but a lot of the trials, is there any data that's different on them, trials that are different? Anything, uh, I've had some friends who were very frustrated because they had…

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SLL and couldn't get into a CLL trial. Can you talk a little bit about that and different outcomes?

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Um, that's been, uh, thrown to the wayside at this point. Um, all CLL trials allow for enrollment of SLL. There might be some weird, quirky thing about the trial where you have to have measurable disease in some weird way, but for the most part, CLL and SLL are considered identical diseases.

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The only difference that I do for my patients for SLL is, so if I have a patient with SLL, I might get a CT scan more frequently, whereas I don't typically get CT scans for patients with CLL, and that's just typically for patients with SLL who I can't palpate their lymph nodes.

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So, let's say their lymph nodes are more intra-abdominal, and I want to get a better assessment of how fast they're growing, I might do a yearly CT scan or something like that.

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This will be the last question before I ask you to kind of review things, but one class of drugs we have not talked about and that seem to have disappeared, but maybe resurfacing are PI3 kinase inhibitors.

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And there's one, and I'm going to macerate its name,..

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roginolisib, which is in studies now. Do you know anything about this? And what are the roles of PI3K, and do you think there's a future for them…

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to be more used? They're still being used, duvelisib and idelalisib, but talk to us about that set of drugs.

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I haven't used a PI3 kinase inhibitor since I became an independent practitioner, so at least seven years. We did use them while I was in fellowship, ah very periodically, but we've largely abandoned them as being drugs that we're typically using.

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And the reason that is, is because of the autoimmune side effects that are associated with them, and now that we have the development of pirtobrutinib and the degraders,..

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they're going to become less and less likely to be used.

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Um, uh, the new PI3K inhibitor that I know that you just mentioned, that I can't pronounce either, um, it is being actively studied in a clinical trial in Dana-Farber, but I don't know much about it beyond that.

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So, this is your chance to talk to the community, um,..

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about what's important for them, what's the takeaway message, anything that you want to get across...

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in a couple minutes here, that you want to make sure that patients walk away, if they're seeing their clinician next, what's an important takeaway for them?

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So, for one, it's something I alluded to but didn't mention.

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Um, a slide that I like to include in all of my presentations these days is ..a.

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study that was done by Dr. Ghia and colleagues, and what they did was they took all of the patients who enrolled into the original ibrutinib studies...

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and they compared them to age-matched controls, and took a look to see how long they lived for.

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And what they found was that these patients lived as long as age-match controls.

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Meaning they had a normal life expectancy. And so, the reason why I like to bring this up is because I think this is a really powerful thing for patients to know about, that with good…

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CLL treatment, um, I can honestly tell my patients that I can expect that they will have a normal life expectancy.

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Um, that being said, cancer is cancer, right? And we need to watch out for these patients.

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We need to monitor them closely to make sure that they're getting the best care that they can get, and sometimes cancer can do funny things that we can't predict.

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But I do like to show that particular slide, because I give, I think it gives, um, a lot of people hope and understanding of how far we've come with our treatments.

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Um, on that same vein, and this is based off the CLL17 study, is that, um,..

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I think I can honestly say that it doesn't matter what you get treated with, um, at this point.

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Um, that as long as you're getting modern-day CLL therapy, you're likely to have a really good outcome, as these drugs really are very powerful.

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And additionally, with the rate of which research is being done to develop new medications is still really exciting. And what we have in just two years from now may be very different than what we're doing today. So overall, it's a really exciting time for CLL, which really has led to a great benefit for our patients…

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leading to, um, longer survival and better and safer options.

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What I like to say to people is there's never a good time to be diagnosed with CLL, but there's never been a better time than today, except maybe tomorrow. And even at this ASH, there was a study that showed…

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whatever decade you're born in, the later your, or when your CLL presents, the better you do.

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The treatments now are better than the treatments ten years ago, which are better than the treatments than ten years ago, which are better than the treatments ten years ago.

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So, the treatments just keep getting better and better, so there's a lot to be optimistic about in CLL, but I'm still pushing, we're still the cure,..

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were on the cusp of the cure, but we're not there yet, so that's what we're still pushing for.

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I'd like to thank our generous donors and grant support for making this event possible.

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And I want to thank everyone for attending and sending in the great questions and apologize for the ones we didn't get to. Dr. Kittai,..

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you were great. This was really very worthwhile, and I think going into the deeper answers were…

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very helpful. Um, this event was recorded, and it will be available on the website soon,..

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um, along with the slides and other, uh, resources for you, um, so take a look for that, uh, there'll be a written transcript of it.

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Um, again, if we didn't get to your questions, uh, please send it to asktheexpert@cllsociociety.org. You can see that on the slide there. Asktheexpert@at cllsociety.org.

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Um, in, coming up, we have, um,..

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our friend and colleague, Dr. Ryan Jacobs, who's another CLL expert, and this is a very much more...

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free-flowing kind of event. It's just the Q&A section. All things go, any questions, um, and...

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please attend that. Doreen Zetterland is an experienced CLL/SLL patient…

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and she'll be leading this and Doreen always does a great job of, uh, moderating this.

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Please remember the CLL Society. We're invested in your long life. Invest in our long life by helping support us.

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Uh, and in, I always close with stay strong, we're all in this together.

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Thank you so much for attending.