Webinar Transcript
Next-Generation CLL Treatments: Understanding Clinical Trials and Future Therapeutic Strategies
July 16, 2025

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

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Hello, and welcome to today's webinar. I am Robyn Brumble, a registered nurse and the CLL Society's Director of Scientific Affairs and Research.

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At the CLL Society, 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 support from both our donors and our industry partners.

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At this time, I would like to introduce our moderator. Thank you.

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

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I am Terry Evans, a 25-year CLL survivor and Director of the CLL Society's Support Network.

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We are joined by our speaker, Dr. Jennifer Brown, Director of the CLL Center…

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of the Division of Hematologic Malignancies at Dana-Farber Cancer Institute and the Worthington and Margaret Collette Professor...

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of Medicine in the Field of Hematologic Oncology at Harvard Medical School in Boston, Massachusetts.

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We will be answering audience questions at the end of this 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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Before we begin, I'd like to share a few important disclaimers. The information provided during today's webinar…

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is for educational purposes only, and should not be considered medical advice.

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

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Please note that whilst the CLL Society may have its own opinions and policies,..

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

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Now, it is my pleasure to welcome Dr. Jennifer Brown.

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Hello, everyone. I'm Jennifer Brown from the Dana-Farber Cancer Institute and today, I'll be speaking about next-generation CLL treatment,..

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understanding clinical trials and future therapeutic strategies. So, we'll just begin by asking, what is a clinical trial?

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So, it's a formal investigation of a therapy that's relatively new to the disease being studied.

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This could be a brand new drug that's never been used in humans before,..

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it could be a drug that's been previously studied, or even FDA approved, in a different disease, that now we want to study in a new disease.

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It could be a new combination of drugs, including a new combination of FDA-approved drugs...

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or it could be a drug or combination previously studied in this disease for which more data are required.

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The outcomes vary. They could include establishing the dose of the drug,..

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establishing the safety of the drug, establishing the effectiveness, which we usually measure by either response rate or duration of response,..

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and then patient-reported outcomes. So, many clinical trials now include patient-reported outcomes, and these are validated questionnaires that we ask participants to fill out;..

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describing how you're feeling, any side effects you may be having with the treatment or the disease, and then we monitor how that changes over time.

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An improvement in those symptoms, obviously, is a desired goal of the therapy.

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So, clinical trials come in phases. Phase 0 trials are often first in human trials, a brand new drug, with 10 to 15 people, to see how a drug is processed in the body...

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and what its effects are. And these are usually people who don't have a disease, they're volunteers who...

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are healthy. Phase 1 trials find the best dose of a new drug with the fewest side effects...

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for a patient population for which the drug will be developed. And this is often also a small study of 15 to 30 patients. And the endpoint of Phase 1 is usually to test safety.

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Although, these days in CLL, most of our Phase 1 trials are drugs that we are expecting to have significant…

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potential benefit for the participants, because we know what good targets are.

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We have a lot of exciting drugs. I would also note that nowadays,...

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if one of the Phase 1 drugs looks very exciting, the trial often gets expanded very extensively, so there may be hundreds of people on a Phase 1 trial, and then they often skip Phase 2 and go right to Phase 3, which is the registration phase.

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Phase 2 trials are designed to better assess safety, as well as starting to assess whether the drug works.

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And there, these trials are often amongst patients with a specific type of cancer and in a larger group of patients.

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And again, new combinations of drugs may be tested here. But a new combination could also start with Phase 1 to make sure that the doses are safe together, and then get expanded into a Phase 2.

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Phase 3 trials compare a new drug to the standard of care and typically enroll 100 or more patients.

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There can be more than two groups in Phase 3 trials, and these trials are often randomized. That means you don't get to pick...

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and your doctor doesn't get to pick what your treatment will be.

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The computer picks, based on certain features of your disease compared to features of disease of everyone else that need to be spread evenly across the trial.

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And these Phase 3 trials are usually needed for FDA approval of a new drug.

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And then finally, Phase 4 trials test drugs approved by the FDA. And this may be in several hundreds or thousands of patients, and these can be used as a way to provide an effective drug to people before it's readily available.

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You can see at the bottom the schematic of drug discovery, from discovery and preclinical…

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to Phase 1, Phase 2, Phase 3, and then FDA approval.

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You can find out about clinical trials at this website, www.clinicaltrials.gov. It's a U.S.-based website that requires companies and investigators to post information about clinical trials in a public forum.

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And all U.S. trials should be posted within about three weeks of when the sponsor, which is often the pharmaceutical company,..

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or the investigator, who can also be the sponsor, plans to start dosing…

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the first patient or subject. And it's pretty easy to navigate…

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by listing, by topic, by disease, by geography or specific search details.

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So, what are the pros and cons of a clinical trial?

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So, the pros are that you get access to new therapies or combinations in development.

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You'll also get extra attention, because there is typically extra staff dedicated to trial participants.

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The drug may be provided free of charge. Although, if it's a combination trial, sometimes one drug will be free and the other will not be.

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We know from clinical trials, themselves, that patients do better when in trials and that's likely because they have more expert care and closer supervision. But it may also be because of the drugs that are available in trials.

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And then you also contribute to new knowledge and help others coming after you with CLL.

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Cons include that there are, there's a high likelihood that you'll have to go into the...

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treatment center more often, that there'll be more visits; the treatment's not going to be as established.

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There's a possibility of extra costs for traveler visits. It's quite likely that CT scans will be more frequent than in standard of care.

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And then some Phase 3 trials have a less strong control arm.

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And this is often because of what is perceived to be the standard against which a new drug has to be tested...

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may not really be as effective anymore. We may have moved beyond it somewhat.

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This can be mitigated if you can crossover from that control arm onto the investigation arm but some studies don't always allow crossover.

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This gets to a principle that we call equipoise. And that means that if you.

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Are going to do a randomized trial, you should believe that both arms of the randomized trial...

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are equivalent, and offer potentially similar benefits to your patients. Namely, you don't know which one's better...

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and that's why you're doing the randomized trial. And so that's what we always hope for but unfortunately, FDA requirements sometimes...

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mean that this is not as true as it could be.

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Although, again, these days, the control arms are also usually highly effective therapies.

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So, what questions should you ask if you're considering a clinical trial?

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So, there's kind of a long list of them, but these are also questions you should think about if you're considering any treatment.

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So, what are the drugs being studied, and why is the trial being done?

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What is the treatment or visit schedule? How many scans and bone marrow biopsies are required, and when are they?

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Would the drugs be supplied by the trial? That means the drugs are free. If they're not supplied by the trial, then they go through your insurance.

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Will my insurance cover the treatment and other related costs? Now, in some states, insurance is required to cover the standard of care parts of clinical trials. That's the case in Massachusetts, where I am, for example.

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But this isn't necessarily true in all states. We always do a pre-screen for whether patients will have coverage for the trial from their insurance.

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How long is the trial? How well have the drugs been working, and what are the side effects so far?

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Well, I know the results of the trial once completed, or can I find them out?

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And then what treatment would you suggest if I did not go on this trial?

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And then, in that case, you have to ask a lot of other questions, too. What are the drugs? What's the schedule -..

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scans, bone marrows, etc. So, it's a lot to think about, but obviously it's important.

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So, before we talk about some of the new treatments that are in clinical trials, I just wanted to outline a bit of…

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the shape of basic CLL therapy right now. So, there's really two main key options for CLL therapy right now. So one is…

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what we call the covalent BTK inhibitors. And you may have heard of this as acalabrutinib, zanubrutinib…

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or ibrutinib. In the US, we use much less ibrutinib now...

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because acalabrutinib and zanubrutinib have both been shown in head-to-head trials…

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to be safer. And zanubrutinib has also been shown in head-to-head trial to be more effective. Acalabrutinib was equally effective in head-to-head trial.

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So, this is why we don't use ibrutinib anymore. And then, the other key therapy frontline, is venetoclax-based, usually with an obinutuzumab. So, in frontline, venetoclax with obinutuzumab for a year…

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whereas the BTK inhibitors would be given continuously. And so, if you're on a BTK inhibitor that you're on continuously, and your disease comes back,..

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then you usually go to venetoclax-based treatment, because we know that venetoclax-based treatment works best in that setting.

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Alternatively, if you start with venetoclax obinutuzumab, you can potentially do it again if you have a long remission…

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before switching to BTK inhibitor-based treatment. This principle guides...

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some of the idea of what we call time-limited therapy. You do multiple drugs for a shorter time, and then you stop.

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And that has the potential advantage of avoiding the development of resistance,..

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avoiding prolonged side effects and costs and then also allowing that you can potentially redo that option later.

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So I think the field is shifting significantly toward these time-limited options, and this was really somewhat palpable at the European Hematology Association meeting…

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this year, with some of the new data, with acalabrutinib venetoclax...

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with or without obinutuzumab, as well as with ibrutinib venetoclax with or with obinutuzumab.

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And so, that's where we're seeing the increasing interest in a combination of a BTK inhibitor, like acalabrutinib or zanubrutinib, with a BCL-2 inhibitor...

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which is venetoclax. And then, we were also seeing emerging evidence that for some patients, especially those with higher risk disease,..

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what we call unmutated IGHV for the aficionados, three drugs may sometimes be more effective than two drugs.

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Now, this has to be weighed against the fact that three drugs usually have more side effects than two drugs.

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So, for example, in a recent study, where we found that acalabrutinib and venetoclax were effective,..

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we found that adding obinutuzumab was even more effective, probably, especially for the higher-risk patients. But it did add some increased risk of low blood counts and infection.

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And so that has to be balanced with what other medical problems you have, and how well you can potentially tolerate this.

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We are hoping for FDA approval soon for that combination. We also heard at the spring meetings this year about…

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zanubrutinib and a new BCL-2 inhibitor called sonrotoclax. And that one.

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in the test tube is more potent than venetoclax. That combination has completed accrual to a registration trial, but we don't know when it'll read out yet. It's probably still going to be a couple of years.

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Another exciting piece of data at the European Hematology Association, which has already been published in the New England Journal of Medicine, is that ibrutinib and venetoclax showed efficacy better than ibrutinib alone...

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when the duration of therapy was guided by measurements of residual disease.

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So I think this is an extremely important finding, because this is the first time that we've actually shown that the time-limited therapy is better than the continuous therapy...

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in a head-to-head trial. And I'm going to explain a little bit what it means to have these measurements of residual disease guiding therapy in the next few slides.

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And then similarly, a German trial, at the European Hematology Association, showed us that the three drugs, ibrutinib, venetoclax and obinutuzumab...

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were also more effective than the two drugs, venetoclax and obinutuzumab, again, in that unmutated higher-risk subgroup.

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And so, all these emerging data are converging on the idea that the BTK, BCL-2 plus obinutuzumab...

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may be our most potent regimens.

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So, what is measurable residual disease, or minimal residual disease? So, we start with a tube of blood or.

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some bone marrow. That's shown on the left. And then, for CLL, we usually use the cells, those are in that buffy coat part,..

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and then you can, you can see to the right, there's a...

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little picture showing the CLL cells coming out of the buffy coat part.

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And so, there's a choice of two ways that we usually do this now.

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The way we've usually done it in the past is with so-called flow cytometry. That's the same test that we use to diagnose CLL.

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Like, if a white count, if your white count's elevated, we use the flow cytometry to tell us that it looks like CLL.

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Well, so, this is a much fancier version that can detect 1 in 10,000 to 1 in 100,000 cells...

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and that's sort of been the standard historically. But it turns out that in the U.S, a method of sequencing,..

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it's called NGS, that stands for Next Generation Sequencing, and this has been sponsored by a company called Adaptive, and they actually have used this method to find up to one in a million CLL cells that could be left.

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And the method's called ClonoSEQ and it's becoming increasingly used in the U.S. because the FDA has sanctioned it for potential decision-making on clinical trials.

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It is more sensitive than the flow cytometry. But in practice, it seems that we only need to get to about 1 in 100,000 cells.

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Whether one in a million is better than one in 100,000 is sort of unclear.

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It's also hard to achieve because we need to have several million cells to be able to reach that sensitivity, and that's often not available.

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So, this is sort of a schematic of how we might think about treatment,..

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how deep we get the response, and then when the disease comes back.

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See, if you start on the left, at the top, you can see there's relapse. And then there are various lines going down that show how effective the disease is. So, the blue line at the top means that we didn't really get rid of all the disease.

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We still see some persisting. The orange line is better, but then that's still a relatively early relapse.

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The green line goes down further, that one gets below our magic number of 1 in 10,000 cells…

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and that leads to a much later relapse. But the idea is, if you can get down even further, down to that one in a million in the black line,..

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that then there'll be a very, very late relapse. Or maybe, if you can get down even further,..

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we don't know how far is required, and there's no disease detection, maybe...

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we can get to relapse or get to no relapse or cure.

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So, the idea is the lower level of residual disease is generally associated with a longer time to progression, and that makes it less likely...

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that there will be relapse. And so that's why, especially with these time-limited regimens, where we stop the treatment.

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Getting a deeper level of remission is important. Now, I should note that if you're taking just a single-agent BTK inhibitor,..

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this doesn't matter so much, because we know that the disease is still going to be there.

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Those drugs don't really get rid of it. But as long as you take the drug...

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the drug keeps the disease at bay. It keeps it inhibited, so it doesn't grow. It becomes very quiescent.

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And that's part of how those drugs are so effective, particularly in the highest risk disease…

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which tends to like to grow back quickly, even from very deep levels of remission.

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So, I just wanted to show you two clinical trials that have MRD-guided decision points, two different ways that this has been done.

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This is the Majic trial, which many of you may have heard of. It completed its accrual about 15 months ago, but it's going to be a little while until we get data.

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But this is comparing the BTK inhibitor acalabrutinib with venetoclax…

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to venetoclax with obinutuzumab. And basically, they treat for…

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12 cycles of combination, which that's 14 total cycles with the acala-ven, when you do a lead-in with acala...

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but it's only 12 cycles for ven-obinu. And then you get an MRD evaluation...

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and this one used the ClonoSEQ test, so that's that sequencing test,..

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and the cutoff was 10 to the minus 5.

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So, if there were, no cells detectable at a cutoff of 1 in 100,000, you could stop after a year.

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But if there were still some cells detectable at that cutoff, .

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then you continued on the acala-ven for another year...

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or ven-acala, for the ven+ O for another year. And in this trial, everybody stopped at two years.

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So, this is sort of the simplest example of an MRD-guided approach. There's just one decision point…

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and then, you either stop, or you do a certain amount of extra therapy and stop, regardless of…

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the MRD test. And again, we don't know how, what the results of this look like yet.

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And then this is the most complicated one. This is the one that was reported at the European Hematology Association.

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So, in this one, they started treatment with ibrutinib venetoclax. And they started measuring MRD by Flow every six months.

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And so, once the so-called undetectable MRD was detected, which is using, again, that 1 in 10,000 cutoff, which is really the most standard cutoff,..

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they would repeat it, and then they would do a bone marrow. And if all of those were negative,..

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you were declared officially MRD negative and the duration of your treatment would be…

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twice as long as it took to reach that. So, if you got to MRD negativity at six months, you could stop at 12.

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If you got to MRD negativity at 12 months, you could stop at 24 months.

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But if you didn't get to MRD negativity until 18 months, you had to go to 36 months.

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So as you might imagine, this trial treated people for a lot longer. Instead of a one versus two year time frame, most patients…

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got two to three years, and some are even still on at four years.

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This is also much more complicated, because the MRD test has to be done every six months.

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This is also the one that showed the benefit of this combination compared to the continuous single agent, ibrutinib.

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So, I think one of our tasks going forward in the next few years is going to figure out,.

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figuring out, can we sustain the benefit of this intensive approach..

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with a simpler approach, like we saw in Majic? And we don't really know that yet, because we haven't had any other head-to-head data of the continuous treatment versus the...

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time-limited one. Okay, so what are some of the exciting new drugs coming out there?

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So, just to remind you about BTK inhibitors. So, we said earlier that covalent BTK inhibitors are a mainstay of therapy, and those guys are shown in the orange here. You can see the orange is attached to the green BTK with a black line.

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It's a C481. That's a particular place in the BTK that the orange covalent inhibitor binds to permanently…

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so it permanently inactivates BTK when it binds. And again, those are the ibrutinib, acalabrutinib, and zanubrutinib…

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do that. Now, we have a new drug, relatively new. It was approved in the United States about a year and a half ago…

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which is actually non-covalent, or reversible. So that means it just kind of sits on BTK.

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It doesn't get hooked up with that tether permanently. I would note that most of the drugs that we have do this. They just sort of associate with what they're inhibiting. They don't get permanently tethered to it.

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But, so you can see in blue, the pirtobrutinib is sitting on the BTK.

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And it's also very effective. But what about, if the covalent inhibitors in orange stop working…

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and then you get the blue inhibitor, and that one stops working?

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So that's what we're studying now. And so here, instead of inhibiting that BTK,..

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we get rid of it completely. So, this is a new kind of drug. There are not, to my knowledge, any of them FDA approved yet.

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The ones that target BTK are kind of in the lead, which is exciting. We have two that are pretty advanced in their clinical trials.

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And so, the way this works is, you can see the BTK in green,..

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and this thing in orange is a normal cellular system that gets rid of old,..

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old proteins. It just helps recycle the detritus of the cell, so to speak.

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So, this degrader molecule that we're studying. It's like a linker, and so it has the orange hookup that pulls in that cellular…

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machinery that just gets rid of all the garbage to the BTK...

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in green. And so, you can see on the right there, they're hooked up.

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And then the orange results in the BTK getting that long string of Ub and blue on it…

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and that triggers it for destruction by this purple thing called the proteasome.

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And so, what's really good about this degrader linker is that it can work repeatedly. It can destroy many, many BTK molecules.

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So, it looks like from the two trials that we have so far, this is very, very effective at degrading BTK.

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And then it doesn't matter what mutations BTK may have acquired in the course of prior rounds of therapy, because…

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the degraders, as far as we know so far, seem to be effective against most of those mutations.

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So, this is a very exciting new class of drugs to keep an eye on.

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Then, there's also immune therapies that are interesting. So, bispecific antibodies have been approved in other kinds of lymphomas for a few years now…

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and they're pretty exciting. They have been a little bit slower in CLL because we know that people with CLL tend to have a bit stronger reactions to these kinds of antibodies.

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And so, the trials have had to require that people be admitted to the hospital for multiple doses for monitoring and such like.

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But epcoritamab on the left, is the one that's most advanced, and we've seen some nice data that that can work very well in CLL that's had many prior therapies.

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And there's also data for Richter's transformation that it can also work in Richter's transformation.

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And so the idea of it is, normally, antibodies like obinutuzumab,..

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they just have the CD20. You can see there it's circled in the blue box. It says attacks CLL cells.

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So that's what normal antibodies like obinutuzumab have. But these bispecific ones have another section in blue on the left,..

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Cd3, it says. That pulls in the T cells. So, the T cells get brought directly to the CLL cells, so that they're right there and they can kill them.

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And so, that appears to be quite effective. It does cause somewhat more reactions than we see with the regular monoclonal antibodies, but that's just a matter of figuring out the dosing and the schedule, which we're all working on.

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And then you're probably all very excited about CAR-T cells. So, what about CAR-T cells?

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So, CAR stands for chimeric antigen receptor. And if you have a look over there at the box on the right,..

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these are engineered in the lab, and they have, on the outside, they have a section of antibody that will bind to the CLL cells or bind to whatever the target is.

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And generally, the ones that we have now are, again, CD19,..

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which is a B-cell target and binds to CLL. Then they cross into the cell across that double orange…

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line. And then inside the cell, they have a variety of sections that stimulate the cell,..

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stimulate the T cell, because this is not a T cell.

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And so, what these do is they go into the body,..

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they bind to the CLL cell, and it's a T cell right there, and it just kill, can kill the CLL cell.

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So how do we make them? That's shown on the left. So, the first thing that happens is you get hooked-up to a machine. It's somewhat similar to,..

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the way that you donate platelets, for example, takes, you know, a few hours to collect the cells, T cells…

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from your body. And then they get sent to the lab, where...

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they will have the, what you see on the right,..

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we call it a molecule or the chimeric antigen receptor will be put into the cells in the lab.

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And then that will be expressed, and the cells will be expanded. And then that's when they get re-infused…

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into you. I usually, there's chemo given before that happens, which is to sort of make room for the new T cells.

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And then the initial monitoring, there's, again, this has even greater potential for what we call cytokine release syndrome than the bispecific antibodies.

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So that's something that needs to be monitored closely. It can also cause neurologic side effects that need to be monitored closely.

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And then over time, there can be delayed low blood counts and infections as well. So, it's not trivial.

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At the moment, we're not seeing quite the same effectiveness as we are in other lymphomas.

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For CAR-T, and I think this has to do with the immune dysfunction that we know…

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is present in CLL. People are working on that. There's some evidence that maybe giving a BTK inhibitor first…

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can help restore some of that immune dysfunction. So, that's what we're working on.

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And this is just an example of some of the CD19 CAR-T cells that are out there. The only one approved for CLL is in the blue box. That's called Liso-cel.

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And the one thing that's sort of interesting about it that...

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is most distinct from the others, I would say, is that when it was developed, they decided to take an even ratio of the two major kinds of T cells.

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With the other CAR-Ts, you just get whatever the T cells are that come out of the process, and it could be a mix, and it could vary a lot from patient to patient.

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But for this one, when they developed it, they decided they were going to take…

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a similar ratio of the two types of T cells, and that's what it says on the bottom. Define ratio of CD4 to CD8.

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And this is the one that's approved for CLL. So, what other hot topics are there in clinical trials right now?

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So, as you probably gathered from what I said before, combination therapy, and preferably MRD-guided patient-specific combination therapy, is a hot topic.

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There's interest in time-limited BTK inhibitor therapy, and this could be based potentially on doing combination therapy from the beginning, certainly with venetoclax we know that'll work.

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With obinutuzumab, we don't see the same high rates of undetectable MRD, and so…

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we need to do these trials to figure out how long…

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the benefit will last from those combinations if we stop. And then there's the potential, for example, to do some treatment with the BTK inhibitor up front, and then do what we call consolidation, and potentially stop the BTK inhibitor.

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This can be done with venetoclax now potentially, and we have some data on that.

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I'm pretty excited about a clinical trial we're going to be doing, where we're going to use a bispecific antibody, the one called mosunetuzumab...

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to do that. There are novel drugs with new targets. I'm particularly interested right now in MEK inhibition,..

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that's just a kinase that's actually been studied more in solid tumors, but we have evidence that after…

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the diseases come back after BTK and BCL-2 would get activation of that pathway.

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And some other targets of interest are MALT1 and something called protein kinase C beta.

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And then, infection control remains, you know, a major issue. I have seen more interest recently in novel IgG products…

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and interest in developing them in CLL, so I think that's exciting.

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And then finally, the question of early intervention, and how do we define the benefits of early intervention? The IWCLL is actually coming out with a position paper on this.

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And, you know, one of the goals, I think, that we're all interested in is immune reconstitution, avoiding infections, avoiding second malignancies, in addition to…

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disease control. But we know that for, even for people who don't need treatment,..

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the issues of infections and second cancers remain a significant issue.

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So, in summary, clinical trials represent an excellent opportunity to access novel drugs or combinations that may soon become the standard of care.

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And even if they don't become the standard of care, they add to the armamentarium of treatments that are available for your individual care.

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This is what I often say to patients. You know, we have a couple of FDA-approved treatments we can use in different combinations, but if you use them all up at the beginning...

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then you might need something, and there might not be something available in a trial.

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Whereas if we mix in trials that are available that are good along the way, we can save some of those FDA-approved combinations for later, in case there's no trial available at a particular point when you need it.

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Research and clinical care is trending toward time-limited therapies and likely more individualized MRD-guided therapies.

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New drugs on the horizon include BTK degraders, bispecific antibodies, novel chimeric antigen receptors and novel targets.

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It's exciting times in CLL research. The advances continue rapidly. I look forward to the Q&A session, too.

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Further elaborate on these topics. Thank you for your attention.

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All right, thank you, Dr. Brown, for the presentation that you just gave us.

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On, uh, clinical trials. And, uh, to get into the,..

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there we go. To get into the Q&A session, we had quite a few submitted beforehand, and we had…

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uh, now we're up to 54 questions submitted, uh, since you started the presentation.

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Um, the first question I have is that: we know that not every patient has access to clinical trials,..

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um, just because of where they go for treatment, or what their particular...

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medical coverage is, but how would you encourage patients to...

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um, get to a place where at least clinical trials are offered to them?

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Yeah, well, it's generally a good idea, and I think the CLL Society encourages this, that people do consult with a CLL specialist if they can, and there are CLL specialists all over the country, and it may not be feasible for you to get your…

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longitudinal care there regularly, but you can consult at sort of key points in...

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the disease, like, a diagnosis, or if treatment is required, or new treatment and that way,..

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you can both get your prognostic test looked at, you can find out what clinical trials are going on, and where they're going on, and also what the…

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sort of benefit, potential benefit of going extra effort to try and seek out a trial is, in your particular case, compared to standard of care.

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And hopefully that's something that many people can do if we're just talking about…

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consultation occasionally, and not necessarily constant care.

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Right, they don't, the CLL expert doesn't have to be your, necessarily your primary doctor, but at least you can bounce…

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ideas off of them, and if you're heading for treatment, you can say,..

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you know, do you agree with this approach, or are there other things...

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I should consider? So, okay, um.

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In your practice, do you recommend, or do you offer clinical trials to treatment-naive patients that are heading for treatment for the first time?

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Yeah, in my practice, we try to have clinical trials for all phases of the disease, and so certainly that includes time of first treatment. You know, people who don't yet meet criteria for treatment, and remember, obviously,..

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we usually don't treat CLL patients right at diagnosis, many people are diagnosed when they're asymptomatic and have a,..

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you know, relatively little disease, and so, heading for treatment means that white count is steadily rising, the normal blood counts may be dropping, so you may be becoming anemic, or the platelets may be dropping, or lymph nodes may be getting large, that sort of.

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time frame. So, when people are on the watch and wait, or watch and worry early phase, we tend to have fewer trials in that space, although there's still interest.

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We haven't actually been able to show a benefit to early treatment in that setting so far. And so that's part of the reason there is,..

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there are not as many options at that phase. There is a national trial led by the Southwest Oncology Group, which is going on right now for, again, higher-risk patients, which is based on a number of different features, which include P53 or 17P deletion, unmutated IGHV, some tumor markers, etc., and so,..

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for higher risk patients, there may be some options for treatment prior to when treatment is actually required,..

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which is investigational. But then, at least from the time when treatment is required, we always try to have the trial open. Sometimes there are gaps if you accrue quicker, or it's taking longer to get something open, but we do generally try to.

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Uh, in your slide presentation, you mentioned high-risk patients multiple times.

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And there were a number of questions in the, in the Q&A about what defines a high-risk patient, and maybe you've just mentioned some of those, but maybe you could…

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define that a little bit for everybody?

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Right. You know, historically, we always really just defined it as 17P deletion or P53 aberration.

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So remember, 17P, that's one of the chromosomes, the short arm of chromosome 17, and if that's deleted, you lose a copy of this gene P53.

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And it's pretty common when that's deleted that there's also a mutation affecting the same gene on the other chromosome, so that both of those copies,..

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they're lost. And so that's really what we mean by highest risk disease. Now, there have been.

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various efforts in more recent years to call higher-risk disease...

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more broadly. And so, then the next major category where we would say potentially higher versus lower risk, but not as high risk as 17P, relates to the IGHV test.

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So, people who have an unmutated IGHV, it's about half of people with CLL, do tend to have more steadily progressive disease toward needing treatment, and then shorter remissions with...

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usually, with time-limited therapy. It's less clear that that's the case with BTK inhibitors.

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But those are probably the two main features that can still count as higher or highest risk now.

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Okay. Uh, you did mention, uh, one trial looking at Richter's, and the question was posed:..

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what percentage of CLL patients develop Richter's and also, are there any other trials that are looking at treatment of Richter's…

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um, out there right now?

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Right. So, we usually say about 5% of people with CLL may develop Richter's over an entire lifetime with the disease, the entire natural history of the disease. It's not clear whether that may be decreasing a bit now, with targeted therapy, now that we're moving out of the era when people have had…

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chemoimmunotherapy. We'll have to see. And there are quite a few trials going on…

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with Richter's. We have one that is using a bispecific antibody called glofitamab,..

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in several different combinations, for people who have had prior treatment for Richter's, or also no treatment for Richter's. There's a lot of interest in these bispecific antibodies.

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And so, there are multiple trials out there for bispecific antibodies. The BTK degrader trials also have Richter's cohorts, because there's been significant activity there seen...

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preliminarily, with some early studies. And yeah, those are, those are probably the hottest ones right now.

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So, the question was also asked, is there any way to test for Richter's before you actually have it?

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There's not a way to test for it before it's there. We can only test for it once there's a suspicion of it being there, and usually that requires a biopsy.

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Okay. Um, Dana-Farber has the NeoVax trial, and has there been any, uh,..

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data yet, um, initial data on a personalized vaccine for CLL patients?

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Right, and so there is no public or published data. That trial that we have is a personalized vaccine. It is based on...

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doing sequencing of the CLL for each individual person and finding what genes are mutated.

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And then, using those mutations to try and stimulate your own immune response to fight off the CLL. And so, we do have a number of people treated on that. It's been going well, there haven't been any problems, but we haven't.

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looked, summarized or looked officially at the data yet. There's also a lot of science going on around it to see how the immune system is being stimulated...

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in the people getting the vaccines.

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Um, in clinical trials, usually there's exclusion criteria, and, and unfortunately, because a lot of CLL patients have a higher risk for developed secondary cancers,..

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um, a lot of times, that exists in their history, um, and if you exclude...

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patients that have had a secondary cancer but they have received curative therapy,...

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like colon cancer or prostate cancer or skin cancer, um, are there.

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trials that are now being more receptive to taking those patients that have...

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had a secondary cancer and been treated successfully?

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Definitely. The trials that we write at our place, the investigator-initiated ones that we write ourselves, we try...

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to actually, potentially not even exclude any second malignancies, or just have some language around if…

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only, it's only an exclusion if the second cancer is going to interfere with our ability to tell how the CLL is responding to treatment,..

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something like that. And certainly, it's pretty common that cancer is treated with curative, intense,..

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you know, at least, oftentimes, in company trials, there's still, it has to have been two years ago, something like that.

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But there are more and more efforts to try and include people, despite...

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those other cancers.

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Right, um. Are there any trials that you know about that are, uh, looking into familial links…

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with CLL? Um, you know, I know that in the past there'd been some talk about this...

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but I don't know of any that are going on right now,..

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specifically.

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Well, I actually run a tissue bank for people with familial CLL and lymphoma.

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And, you know, so, it's very much research. We don't have any planned testing or return of results, but we are doing,..

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I have a grant, and we are doing a big effort right now where we're sequencing the...

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DNA that you're born with across a number of people with familial CLL to compare to controlled people who don't have CLL…

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to hopefully see if we can find some more genes. In some prior work that we've done, we did find some suggestion that the tumor suppressor gene ATM...

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sometimes has mutations that people are born with that may associate with CLL. But we're still working on sorting that out. It's a little bit of a complicated problem, because it's a very big gene…

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and there were a lot of different mutations, all of which separately need to be tested...

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to see if they have impact.

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Okay. Uh, during your slide presentation, there were a number of…

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topics, questions asked about length of relapse, an early,..

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long and very long relapse and how that's actually defined in number of months, number of years.

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Could you maybe expand on that a little bit?

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Sure. So, this comes up when we're talking about a time-limited therapy, so you do therapy for a year, and then you stop.

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And, you know, honestly, we don't really know exactly what the parameters are. So, I can tell you, relapsing within a few months, 6 months, even a year, is definitely short.

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And, you know, being in remission for 10 years is definitely long. None of us know exactly what the best cutoff is to say, well, that's long enough that you can do the same treatment again.

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We're kind of basing it on what we know from the old chemo era, where usually two to three...

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years of remission after finishing the treatment was considered enough to potentially retreat it,..

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retreat with the same option. And so that's what's being tested. For example, there's a trial testing using venetoclax and obinutuzumab again, mostly for people who had at least a two year remission, but some people who had just one year are also...

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being able to be enrolled in that. So hopefully in the next years, we'll get a better idea of sort of how that breaks out in those several-year range.

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But certainly, if you had a five year or more remission, that's reasonably long, and it's…

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pretty reasonable to do the same treatment again, if that seems like a good option.

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Um, there were a number of questions that were asking about,..

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what do you think the potential impact of the federal cuts to the NIH and the FDA are going to be for…

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cancer research and clinical trials in general?

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Yeah, and unfortunately, I think it's potentially pretty devastating. Yeah. We're all very worried about it.

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Are, are there, um, any criteria that would make a patient either...

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more, let's say, uh,..

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make a doublet or a triplet available to them versus patients that you wouldn't ever give a doublet or a triplet to?

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So, I would say that the doublets and triplets do usually have a little bit more side effects, in addition to being a lot more work in terms of visits coming to the hospital, at least in the beginning when you get started.

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So, I think people who have a lot of other medical problems, who are older or more frail,..

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those are certainly people who would be more inclined to favor just doing a single agent.

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And single agents, BTK inhibitors are very, very effective, so there's no reason to feel badly about doing that, even though there's so much excitement about time-limited therapy now. They're also extremely convenient.

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And so that can be a big advantage for some people as well.

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And, I mean, as, as those next generations come out, it seems like the,..

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um, adverse events seem to, you know, they're more targeted and less adverse events than the previous versions that came out…

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so?

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Absolutely. But there's still a little bit more, you know, low counts and infections, probably, with the three drugs.

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Right.

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Versus two. So, the two-drug regimen, acalabrutinib and venetoclax, did look extremely safe in the AMPLIFY trial, and so that one may be...

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possibly an exception. We'll have to see how it goes in the real world.

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Um, I mean, in a patient that's doubling, maybe triple refractory, they've gone through both,..

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covalent, non-covalent BTKs. I mean, really, the options for them are...

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clinical trial, um, or a CAR-T therapy, um….

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or something, you know, that we haven't even talked about yet today that's in the works, so…

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you know, when you have patients like that, do you, is that the way you direct them into basically looking at a degrader or a...

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bispecific, um, or CAR-T, um, therapy when they've...

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basically, you know, all those other treatments have failed for them.

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Yeah, and you know, I think, I'm still mostly, we usually have trials at our place that are available…

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uh, for people, and so that's what I'm still mostly turning to. I'm hoping that in the next few years…

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our ability to harness CAR-T most effectively for CLL will continue to improve. And so, in that sense, a bit of a delay is good.

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The other thing is that we know that CAR-T works best if you don't have a lot of disease.

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And so, if you're in that place, then that might be a good time to consider a CAR-T. But if you're not in that place, then doing a trial to try to get a little closer to that place might be better before going straight to the CA- T.

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So, sometimes the timing of it is important as to where you are, right?

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Absolutely, yeah.

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Yeah. Um, do you have any idea of when, uh, acalabrutinib and venetoclex combination might be approved…

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by the FDA? Okay.

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No. I do hope that it might be soon, but I don't know.

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Okay, okay.

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Uh, I can't say that I can get it. I usually can get it, even though it's not approved.

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And you just do it as two separate, pre-approved treatments and...

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they just get them at, yeah.

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Exactly. Exactly.

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So, in effect, they're getting the combination therapy, but doing it in a different way for a patient, yeah. I mean, is it true that you have to fight for patients sometimes to get therapy approved for them?

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You know, they, the insurance companies won't, won't approve it, or and some places, they won't approve combination therapies, because they say, well, you already have one that…

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will treat your disease, but when you want to use a combination therapy, does it make it a little bit tough for you?

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To get the approval for that?

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We haven't had a problem. You know, I haven't…

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Done a huge number, but probably 10, 15, 20 frontline, and haven't had a problem. I, you know, we do have to fight sometimes. Honestly, my biggest fights are on IVIG.

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Insurance companies really do not want to cover IVIG, and that can really be a problem.

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Yeah.

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And that's when, yeah, and it does vary across the country, also, I understand, in terms of the insurance for the targeted drugs that I think other parts of the country, sometimes people have more problems, but in Massachusetts...

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been pretty fortunate that usually we can get it.

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Yeah. Um, one of the things you talked about as a con in a clinical trial are CT scans.

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And are there number one, if you, if you're in a clinical trial and you refuse the...

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CT scan, would that disqualify you from continuing the trial? Or number two, could you...

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ask to get MRIs instead of CT scans, um, as your scanning mechanism?

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Right, so that completely depends on the trial and how it's, how it's written.

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Sometimes, you know, again, investigator-initiated trials run by the investigators tend to be a little more…

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flexible, so sometimes as, you know, people have been on the treatment for a couple years, we, we just have…

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a lot fewer CT scans, whereas trials that are run by the companies, which often are for registration, the FDA requires that these scans be done. And so, in that type of case, it probably would be the case that you could not continue if you declined to have it.

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Whether you can get an MRI instead depends on how the trial is written, usually.

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MRIs are a little bit harder to read in the sense that…

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you can't really do a whole body MRI exactly the same way, like, you have, it has to be designed to take measurements differently for different organs, and so...

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it tends not to be our go-to that's easily interpretable in the same way.

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Okay, um, you did talk about this a little bit on the cost of clinical trials...

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and what's covered and not covered in some states cover different things than other states,..

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um, but just in general, uh, what costs are covered…

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by the investigator and what costs are then the responsibility of the patient?

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Right, so anything that's assigned as a research intervention is covered by the trial.

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So that usually includes some drug. If it's, if it's a company-sponsored novel drug, a drug that's not FDA approved, it will include all the drug, because there's no other way to get the drug. If it's a combination study that an investigator's running, it might only include one out of the two drugs, and then the other one needs to be covered by…

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insurance. Uh, the visits, typically the visits in the labs are usually covered…

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and the CT scans, because those are things that could all be potentially needed as part of regular treatment that you'd be getting if you were not on the trial.

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So, or, excuse me, they're not covered by the trial. They're covered by insurance. And so, we always check…

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when someone potentially is interested in a trial, if their insurance will cover what we call the standard of care associated with the trial. And again, in Massachusetts, that's actually required, that the insurance will do that, but not all states have that requirement.

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And so, it's a good thing to ask about and check into.

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Um, there's a question about CAR-T and the, the, uh, chemo treatment before CAR-T therapy...

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and the question was, can you opt out of the chemo treatment prior to CAR-T?

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No, you need to do it to kind of make room for the new cells to take.

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Otherwise, there's too many cells hanging around that might fight off your new cells.

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Yeah, yeah, um, you mentioned that.

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In combination therapies, there's generally more adverse events, just because you're combining,..

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you know, multiple drugs together. And is there any way to assess that ahead of time,..

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um, in making the decision whether to, you know, use a combination or just use a single agent?

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You know, definitely in, so, the healthier a person is, the fewer other medical problems they have, the more active they are, the less of a problem.

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The potential increased side effects are, uh, you know, but someone who's older, more frail, or has a lot of other medical problems…

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is more likely to have problems with the increased side effects. And you can't tell 100%,..

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you know, for sure. But that's generally how we kind of think about it. And this is why, you know, some of the clinical trials assess these so-called comorbidity scores...

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where you look at what other medical problems people have, what medications they're on…

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as sort of an assessment of how well they're likely to do from a side effect standpoint…

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on the trial.

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Okay, there's a couple of questions about specific trials. One of them is the Alliance,..

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um, A041702, the Obinutuzumab and ibrutinib versus...

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those two, plus venetoclax, and uh, the question was, anything learned from that?

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So, you know, I think, well, as people may, may or may not know, that trial was officially stopped…

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early, because it was determined that it wouldn't be able to show an advantage for the three drugs over the two drugs. And the main reason it wouldn't ever be able to show that advantage was because there were early COVID deaths. The trial went on,..

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was carried on at the height of the pandemic, and there were early COVID deaths, and there were somewhat more COVID deaths on the three-drug regimen compared to the two.

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You know, it looks with longer follow-up, that if you sort of…

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control for the COVID problem, that the three drugs may be emerging to be better than the two, but we don't really know. Fortunately, we're being allowed to continue to follow that, so we'll see.

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And, but, you know, I think this observation is potentially consistent.

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AMPLIFY also had a three drug regimen versus a two, and obinutuzumab in the three drug regimen, there were more COVID deaths. Again, this was also carried on at the height of the pandemic…

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in that three drug regimen versus the two. And from AMPLIFY, it's quite clear that the CD20 antibody, and especially the…

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triple drug regimen aas associated with a greater risk from COVID.

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Now, we're pretty sure that the COVID risk is now much better, because COVID is not…

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as aggressive, and because most people have antibodies now from vaccination and or infection. And so it was a fairly unique point in history that affected both of those trials, but it does underscore what I'm saying about how there is…

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potentially this increased risk of infection or serious infection, which still applies, but I think is much more…

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manageable in general now, compared to that initial part of the pandemic.

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Yeah, I think that's skewed some of the results, unfortunately, so…

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Yeah, both of those trials, it did skew, skew.

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Right, right. There's been several questions about stopping treatment, especially the...

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BTK inhibitors if they've been on for a long time, let's say.

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Some of this person's seven years has been on it. I mean, number one, there's a chance of developing a mutation.

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Um, but, but if they're, let's say their counts are in normal range,..

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they're probably flow, probably shows some disease. But what are your thoughts on…

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stopping it, or and let's say they're not really having any adverse events...

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with it at all, but the risk of developing the mutation is there with longer use, but…

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you know, should people consider stopping it if everything appears to be semi-normal with them, or…

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do you think it really, truly is a forever, uh, therapy?

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So, I think that's a very personalized decision. So, the drugs were obviously developed to be continuous indefinitely, but we know that lots of people drop off…

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actually more for side effects than actually with progression, but also progression, too...

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over time. You know, especially if someone's on ibrutinib, I'm happy to take kind of any excuse of adverse events, even to potentially stop if they've been on a very long time or in a good remission.

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But, and you know, I found that people who have been on a long time like this, five, seven, 10 years, who stop, often remain in remission for a long time.

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But it's important that your prognostic factors of your CLL be considered when thinking about this. So, people with that highest risk 17P deletion, I'd be much less likely…

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to do that. People with the lowest risk disease will do better if you stop, but even people with that intermediate risk, the unmutated IGVH, I have people who've done well for years…

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after stopping. So, I'm actually more inclined to do that if people have been on for a number of years than I am to switch to one of the other, like, second generation, say, with ibrutinib..

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So, you know, it depends on prognostic factors, how you're tolerating the drug,..

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how long you've been on, and the depth of remission, I would say.

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But it's not unreasonable, at a long time. Now, this shouldn't be interpreted to mean you can stop after six months or a year, or even two years, because that's actually very different. These drugs have…

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slow, ongoing effects that build up and deepen. And I don't think stopping at two years is at all nearly the same as stopping at five years.

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So, that's just something to bear in mind.

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If somebody wanted to change, um, would you recommend them going to a,..

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you know, either a, you know, acalabrutinib or zanubrutinib. I'm not sure if it's working.

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They're either going to stop or not stop, right? I mean,…

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so, I'm not sure that would be a something that you would offer, say, oh, let's just switch you to this…

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for no reason yet.

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Yeah, right. No, that would be more for adverse events where you felt you needed to continue the drug. But like I said, I usually just…

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Right.

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tend to stop if I don't feel I need to continue the drug, which is often the case, and these people have been on five plus years.

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Right, right. Um, there's been some talk lately about statin drugs, and statin drugs taken in conjunction with…

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CLL drugs, and, and they appear at least to help in the treatment. Um, do you have any thoughts on that?

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I think it's intriguing. You know, I don't think it's convincing enough yet, or that we understand it well enough that everybody should go out and get on a statin.

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But if you're on one, then that's good. Not going to hurt, apparently and maybe help.

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Yeah, yeah.

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Um, let's see, um, if I join a clinical trial of a combination of a BTK inhibitor with a...

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BCL-2 inhibitor and it does put me in remission,..

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what are my options? I think they're saying. Can they stop?

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I'm trying to read into that question a little bit, about most of those are time-limited therapies, right? I mean…

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combinations, yeah.

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Right. Yeah. Most of them are planned to be time-limited, but exactly how long they are, whether there's testing to determine the minimal residual disease and stop based on that, is all going to depend on the trial.

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And so, I mean, that's another question that you should ask if you're thinking about a clinical trial, is, you know, how long will I be on this, and what are the criteria…

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for determining how long I'll be on it, and that sort of thing. But in general, if you're on a trial, you have to follow what the trial says.

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Right, right. But if let's say they're getting an out, you know, not on a trial, but they're getting a BTK and a BCL-2 together,..

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um, you know, should there be MRD testing along the way, just to see how they're doing?

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Um, or do you think it's necessary?

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So that's really complicated, right? So it, we have different regimens that have been studied in different ways, right? So, so for AMPLIFY, we have 14 months of a

acalabrutinib and venetoclax, or 14 months of acalabrutinib and venetoclax or obinutuzumab…

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without MRD testing, and the results are very good. And so that's one option, right?

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It is true that the best results that we've seen so far are with this trial that I discussed in my presentation, the one that was just presented at the European Hematology Association with ibrutinib venetoclax, where people are on it for two, three, four years.

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But it, you know, it's still a little hard to tell if it's worth it.

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Well, so first of all, I wouldn't use ibrutinib. And then the other question is, do you need to stay on for the three or four years and do all that testing, or can we sort of back off from that…

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with less testing and still get the same benefit, and I think those are questions that we're asking now.

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Now, I will say that if I'm giving one of these regimens to a patient, I will usually check…

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the MRD. You don't want to check it too soon, uh, but or with venetoclax obinutuzumab, for example, I'll check at nine months and 12 months to see…

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because that way you have a trend. So if you're planning a year or two,..

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you can check it a year, potentially. Two years, uh…

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mostly, I have not been doing MRD-guided therapy. I've been doing treatment durations that have been established that we have data for how long the remission will last, based on the trials.

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But I think we're going to increasingly have data where we do actually have results based on the MRD-guided...

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outcome, and where we will be doing that more and more.

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Um, a question was asked about bone marrow transplants, um, for relapsed patients. How often is this used now…

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and is it really considered for a CLL patient?

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So, it's used much less than it used to be before the targeted therapy, but we still do use it some. And there's some discussion about whether CAR-T should be done first and then followed up by a bone marrow transplant,..

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uh, potentially. But the bone marrow transplant has a much longer follow-up...

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and so that is established as potentially able to cure CLL, which we don't really have that follow-up for CAR-T yet, to know whether…

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that's possible. And so, you know, if a person is young and healthy enough and has disease that's progressed after BTK and BCL-2 inhibitor, and now also after a non-covalent BTK, it is something that should be considered.

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Um, there's a general question about vaccines and getting vaccines, and obviously...

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people in watch and wait should get as many vaccines as they're eligible for,..

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um, because your immune system will probably be in the best shape at that point in time.

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But going forward, um, getting vaccines while on treatment…

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because I know that, you know, a monoclonal antibody, being treated with monoclonal antibody,..

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you know, your vaccines will probably have much less response. But is there a timing issue that you would say, if somebody is on treatment or off treatment, or are there...

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specific treatments that you would say, you know what, I wouldn't...

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necessarily bother with vaccines right now, and people are asking about general vaccines as well as COVID vaccines, as well.

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Right. So, the vaccines that are for the sort of short term, like flu that's for this year, or COVID that's for this year, so we give those to everybody, regardless of what treatment they're on, because whatever benefit you get…

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is the benefit that you have for that year. And there is, and in the AMPLIFY trial, we actually found that…

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even if people were on treatment with the acala-ven or the acala-ven-obin,..

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getting the vaccine reduced the likelihood of dying of COVID. And we hypothesized that this may be because even though when you get the obinutuzumab and the acala, it's hard for your….

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B cell type of immunity to respond, you can still have your T cells respond.

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And so, we hypothesized that that may be going on, despite that. And so,..

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I think any of these shorter-term vaccines, you should just get regardless of treatment. Now, if it's something like a Tdap that you get once every 10 years, that's the tetanus pertussis one,..

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or even, like, RSV that's one and done, or Prevnar that's every five years,..

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I try not to do those. I try to do those when people are in remission, off treatment, but we do know that even, say, if you're on a single-agent BTK, you can still boost your immunity with the pneumococcal vaccines, as long as you had had prior exposure to those vaccines.

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So, in general, I'm always in favor of doing more vaccines rather than fewer, but you might just want to have judicious timing around some of them. The strongest indication to not do those ones that you need to work for five or 10 years would be if you're immediately…

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having gotten a CD20 antibody, or very shortly thereafter, like, in the time on it, or six months thereafter, probably might want to try to delay getting things that…

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are the five or 10-year vaccines.

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The question was asked, uh, are there any duplicate trials, I would assume,..

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there'd be trials that are similarly run by, uh,..

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an investigator, which would usually be the pharmaceutical company, at different research sites. And I think that's where..

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Clinicaltrials.gov comes in, where somebody can say, where are these, is this trial available?

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Um, and it'll list of all the sites, right, that, you know, it could be one in Boston, could be one in New York, in California, or wherever, so…

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I think that's your best resource to find out where the trials are actually available.

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So, um, there's been, uh, there's several questions asked about…

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decreasing dosage of your drug after a period of time.

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And I know this comes up a lot with patients, you know, well, I've been on,..

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you know, say acalabrutinib for four years, can I, but I'm having some adverse events, can I reduce the dose?

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Do you have recommendations for patients on that?

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I have to say, I kind of try not to reduce the doses very much, uh, but it is one option, and especially if you've been on for a number of years or in a good remission...

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then it is one option to potentially stay on the BTK inhibitor. A lot of times, I'll do it as sort of a test, like either hold the drug completely or reduce it to see if the side effect actually gets better…

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because sometimes they don't always get better, because they're due to multiple things, maybe partly the drug, partly other things, too. So, you do, like, a test like that.

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And then based on how the test goes, we could decide to restart full dose, restart reduced dose, or potentially stop.

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When you're doing testing for MRD. I mean, is the sequence, you do the Flow first, and if the Flow…

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I mean, obviously, if the Flow shows disease, there's no sense in going further…

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with the testing, right? But then, then, do you go to…

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Right.

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uh, you know, a higher level of measure, let's say an MRD,..

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you know, five, uh, or directly to ClonoSEQ, and try and get,..

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you know, the deepest test that you can get on a patient?

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So, the issue with the ClonoSEQ is you have to send a baseline sample.

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Yeah.

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So, once you've sent the baseline sample, then, to some extent, you can just do the ClonoSEQ as your only test.

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And you do, you can interpret it at a 10 to the minus four or a 10 to the minus five level, and whether you get to the full 10 to the minus six depends how many cells there are, which sometimes there aren't always enough.

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Um, Flow is still more standard, but in the U.S, because the FDA has sort of authorized ClonoSEQ, and is actually not willing to use Flow for decision-making on trials,..

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it's likely that ClonoSEQ is going to be increasingly used. And I certainly wouldn't do three different tests.

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You know, like, you know, the float is sort of between 10 to the minus four and 10 to the minus five, it often approaches 10 to the minus five, and then the Clono, you can almost always get 10 to the minus five for everyone, but, and then you may or may not get 10 to the minus six, depending how many cells you get.

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Right, right. Let's see, uh…

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when you mentioned higher risk disease, 17P, I know that can change over time.

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Based on your treatments, especially for people early on, who had chemotherapy,..

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you know, you could not have it, and then all of a sudden you could develop it. But with the newer agents,..

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is the development of 17P still happening with patients?

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That is an interesting question. You know, I think it is, but less than it did.

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So, it turns out that a lot of the 17P or TP53,...

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maybe there at the beginning, like, at very tiny levels that you don't find, and so, if that's the case,..

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it will tend to grow out after any line of treatment, because it is relatively resistant…

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to any of the treatments. So, we are still seeing it emerge...

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sometimes, but less than before is what I would say.

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Okay. And then, obviously, there's, there's, the question about when should you get tested, have FISH tests done...

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uh, for a patient, and, and, you know, at the CLL Society, we say, well, anytime you're going to start a…

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new treatment, you should be tested. Test before treat, and is that what you generally recommend at Dana-Farber?

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Yes, for sure. I mean, we do diagnosis as well, and then we do before first therapy, before each therapy. We don't generally do it in between.

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Right. Yeah, but only when you're, going to start a new therapy, or change it, yeah.

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Yeah, although if you're getting close, sometimes it's helpful to do it a little bit before, especially with first-line therapy, just or, well, even with later lines of therapy.

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Just because then you can start thinking about it, because it takes a little while to get the results back, and so if you don't send it to, you have to start the treatment right away, then...

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you don't get to think about it for longer.

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Right, right. Um, let's see, um…

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you mentioned in the combination therapies,..

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basically, especially a triplet, you're basically using all your therapies at the same time. And then, if you,..

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if you don't have, uh, success with that, then what does a patient do? I mean, where do they, I mean, number one,..

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which one do you feel like didn't work more than the other one..

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or do you revert back to single agent with a patient or…

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how do you deal with that?

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Yeah. So fortunately, that seems to happen very little. Insofar as we can tell, like,..

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pretty much everyone will go into remission. If they didn't, I would be very worried about Richter's. I would definitely evaluate for Richter's and probably need to get…

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another biopsy. And so, you know, if in fact someone really didn't…

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respond at all to the three drug regimen, I would be, what's most concerning is the lack of response to the BTK inhibitor, really, but…

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what would you, if it wasn't Richter's, you would probably have to go to a non-covalent BTK…

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but possibly in combination as well, because the three drugs not having worked makes it less likely that a single drug will work, probably.

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But like I said, fortunately, this seems to be very, very rare.

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Okay.

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And then, insofar as we can tell so far, which we're still getting more data, it does seem that people will respond again…

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to more or less any BTK inhibitor, venetoclax and an antibody…

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later.

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And do most of them get to undetectable disease on the triplets?

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So, in the AMPLIFY trial, for the patients who had MRD…

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checked on the three-drug regimen, 95% had undetectable MRD. So, yes.

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That's pretty high rate. So, um…

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there's been several questions from people that are doing well on a treatment, but…

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want to change to another class of drug. I mean, what's your general recommendation?

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For somebody that's doing well and not really having any adverse events that would,..

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you know, make them stop but just want to change to a different treatment,..

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so I wouldn't really recommend that, because you're doing fine with one, so why use up another one?

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I mean, is that…

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right, right. Yeah.

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Right. You know, if it's because you've been on a BTK inhibitor for years and you want to get off,..

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uh, then that kind of goes back to what we discussed already, in terms of the options for thinking about that.

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You may be able to just stop. Sometimes you might be able to add something. So there are trial, there have been trials done, and there are trials ongoing to add venetoclax for a year, and then gets undetectable MRD, and then stop.

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And so, ghat's a little bit different than just changing to venetoclax and then being on that indefinitely, which I wouldn't really recommend. And there are, we have a consolidation trial that's starting with a bispecific antibody.

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So, we're using the bispecific antibody for people who have been on BTK for a while, and…

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then to potentially try to get to undetectable MRD, and stop.

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Is it, is it too early to tell how some of these new drugs might be used as first-line therapy?

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Let's say the degrader, uh, maybe even pirtobrutinib,..

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um, or the bispecifics. I mean, do you think that there's a chance those will be moved…

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uh, into first-line therapies for patients?

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Yeah, I mean, pirtobrutinib is already in two first-line trials. There's one, a randomized trial versus chemo and there's a randomized trial…

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which is partly frontline and partly relapse against ibrutinib. Then MD Anderson has done a three drug regimen with pirtobrutinib, venetoclax and obinutuzumab, which looks quite effective, but also had more toxicity than the other three drug regimens.

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So, there's a lot of interest in that already, although I'm a little cautious about that, just because we don't understand what the…

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impact of doing pirtobrutinib before a covalent BTK is, especially if you're on the continuous pirtobrutinib. If it's time-limited, you're just doing it for a year and you stop, then that's probably okay, but if you stay on it…

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and become resistant, we don't know if that may impact on your ability to do covalent BTK, and so that's a reason to be cautious there. And similarly with the degraders. So, people want to bring them up front, want to do a degrader with venetoclax or obinutuzumab...

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et cetera, but I'd be a little cautious, just because it's still early, and we don't really understand the mechanisms of resistance.

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But they certainly may end up moving up there. And I think bispecifics should…

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probably move up there. Like, I, it may be a, of interest to use them for consolidation after frontline time-limited therapy to try and get more people to undetectable MRD, or those who are already undetectable, to get even deeper.

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Like, maybe this is a way we could cure people, is, you know, my thought. So, I'm pretty interested in that.

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Get them deep but get them deeper, basically. Yeah, yeah.

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Exactly, exactly.

01:29:44.000 --> 01:29:49.000
Okay, um, let's see. Um, I,..

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there's been a lot of talk, and you mentioned a little bit about the reconstitution of the immune system…

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with treatments. And, you know, because, you know, we're immune compromised, and then we go through treatment, and sometimes we become more immune compromised because of the treatment.

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But how are we looking to make patients healthy again...

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with our immune system, and you know, have you seen any data that…

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points to one regimen or another that might be better at doing that?

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Unfortunately, not really. We haven't had a huge amount of luck with that. There was some early data with BTK inhibitors that you could restore…

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one of the types of immunoglobulins, a little bit. But it's only out to a year. And my personal experience is that if you're on longer than that, I think that that effect is diminished.

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I've certainly had people end up needing IVIG because they're on BTK inhibitors for a long time, and…

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that inhibits your ability to make your own antibodies. So, it's still very much a problem, this question of how to repair the CLL immune system. And, you know, I think there is…

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significant interest in it, and we're certainly getting more and more data on how the immune system is…

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modulated, but we're not, lenalidomide also had a little bit of activity restoring…

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the, uh, immune system, but…

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Yeah, yeah. It's, yeah, it's a tough one, I know.

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I'm sorry to not have a better answer for that.

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Um, when you consider first-line treatment versus relapse treatment, let's say a patient…

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had BR (bendamustine + rituximab), eight years ago, and they did really well on it, and now...

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they're relapsing. Would you ever consider them to be, that to be the next treatment to be their first-line therapy...

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or are they always going to be relapsed because they had this therapy years and years ago?

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Yeah, I would still count it as relapsed, but if it's not a targeted therapy, then,..

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you know, the options are endless, right? So you have BTK inhibitor, you have venetoclax, you have combinations, so…

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in that sense, even though you're relapsed, it is not, it doesn't have the same implications in this era where we have so many targeted therapies.

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Yeah. Um, you did mention that there, you've seen some success...

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on the trials for sonrotoclax and, but is there any concern about, uh,..

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BeOne being a Chinese-based company and the issues with the tariffs, and...

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what that might cause to treatments that might come out of,..

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you know, because they've got, you know, Zanubrutinib, they've got a degrader, they've got,..

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Sonrotoclax and so, you know, potentially some very, very effective drugs for CLL.

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But do you think that there might be an issue because they're…

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a Chinese-based company and the tariffs?

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You know, I haven't heard any concerns about that. They actually have a large U.S. operation now…

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too. So, and obviously, they already have approved drugs in the U.S, so…

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Right.

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I haven't been too worried about it.

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Yeah, yeah. I mean, there's a lot of talk about…

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time-limited therapy versus, versus continuous therapy for patients, and…

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are most clinical trials time-limited, or….
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are they still a mix of continuous and fixed duration?

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It's still a mix. You know, I think, especially as people who've had multiple lines of therapy and get later…

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in their disease course, sometimes continuous therapy is better to keep the disease in remission longer. So, like, the degrader trials, that's continuous. pirtobrutinib and relapse,..

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is continuous, and that's likely to continue. And, you know, I mentioned in my talk that we, we haven't, we actually have very little data that time-limited is better than continuous, even though we have a lot of rationale for why we think it might be.

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The first data actually showing that for a subset of patients was this trial that was just reported at the European Hematology Association. So, there's another trial comparing…

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continuous ibrutinib to ibrutinib venetoclax to venetoclax to obinutuzumab, which we're hoping we'll hear at ASH this year. And then we're also designing an intergroup trial in the U.S, which is comparing continuous zanubrutinib to zanubrutinib venetoclax time-limited for older patients. Again, because…

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it's the older patients where the risk-benefit may be a bit less clear with some of the time limited, if there are more side effects, versus the continuous, which is very effective. So, so it's still very much an important question that, that we actually don't…

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really know the answer to. Which is better, or are they equal, or for certain types of patients, is one better than the other?

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It is true that probably most single-arm trials these days that are not in that heavily relapsed refractory setting are probably time-limited, if they're frontline or early relapse.

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But, you know, that's just because there's a lot of work to be done there, and we want to increase the options that people have, and our understanding of how…

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these trials work.

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We know from data that, uh, the access to clinical trials in the U.S. is much lower...

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for patients than in Europe, and I mean, what, what can be done to increase…

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access in the U.S. for patients to get into clinical trials, and…

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have more of us in there.

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Yeah. This is a big...

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concern that I have, because I think that trials really do offer great options for patients, and…

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bring in additional drugs to help, you know, manage the disease over a long disease course, right? But in the U.S, so few patients are enrolled in trials, and especially,..

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Right.

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you know, we don't want to use up BTK and BCL-2, and then…

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have people come who whose options have been much reduced, right? We'd like to see people at CLL centers earlier, so that we can try and get them…

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on trials, or have, have more options, if possible. You know, more funding would certainly help. It's become harder and harder to…

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be a clinical investigator trying to run trials, because the opportunities to fund trials, and you know, we mentioned NIH earlier, the opportunities to fund trials through NIH are actually very limited. Most of the trials that we do, even if they're investigator-initiated, we have to try and get company funding. You know, that means you have to negotiate what you're trying to do with the company, which sometimes your,..

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your thoughts are aligned, but sometimes they may be a little different. So,..

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Right, right. I mean, do you,..

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Yeah.

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Have trials that you initiate, as opposed to trials that are brought to you by the pharmaceutical companies.

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You do a lot of investigator-initiated trials at Dana-Farber, right?

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Yes.

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And, do you think more places should….

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really use that approach, as opposed to waiting for the pharmaceutical companies to come with them and say, okay, here's a trial,..

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you know, let's do this. I mean, it seems like your approach…

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gives patients much more options in terms of, of what you can do,..

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in terms of combining drugs and I think you have a little bit more flexibility in how you run the trial,..

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um, as well, so, um, I think...

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initiated trials are really sometimes more beneficial to the patients.

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Yeah, yeah. No, I agree. But also, you know, companies are the ones who bring the brand new drugs to trial, and we can't often afford that as investigators, so it's kind of a mix, but I do think more investigators doing more investigator-initiated trials…

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would help patients. And we need, this is how we manage to have trials for all phases of the disease, is by…

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having our own ideas and investigator-initiated trials, but it can be hard to get funding.

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And it has gotten harder over the last decade or two, unfortunately, to get that funding.

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Right, right. I think we are reaching the end of our session. We had a lot of questions that did not get answered, and I'll address that...

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a little bit later, how you might, uh, send us those questions, but Dr. Brown, do you have any closing thoughts for patients out there today…

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that attended this session?

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Sure, well, I would encourage everyone to try and get an opinion with a CLL expert and try to find out what clinical trials are out there, as well as what your prognostic factors are for your disease, because all of that's going to be really key to…

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kind of managing it over the long term. And, you know, we have great treatments, we have great trials, so there's not really a wrong decision about your treatment.

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And, yeah, we can manage CLL for the long haul.

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More treatments are coming, too.

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Exactly. And those come through clinical trials. Yeah. So…

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Exactly.

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we want to thank our sponsors, um, of this event. And, uh, it's made possible through the generous donors…

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and grants from BeOne, Genentech, and Lilly. And, uh, if you, uh…

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have any questions that you didn't feel were answered or have additional questions,..

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you can send an email to asktheexpert@cllsociety.org...

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and, uh, keep in mind that this event, um, was recorded, so it will be put up on the website…

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um, uh, in probably a week or so. And feedback is very important to us, and if you can fill out the post-event….

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survey, um, that is very helpful to us in putting these events together.

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And you can join us for our next virtual event, which is from Service to Support:..

01:40:27.000 --> 01:40:34.000
Managing CLL/SLL in the Veteran Community. We know that CLL is much more prevalent, uh,..

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with veterans because of what they've been exposed to and that'll be on August 28th.

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And the CLL Society is invested in your long life. And please invest in the long life…

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of the CLL Society by supporting the work. Uh, with the link, https://cllsociety.org/donate-to-cll-society/.

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And I want to thank Dr. Brown again for her time today and her presentation...

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on the ever-changing world of CLL treatments. Thank you very much.