Webinar Transcript
ASH 2024 COMES TO YOU!
January 9, 2025

In science and medicine, information is constantly changing and may become out-of-date as new data emerge. All articles and interviews are informational only, should never be considered medical advice, and should never be acted on without review with your health care team.

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

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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 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 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'd like to welcome our audience to today's event.

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I'm Dr. Brian Koffman, the Executive Vice President and Chief Medical Officer of the CLL Society and a CLL patient myself.

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And we are joined by Dr. Nitin Jain. He's the professor of medicine in the Department of Leukemia at the University of Texas MD Anderson...

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Cancer Center in Houston, Texas. We will both be presenting on important research from the American Society of Hematology, or ASH's annual meeting that's related to CLL.

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Just a word of warning. This webinar is fairly advanced...

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but all are welcome to participate and learn. There will be things on the slides, because both Dr. Janin and myself are using the slide decks that were actually presented at ASH,..

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that use acronyms and language that may be fairly advanced but we'll try to slow down and make sure we explain everything that goes on.

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And that's why we have the questions and answers. Please feel free to ask any questions on things you don't understand.

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The recorded webinars and the slide deck and a transcript will be available for everyone after this event.

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Before we begin, a few quick disclaimers. The information provided from today's webinar, it's for educational purposes. It shouldn't be considered medical advice.

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

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Please note that while the CLL Society has its own opinions and policies,..

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

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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 that opportunity and ask your questions in the Q&A box.

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So, let's begin.

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ASH 2024 comes to you. Why should you care? ASH is the acronym for the American Society of Hematology's annual meeting and exposition.

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It's the premier hematology conference and people from all over the world come but it's aimed at hematologists. It's not aimed at even other doctors, and it's certainly not aimed at patients and advocates but it's where you're most likely to hear the most important research. People hold their research to present it at ASH.

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Patients should pay attention to it because they can learn a lot. It's where practice-changing research is first presented.

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The first study showing that ibrutinib was superior to chemotherapy made a big splash at ASH.

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New therapies that are likely to be approved are first presented at ASH; acalabrutinib and venetoclax, which Dr. Jain will be talking about later.

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New treatments that are coming down the line that are still experimental, degraders, bispecific CAR Ts that we'll be covering later, and new trials that are open or opening that might be a good choice for you.

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And it's also where we find out about problems. We found about all the issues with COVID, the cardiac issues with ibrutinib,..

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so ASH news is news that you can use as a smart patient to get your best care.

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I'm going to be discussing three immunotherapies from ASH. One is with a CAR T product called liso-cel used in combination with ibrutinib. Bottom line, ibrutinib improves the outcomes.

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Another is the bispecific T cell engager, which I'm going to explain what that means.

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And the last is the most futuristic, which is inside your own body, in vivo building CAR T cells by being injected with viral particles. It's been done in monkeys, but it's coming to humans soon.

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So let's start with the liso-cel with ibrutinib difficult to treat group...

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in the TRANSCEND. So, liso-cel is autologous. That means it's made from the patient and it's directed after at CD19, which is a marker on the top of the surface of CLL cancerous B cells, but also on all normal B cells.

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And it's been shown to work and to get rid of this CLL in patients, the complete response rate's been about 20% and the overall response rate has been 40%.

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But there are problems with it. Excessive enzymes called cytokines are released, which can lead to inflammatory responses. There can be neurological events…

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which can be mild from a little confusion to as serious as seizures and coma. The hope was that adding ibrutinib might improve outcomes and let's, so the idea was to see whether it could help control the CLL while we're waiting for the drug to be manufactured.

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Whether it lowers the risk of cytokine release syndrome being serious, and does it help the T cells? Does it tweak them to make them better killers?

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I'm not going to go through all the details here, but this tells you what the inclusion criteria were to get into the trial. And essentially, you had to have CLL, you had to be fairly functional, you had to have been on a BTK inhibitor...

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and other medications. You couldn't have Richter's and the CLL couldn't be in the central nervous system.

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The protocol was that the leukopheresis, which is where they draw off your white blood cells and spin them,..

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was done. The liso-cel cell was manufactured when the patient's eligibility was reconfirmed, they were given chemoimmunotherapy of fludarabine and cyclophosphamide, and this is to prevent you from rejecting these engineered cells that were taken out of you and engineered. You got the liso-cel and then you were assessed. There were two dose levels, dose level one...

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which is 50 million CAR Ts and dose level two, which is 100 million.

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And we were going to look at complete response rates and MRD and overall safety.

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So what happened here? Sixty-five patients had their blood drawn. But not all of them could go into the trial for various reasons, they didn't meet the criteria anymore.

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Fifty-six were studied, the vast majority were at the dose level two, the 100 million CAR T cells.

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It was a difficult group to study, to expect good results on. We can see the age was a little bit younger, but they'd been through a whole bunch of therapies…

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and they had very high risk disease, with the majority having, 98% having high risk something or others like 17P, TP53. Most had unmutated IGVH, a very tough group.

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So how did they do? This is looking at the response by the doctors running the trials.

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And remember those numbers that we looked at before, so the complete response rate here was 45%,..

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In monotherapy was 20%. The overall response rate was 86%...

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compared to 44% when the drug is not adding, the ibrutinib is not added.

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Let's look at undetectable measurable residual disease or uMRD results. And we can see these are extremely high and when we're looking at the green boxes in the marrow...

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in the orangish brown box is in the blood and we can see that there's very strong correlation which is a really good thing to see and that's not always a given.

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We can see that the uMRD rates, the undetectable measurable disease rates,…

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was very high in those who reached a complete remission but was still high even in those who did not read reach a complete remission.

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How durable were these responses? Again, if we look at that top line for the people who completely responded, we see that they were very durable, 85% were still in a progression-free response at two years and of all the patients, 62% were. We do see if you didn't respond, you didn't do very well.

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The overall survival was even better. What were the common adverse events?

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Well, the cytokine release syndrome was common and seen in the majority of patients…

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and low blood counts, anemia, neutropenia, which is low neutrophils, was quite common. And fevers were another issue...

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though there were other side effects too. Some of these low blood counts were persistent and serious. There were serious infections. And if we look at what the deaths were, and there were 19 deaths, all occurred more than three months after the infusion.

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Six were from progressive disease, six were unknown, but three of those were probably progressive disease,...

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Covid-19 led to three deaths and sepsis, blood infection, and cardiac shock from that was one other cause of death.

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This is encouraging to see, it's the last slide that I wanted to share in terms of the data, and that is that the CAR T cells persisted in some cases up to 42 months after, so they continue to play whack-a-mole with the cancer.

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So in summary, the combination with ibrutinib drastically improved the outcomes. There were no new safety signals and this may be a path forward. I'm going to move onto the next study, which is epcoritamab,..

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which is a monotherapy in CLL and this is a bispecific antibody. This trial is personally important to me because I'm in this trial, international trial.

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And, what this does is it uses an antibody like rituximab or obinutuzumab that attacks the CLL cells by latching onto the CD20 found on the CLL cells in all cancer cells.

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But it also attaches to the T cells, which is the CD3. An antibody has two arms, is kind of Y-shaped, and one arm attaches to the cancer and the other brings the T cell over. So kind of in a vial, does exactly what the…

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CAR T cells, Ido, but it's off the shelf and ready to go.

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There were two arms to this trial. I was actually in the second arm where they added another step-up dose and improved the prophylaxis for preventing cytokine release syndrome.

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Again, a very difficult group to treat with high risk factors. One hundred percent of the patients that had BTKi like ibrutinib and acalabrutinib, some had pirtobrutinib, zanubrutinib.

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In the majority, it had a BTK inhibitor, mostly venetoclax. We can see that there were significant adverse events. Essentially, everyone had some kind of cytokine release syndrome and occasionally it was severe. And again, the low blood counts, the anemia, the low hemoglobin, low platelets, which is a thrombocytopenia...

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and also on neutrophils, the neutropenia, but also diarrhea. And some of these were very serious and we saw that there was COVID and other issues too.

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How well did the patients do? Well, the majority were progression-free at the end of a year in this difficult to treat…

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and 70% overall survival. So, in summary, this subcutaneous shot in the belly in these difficult to treat patients showed a 61% overall response rate and almost four out of 10 patients had a complete response rate, an undetectable measurable residual disease, and three out of four of the patients who responded…

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and 100% of all those who reached a complete response. Very encouraging data that's important to compare to CAR T.

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The last thing I'm going to go over here is the new changing, exciting...

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different approach to CAR T. Now, we talked about how CAR Ts were done and all the difficulties with this.

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This radically changes, this is a study that's only been done in non-human primates, actually macaw monkeys.

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It's not been done in humans yet. But the FDA has approved those trials and they're coming. There are lots of problems with that, as we discussed.

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The high cost, the preconditioning with the chemotherapy to allow you to take the drug…

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and not reject the CAR T cells. What this does is inject the viral particles either through a lymph node or directly intravenously...

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into the patient down the line. Right now, this study was done on normal monkeys, these monkeys did not have cancer, were not immunocompromised...

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to see whether the CAR T cells could be manufactured inside the monkey by sending the viral particles with the instructions on how to make the CAR T cells and see what happened to those monkeys. No lymphodepletion, no chemotherapy.

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So what happened? It was well tolerated, whether it was IV or injected into a node.

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There was some mild cytokine release syndrome noticed in the monkeys by checking their labs and looking for these enzymes.

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These viral particles were to attack CD20, a marker found on B cells. That's what ibrutinib, I'm sorry, that's what rituximab and obinutuzumab attack.

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And they were found in the blood persistent up to a month later and up to 42% of the T cells showed, um, became these CAR T cells.

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And the great news is the B cells started to disappear on day six or seven.

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So, the B cells were being wiped out. This was an effective therapy. So in conclusion,..

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this is a potentially different game-changing way to do CAR T, in vivo that could democratize how CAR T is done. So instead of going through these very expensive, tedious...

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and not always successful CAR T manufacturing, you could be shipped a vial of cryopreserved viral particles, take it intravenously and let your body do the work.

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There's no need for chemoimmunotherapy to allow your body to accept this.

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And so this is really groundbreaking technology. Whether it's going to work or not in humans, whether it's going to work in cancer, we don't know yet. But it does seem like it could be a transformative therapeutic platform and the first human studies are coming to us soon.

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So I'm going to finish on immunotherapy with that. And it's my great pleasure at this point to introduce to you my friend and colleague,..

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Dr. Jain from MD Anderson.

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Hello, welcome everyone. My name is Nitin Jain. I'm a professor in the Department of Leukemia,.,

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at MD Anderson Cancer Center, and I'm really happy to share with you some of the updates for data at the American Society of Hematology meeting…

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which happened in December of 2024, in San Diego.

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So, I wanted to cover three specific clinical trials with you, three important clinical trial data...

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and so we'll spend the first slide I wanted to cover with you, is a trial which the so-called call AMPLIFY trial. And this is the trial which was kind of one of the major, I guess, highlights for ASH meeting…

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in terms of CLL abstracts. And it was a kind of really a weighted abstract, we knew about the data for some time but this was the first public presentation of this data.

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So, what was this abstract or this investigator's data was they identified patients who were newly diagnosed for CLL…

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and they had no prior therapy. So, this was their first therapy…

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and they needed treatment, which means is that their blood counts were low or their lymph nodes were big or they had a lot of symptoms.

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So, they really needed treatment for their CLL. And so they wanted to ask a question,..

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that which of the three treatments would be better in a way? So, if you see on the right side of the slide,...

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they randomized patients, meaning the computer decides which arm you go into...

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once you're eligible for the study. So, the first time was AV. A is acalabrutinib, V is venetoclax...

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and as many of you may be using these drugs or taking these drugs.

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And these together were given for 14 cycles. You start with acalabrutinib for two months and then you add venetoclax, and then both together go on for one year so that that makes it 14 cycles.

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Or, you do what is called AVO. We also call it a triplet study, where you're using acalabrutinib, venetoclax but you are also, in addition, adding obinutuzumab, which is the IV infusion antibody.

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And acalabrutinib venetoclax are given at the same dose as you did in the first regimen, the AV regimen. And the third was what is called the control arm, or to say where patients got chemotherapy, it could be chemotherapy called FCR.

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Which is a fludarabine, cyclophosphamide, rituximab or bendamustine rituximab, also called BR. And these are, you know, I would say historical chemotherapy, we don't use these anymore for patients with CLL but this was done at that era or started at era

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timeframe where these were still considered appropriate. So, this was the weird three kind of regimens patients were given...

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after they were identified to be treated in the study.

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So, what I'm showing you on the figure here is what is called progression-free survival. And how you read it is that on the x-axis is months…

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and so what they reported is 36 months data, which is three-year data.

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And on the y-axis is what is called progression-free survival percentage, it basically tells how many patients are alive and without disease progression at that time point.

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So in this, the top arm or the purple color is the AVO, which is the three drugs together,..

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three investigational drugs together. And it was 83%, meaning 83% of the patients of whom we started the study with are alive and without disease progression at the three-year mark.

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With the two drugs, the number was numerically slightly lower at 76.5%.

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And with chemotherapy, it was actually much lower at 66.5%. And this was what is called the primary endpoint of the study, which basically tells us if a clinical trial is positive or negative. And this was this data set…

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and that this trial is positive in favor of the investigational arm.

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So again, to kind of reiterate, both the investigational arms whether you get acalabrutinib venetoclax…

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or you take acalabrutinib, venetolcax with the antibody were better…

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for what is called progression-free survival compared to chemotherapy. So again, one of those trials which makes a point that we should not be using chemotherapy for patients with CLL…

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and we really should be using targeted therapy. Now, many of you who obviously have CLL may be aware of their, what is called IGHV status.

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And IGHV is a very important marker, genetic marker for patients with CLL because we know that unmutated IGHV, which is shown in the slide here,..

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and I will show you mutated in the next slide, unmutated IGHV historically has been associated with slightly more aggressive disease. These cells, CLL cells tend to multiply faster.

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So in the same trial, the investigator asked a question, what if we just look at outcomes of patients who have unmutated IGHV?

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So, this is the higher risk patient population to say. And as you can see, the curves kind of separate out a bit. The triplet of AVO is now at 82% or 82.8% to be exact.

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The AV doublet is at 68.9%. And then the FCR, BR chemotherapy is down to 56.8%. So, you see more separation of the curve…

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and, you know, someone could argue that the triplet arm is doing the best, at least numerically, it seems to be doing the best.

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What about if you have a CLL which is mutated? So this is a patient, historically patient group which tends to do better with basically anything we do.

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These patients who have mutated IGHV, when we're using chemotherapy used to respond to chemotherapy quite well

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Now that we're using more target therapy, though the outcomes have of mutated, unmutated have kind of come together a bit…

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but still mutated IGHV patients in most trials will end up doing better...

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than unmutated patients. So here you can see practically all the three curves are kind of higher up.

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And the acalabrutinib venetoclax, the doublet is at 86% and the...

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triplet is at 83.6%, so pretty close to each other. And FCR/BR chemotherapy is at about 80%.

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So, basically what this trial tells us and why it's important is that it's showing that potentially you can use two drugs together;.

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namely, acalabrutinib and venetoclax together as a 14 cycle treatment for your patients with CLL, and I will come back to that point in the next couple of slides.

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Now, the previous slide I showed you what is called progression-free survival. So progression-free survival, as I mentioned, is how many patients are alive without disease progression.

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But then you can also ask a question of survival, like overall survival, basically asking a simple question, how many patients are alive? It doesn't matter if they're with disease or without disease or what happened, we're just asking a question, how many patients are alive at a given time point?

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And if you look here at the two-year mark, you know, really the majority of the patients are alive, which is obviously fantastic.

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One thing to note in the study is that the study happened during the time of COVID.

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So, the study started in 2019 and the patients were still getting accrued when COVID hit in early 2020.

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And unfortunately, several patients in the study died from COVID-19 infection.

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But we knew at that time, and we know now I guess, that patients who got antibody treatment like obinutuzumab or rituximab,..

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those patients were more likely to die from COVID. If they were to get COVID when they're getting the treatment with those antibodies.

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And that's what this trial also saw, where more patients in the triplet of acala and obinituzumab and the chemotherapy died from COVID-19 infection as opposed to getting the two pills together of acalabrutinib plus venetoclax so on the right side curve, when you remove the COVID deaths because,..

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yes, COVID is still there, but not as aggressive as it was back in 2020, 2021 timeframe,..

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we see that survival is really excellent for all three groups.

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So why is this study important? I think this is the first study looking at a second generation BTK inhibitor, namely acalabrutinib...

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with venetoclax together as a time-limited approach. We expect that FDA, and again, we don't know the timeframe here, and again, we don't know for sure, but we expect that FDA will approve acalabrutinib plus venetoclax, maybe with and without obinutuzumab…

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as a first-line therapy for patients with CLL, in a time-limited approach. So, this will add to the new treatment armamentarium for patients with CLL, where now patients with CLL, because right now, the only time-limited therapy approved in the United States approved

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for CLL, and many of you maybe have received that or maybe thinking about it is venetoclax plus obinutuzumab for one year.

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But there you have to give an infusion of obinutuzumab. Here, the argument is that you can use two oral drugs,..

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no infusion, potentially together or you could do a third drug with infusion as well. But, I think, apparently this would, as I said, lead to FDA approval and I think many of you as patients and the physicians,..

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I think in the next coming year, will start likely using it. So, this will be, I think, a practice changing study where many of treating physicians will start using it.

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Now, next I want to talk quickly about two different abstracts but they talk exactly about the same concept. So many of you patients may be on what is called a BTK inhibitor.

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There's also a drug investigation called nemtabrutinib. These are all what is called BTK inhibitors, they inhibit the BTK protein by binding to a certain pocket or binding to forming a bond with an enzyme, with a protein...

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amino acid. But that's when they bind it, they inhibit the protein, they inhibit the BTK protein, and that's why it's called a BTK inhibitor.

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But this new class of drugs are called BTK degrader which they don't bind to a specific point,..

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protein moiety, they basically, you can think of it as a simple way is gobble up the entire protein and degrade it.

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And they degrade it with this, what is called ubiquitination and proteasomal degradation pathway inside the cells itself. So, the entire protein is gone.

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So, degrade the entire protein. Now, the thing about these drugs, and there are multiple of them, the first one I'm showing you, this one is by Nurix.

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And then the second one I'm going to show is by BeiGene.

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But AbbVie has a similar BTK degrader, which the data is not public yet and then there are other companies which are developing BTK degraders as well.

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But these two were presented at ASH meeting, one from Nurix and one from BeiGene, which I will show you in the next few slides.

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The thing about these degraders are that they are oral drugs...

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so they're exactly like your inhibitors, like ibrutinib, acala, zanu, pirtobrutinib. In this particular study, the investigators treated 60 patients with just this pill of BTK degrader. Now, these patients had received four prior lines of therapy. So, these are patients who had multiple treatments over the many, many years…

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and then they were coming to this treatment and you can see that all of them had practically received covalent BTK inhibitor...

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which will be ibrutinib, zanubrutnib or acalabrutinib.

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Seventeen patients also received non-covalent BTK inhibitor, which could be pirtobrutinib or similar drugs,..

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83% of patients received venetoclax. So, you can see these patients had received a lot of different therapies…

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and they had a lot of high-risk mutations which they came to the study.

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This is a complicated slide to show, but the point here is, and maybe you can see a bullet, a summary bullet on the right side, is that the drug was really well-tolerated.

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They did not see significant toxicities from this pill, from this drug.

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The most common toxicity was what is called neutropenia, which is your infection fighting cells are low.

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This was seen in about 18% of the patients. But otherwise, we're well managed.

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And the excitement about it is that this is what is called a swimmer's plot, again, just for your understanding, anything which is green and with a checkmark on the right side means that the patients are still taking the drug and they're on the study and they're…

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benefiting from the drug. And as you can see here, practically all the patients, some patients are as far as at almost two years, some patients just started the study...

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but the majority of the patients, it looks like, are still in the study, benefiting from the drug…

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and achieving a response. So, this is quite encouraging. Not just with one pill, where practically most other therapies have failed, the enduring benefits. So, to me, this is very, very encouraging.

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And very quickly in the last couple of minutes, again, BeiGene has a similar compound, again, an oral drug, very similar kind of a concept, I guess to say.

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It just so happens they also treated 60 patients in the study.

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Just so happens they also had patients with four prior lines of therapy very similar to the Nurix drug in terms of the side effects, again, very well-tolerated drug. The same side effect of neutropenia, which was 18%, was about similar percentage here, about 20%, 21%.

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And very similar to the previous trial, you can see any of the check mark on the right side, shows, the arrow shows ongoing treatment, as you can see, practically most of the patients are still on the treatment.

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So to my summary of these slides, and this is my last slide,..

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is that these BTK degrader trials, I think, are quite to me quite encouraging.

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They're oral drugs. They're working for patients who have practically failed all other therapies...

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and they're showing very nice responses. And most of the patients on these trials are still on the drug.

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Now, I would only say that most of these patients have been on the drug for a few months to six months to maybe one year…

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so we really need to see long-term data to really make a point at how well it is working.

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But so far, many of you who have received ibrutinib, acala, zanu, these BTK inhibitors,.

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They can have toxicities, right? Atrial fibrillation, bleeding, hypertension, arthralgias. But those kind of BTK toxicities, so far, has not been seen with these degrader trials. So, I personally, I think are quite optimistic about this class of drug and there are plans to…

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for these class of drugs to rapidly move into the CLL sphere and there are plans there are already trials happening, all these trials, which I showed you and others to hopefully, eventually get these drugs to be FDA approved, but that's still some time away.

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So, I will stop here and we'll go for the discussion.

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Well, Dr. Jain, thank you so much for that very clear and elucidating discussion. There's so many great trials and information coming out of ASH.

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It's hard just to choose a few, but I thought that was very helpful and I'm most appreciative of what you did. And I hope others find this useful.

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We're going to begin answering some questions and we're trying to get to as many as possible. If we don't get to your question...

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for any reason, please email it to our Ask the Expert email address that we'll give you. It's on the website and we'll give it to you after the event…

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and we'll share that in our closing slide also. So let me start with some of the questions that were sent in advance and I'm going to generalize this. Somebody asked about CT scans.

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And I was talking, the other day with Dr. Con Tam, who you know well, who's now practicing in Australia,..

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and he was talking about some studies that suggest that the size of the lymph nodes at the end of the treatment really didn't make that much of a difference…

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and what really mattered was how much CLL you had in your blood or in your bone marrow through MRD testing.

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So could you talk a little bit about CT scans in CLL and then I want to also specifically look at SLL as a different question, the role of CTs in SLL might be a little bit different. So, I'll just…

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make it a big, broad, general question for you, Dr. Jain.

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Yeah. Yeah, no.

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Great to be here. So, I think the CT scan is one thing, you know, so CT scans are part of the response criteria for CLL.

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And so, if you are enrolled in a clinical trial for CLL, very likely your physicians will be recommending at the time of response assessment...

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doing maybe a bone marrow biopsy and a CT scan because that's part of the response criteria. And if you don't do CT scans, then ideally you cannot grade the response per the criteria.

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What Con Tam or what has been reported now in several studies, including one study from CAPTIVATE data, which is combining ibrutinib plus venetoclax at the ASH meeting,..

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was that the small residual lymph nodes, let's suppose the guideline says all lymph nodes have to be less than 1.5 centimeter to call a complete remission,..

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but there are some patients in which the lymph nodes could be 1.7 cm or 1.9 centimeter. So, they are just above the cutoff…

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but they are still there on the CT scan and some of the data suggests that, that small residual lymph nodes are not really important…

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and what's more important, as Brian, you were saying, MRD testing in the blood, in the bone marrow, whether it's done by flow cytometry or next generation sequencing.

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So that seems to be the case, that CT scans may not be as helpful as we think about them.

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And as I said, you know, our practice, I think in my clinical practice,..

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certainly as part of clinical trials, that's still required and we do it. But outside of a trial setting,..

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yes, I do it for patients who had big bulky lymph nodes and especially intra-abdominal lymph nodes, which we cannot really feel,..

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I want to see how much benefit they're deriving from the treatment but outside of that, many times I just rely on peripheral blood flow cytometry for MRD detection…

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and less on CT imaging studies.

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And let's talk specifically about SLL in those patients. Maybe you could just remind us the difference between SLL and CLL and when would you treat SLL when it hasn't spilled into CLL and what's the role of imaging then and then I have a follow-up question on that.

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Sure. Yeah. So, you know, I think there are in all fairness, there are three kinds of similar but distinct entities. One is CLL and SLL, which many times we use these terms interchangeably...

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because for clinical trials, we also enroll patients with most of the trials really are used, we use CLL and SLL as the same entity and we enroll them in the same trials.

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And basically, in the big picture view, if you do not, if your blood counts are normal…

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but you have lymph nodes present, that will be considered SLL, small lymphocytic lymphoma.

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However, if you have CLL cells in your blood and there's a specific cutoff of at least 5,000 per microliter or you have low blood counts, let's suppose your hemoglobin is 9.5, your platelet count is 50,000…

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that would, by definition, be considered a CLL. And then there is another related entity called MBL, monoclonal B cell lymphocytosis, which is a kind of how you can think of a precursor to CLL where the doctor does a blood test, they see a little bit of CLL clone like blood flow cytometry, like some CLL cells...

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but it's not 5,000 cells per microliter, there are no lymph nodes and your hemoglobin platelets are fine. You basically feel fine.

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And those patients are labeled as MBL, monoclonal B cell lymphocytosis.

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So SLL is predominantly a lymph node-based disease. You can think of a lymph node-based CLL disease.

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So there, the role of CT scan may be slightly more important in a way because these patients have lymph nodes.

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Certainly, you can examine the lymph nodes by examination and see if the lymph nodes are growing but especially if someone has significant intra-abdominal lymph nodes…

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which we cannot really palpate, then there will be slightly more role for CT scan for monitoring those patients.

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But from a clinical trial standpoint, from a management standpoint, I view and not just I view them, I think we view them as the same, I think, in terms of the treatment, Brian, you were asking for SLL patients, generally it's a matter of big lymph nodes, bulky lymph nodes, their lymph nodes are growing...

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four or five centimeter lymph nodes in the neck, 10 centimeter lymph nodes in the abdomen.

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Significant symptoms, those will be the reason to treat. Some SLL patients will kind of morph into CLL, like their blood counts were normal, but two, three years later…

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you will start seeing the blood counts rising as well. And then technically now, they are CLL.

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And if the white count continues to jump along with low hemoglobin, low platelets and then, you know, certainly that may require treatment as well.

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So, another question that was sent in, and thank you for that. And I think the role of CT scans is diminishing and I think it's at some point. And one of the points that we make is.

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Sure.

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Unless there's a reason when you're diagnosed with CLL, that doesn't mean you have to have a CT scan at that moment either.

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Sure. That's true. I think it's an important point so we do not do CT scans at the time of diagnosis of CLL.

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So…

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You don't need bone marrow biopsy to confirm a diagnosis of CLL...

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and you don't need CT scans. So pretty much for most patients, there are exceptions to the rule, but for most patients…

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blood test, peripheral blood flow cytometry and a physical examination and that should be it. So we do not do CT scans…

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for newly diagnosed patients with CLL. Unless there is a reason to do it, unless we are really worried about something, but it is standard practice, no.

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And the other nuance I would add to this is that I've been in trials now where you have the option of a CT and an MR. And an MR is not as good at looking at nodes...

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but it's pretty close. And what we're really worried about, as you pointed out, isn't whether the node is 1.6 versus 1.5 centimeters. What we're worried about is that one centimeter or five centimeters in an MR can certainly tell you that.

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Sure.

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In the MR, avoids the risk of ionizing radiation so they take longer, they're more expensive, you've got to get your insurance to pay for it.

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But I think MR imaging is being used more and more in clinical trials, and I think that's a win for the patients.

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If a patient is taking ibrutinib and doing well on it with no adverse events…

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should they consider switching to another BTKi? I mean, this must come up in your clinic.

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Yeah, I mean, I think it's a common question these days.

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You know obviously ibrutinib had been a fantastic drug, FDA approved for CLL in 2014 so like just over 10 years now, 11 years now. So, over the years now we have realized and we have that there are at least two other new BTK inhibitors, second generation BTK inhibitors, namely acalabrutinib and zanubrutinib in the first-line setting and also pirtobutinib now...

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in later lines of therapy which appear to be safer and not, I should say appear, they are safer in randomized studies…

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compared to ibrutinib. So, we have actually, in our practice, I have stopped using ibrutinib for patients with CLL. I'm really using acalabrutinib, zanubrutinib as second-generation BTK inhibitors.

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Now, if a patient is on ibrutinib, I presume that this is their maybe first or second line therapy. They have been on it for many, many years.

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There have been data in the last several years that there are risk of ventricular arrhythmias, sudden cardiac death, patients found unconscious or, you know…

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dead in a way from presumably from arrhythmias, ventricular arrhythmias which have been really described.

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The irregular heartbeats where their heart irregularly doesn't pump the blood properly.

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Right. Yeah, basically the heart goes into a rhythm which is not a salvageable rhythm unless you shock the patients right away like a CPR and so those have been really described with ibrutinib. They have been, there have been none to very, very rare with the second generation BTK inhibitors.

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So, in that regard, I think this question comes up for patients who have been on ibrutinib for many, many years…

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that should they switch their ibrutinib to a second generation BTK inhibitor. In my practice, I have talked to all my patients who are on ibrutinib for long term and given the options of either switching to a second generation BTK inhibitor…

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or sometimes, I have also used a drug-free holiday where if they have been for many, many years and I have given them a drug-free holiday to say, and many times patients just do fine...

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after the disease has been well controlled for a while. And I would say there are many patients who have just continued ibrutinib. They feel that they have been on a drug for seven, eight years, six, seven years, doing well.

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They haven't had side effects. They're tolerating it well, why to switch to a different drug? And so, I think those are good questions. These are not straightforward answer, but I think I certainly think that you should discuss with your…

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treating physicians, treating oncologists about these options and then make a decision for yourself if you want to switch versus stay the course.

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There was a question, in fact, a few questions on low IgG, and I just want to point out that IgG and low neutrophil count are entirely different things. Sometimes you see them in the same patient, but they're entirely different entities. So, neutropenia is the medical term for low neutrophil count.

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And low IgG is a low immunoglobulin. That's pretty common in CLL. And what do you recommend to your patients who have low IgG? Should they wear a mask when they go out and about? What are you telling people now?

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This is really a tightrope, isn't it? We don't want people to stay at home, be secluded, become socially isolated.

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At the same time, we don't want them to get COVID or RSV or pneumonia or influenza.

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So, let's specifically look at that person with a low immunoglobulin.

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Yeah, I don't think there's a standard practice and I would say, every maybe CLL doc practices a bit differently. I think, I would say low IgG per se, you know, if you're not having frequent infections, so I mean, so there's one component is IVIG supplementation.

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That one should supplement IVIG for a patient of mine who has low IgG.

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So, the practice and general recommendations and the same practice we follow, I follow in my clinic, is that if someone has low IgG, so typically depending on your lab, it could be less than 600 or less than 500 range…

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and a patient is having significant infections affecting quality of life...

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or at least one hospitalization each year for pneumonia or something like that,..

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that would qualify a patient to get monthly IVIG supplementation. And for some patients, that can work like really a miracle where patients really improve significantly the quality of life after starting IVIG.

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So, that's the kind of the guideline of starting IVIG. But there are a lot of patients with CLL who have low IgG level but they're just fine. They do not have frequent infections.

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And in those patients, I don't recommend anything different to say I don't recommend IVIG supplementation.

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Regarding wearing masks, I think that is a bit of a you know, uh, I would say I generally, it's only I mean if they're going to crowded places things like that, that's a general recommendation for CLL patients in general.

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I would say I don't make that distinction per se in my practice based on IgG level to say...

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but certainly I think it would be a reasonable thing to do. But again, I would say this is a practice which may be different among different CLL physicians.

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Yeah, on a personal note, I wear a mask in a crowd.

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Sure. Sure.

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If I'm outdoors, wearing a mask. I'm standing in a big line or a crowd, if it's crowded and I'm indoors, I tend to, to mask.

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Yeah.

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You mentioned something in your discussion about ibrutinib, and there are some questions about intermittent therapy with BTKis, and I guess In Europe, there's some research going on. It doesn't tend to be used that way here. And let me ask you also to segue from that to PI3 kinase inhibitors…

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because they're very active drugs, but they also have been quite toxic and there's been thought maybe if we used intermittent therapy. So maybe I can get you to talk about intermittent therapy

with the BTKi's and intermittent therapy with the PI3 kinase inhibitors. Maybe remind people what a PI3 kinase is…

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before you get to that.

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Sure. Yeah, so currently, you know, the BTK inhibitor therapy is recommended to be taken continuously daily until your disease progresses or you develop untoward toxicities.

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So, there have been some efforts, I will say limited efforts, in fact, we have a trial at MD Anderson as well looking at two years of acalabrutinib…

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plus obinutuzumab and then patients stop therapy at two years of acalabrutinib irrespective of the response they're in.

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And then we watch them and then if their disease progresses, then we resume acalabrutinib. So basically,..

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a time-limited approach, then stopping it, then resuming it at the time of disease worsening.

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But again, these are small studies, and we'll have to have longer follow-up to make some conclusions from these trials.

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So, I would say the standard practice still unfortunately is not what it is, indefinite therapy.

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I would say that there is data out there, that there are patients with ibrutinib, where most of the data is.

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Let's suppose patients get atrial fibrillation, some side effects and you decide to hold and then basically keep holding the ibrutinib.

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There's data that you can get sometimes a couple of years out after stopping ibrutinib where, when eventually the disease may progress down the line.

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So, I will say not great data in terms of stopping ibrutinib monotherapy itself after one or two years.

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However, and as I discussed in the presentation, we expect acalabrutinib second generation BTK inhibitor, plus venetoclax to be approved as a hopefully as a one-year therapy. It's not done yet, so we will have to see when it gets approved.

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And thereby then you are using a time-limited BTK inhibitor, right, for the first time in the United States…

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where you give one year of acalabrutinib, which is a BTK inhibitor,..

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one year of venetoclax and stopped. So that's where I guess some of the data is in terms of shortening the duration of therapy…

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is combining it with venetoclax where I think the most medical data is at this time.

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For the second question about PI3 kinase inhibitor, so PI3 kinase is another pathway in the cell which the drugs have been developed over the years…

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for it. And early on, like 10-12 years ago, there was a lot of excitement about this pathway and many drugs were being developed. Two of them are FDA approved;..

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namely, idelalisib and duvelisib. There was a third one called umbralisib which was in development, but then development was halted some years ago.

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They are good drugs, but there are some issues with using those drugs. They can cause some immune side effects,.

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diarrhea, colitis, inflammation of the bowel, pneumonitis, inflammation of the lungs,...

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increased liver function tests, increased risk of infection. So those have been concerned However, they work for some patients and, you know,..

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they're not something to be used for a newly diagnosed patients…

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but I've used them in occasional setting where patients have failed all the other standard therapies, for example, BTK inhibitor, venetoclax, maybe CAR T-cell therapy…

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or and we want to do some kind of a temporizing therapy before we can do maybe another clinical trial or do something else.

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So, in those situations, I think these are oral drugs and could be but again, it's a small patient population to say but certainly a consideration they're FDA approved drugs in that multiple relapsed refractory patients who have failed practically all other FDA approved therapies.

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I know there was some interest in using these intermittently, not in the sense of using them like for a year or two years but using them for maybe a loading for a while and then taking one week on, sometimes as long as three weeks off, one week on.

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These kinds of things to see if it can control. Is there anything going on that you know in that area to reduce the toxicity of these drugs?

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Yeah, so there were some trials, I will say maybe a couple of years ago, a few years ago, which were planned or with this PI3 kinase inhibitor, which exactly what you're saying, Brian.

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Kind of in a short term, you know, two weeks on, two weeks off, one week off, one week off kind of a schedule to mitigate some of these toxicities especially for the PI3 kinase inhibitor.

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But a couple of years ago, you know, two, three years ago, when one of the other drugs called umbralisib kind of failed in the trials.

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And then FDA was, kind of have been a bit strict or, you know, about. PI3 kinase inhibitor as a class of drug so, I think some of the interest in developing these drugs for patients with CLL has, you know, waned so I don't know if the trials are still being pursued. I highly doubt it…

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for any PI3 kinase inhibitor in the context of CLL anymore...

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just because of so many other drugs are coming along. We talked about the degraders and bispecific antibodies and CAR T-cell therapy.

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But certainly, I think that's an, an area of research. But again, I don't think of it's being done at this time, as far as I know.

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Well, I'm going to ask you a question that was asked, and I bet there isn't a definitive answer to this, but I wanted you to talk a little bit about the role of CAR T therapy in CLL.

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And the second question along that line is, are the benefits specific to ibrutinib if you add it in, or could you take acalabrutinib or pirtobutinib or zanubrutinib and get those same benefits? And I know you may not, some of this is a data-free zone here but…

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what are your thoughts on both of those questions? First, the role, how do you use CAR T as a clinician?

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Yeah, so, you know, just as a background, CAR T was approved. Liso-cel is the only CAR T approved for patients with CLL is a CD19 directed CAR T cell therapy…

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approved in March of last year. And since that time, we were involved in the development and the clinical trial as well, but now since it's approved, last year, we have treated several patients with CAR T cell therapy. And in our practice, we use it for patients who have received at least…

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both a BTK inhibitor. – it could be ibrutinib, acalabrutinib, ibrutinib, …

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and venetoclax. And then if they have failed both of these therapies, then suddenly it's an appropriate strategy to do.

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Obviously, we also have pirtobrutinib approved for the same patient population. So what has happened, at least in my practice, is that I have started the patient on pirtobrutinib,..

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that will help debulk the disease, and then try to get them to CAR T-cell therapy while they are still on pirtobrutinib.

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So that leads into the second question that which is the best drug to combine the data, Brian, you presented from ASH meeting…

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was liso-cel plus ibrutinib. And I think a big unanswered question in the field is…

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will you get the same benefit if you were to use acala, zanu or pirto or nemtabrutinib for that matter?

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And there are some clinical trials which are being planned right now of combining these newer BTK inhibitors with CAR T cell therapy and that remains to be studied at this time.

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I would say there was some data presented in a more of a basic science session at ASH in an oral representation…

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where the investigators looked in the lab different BTK inhibitors, including basically acalabrutinib with CAR T cell therapy and they compared it to ibrutinib with CAR T cell therapy and their conclusion was that acalabrutinib has a similar benefit or synergy. And again, it goes into more science where they say it's…

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related to one of the immune cells called myeloid-derived suppressor cells in our lymph nodes and bone marrow.

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And which both ibrutinib and acalabrutinib decrease and thereby it improves the efficacy of CAR T. Again, that's lab work, not in the patients.

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And as Brian, you said, it's a data-free zone from that aspect. And I think maybe in the next year or two, we will have clinical trial data in that regard.

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There's a number of questions on combinations and one of the trials that excited me there was the CELESTIAL trial and a patient asked about that, and that's a combination Zanubrutinib and sonrotoclax so maybe you could tell people a little bit about…

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that trial in what do you think the prospects are for zanubrutinib is already approved.

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But what do you think the prospects are of sonrotoclax and being approved? Somebody's asking about that.

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Yeah. So sonrotoclax is another venetoclax, kind of a similar class of drug called a Bcl-2 inhibitor.

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We don't truly know if head to, I mean, no trial has been done head-to-head comparing them, but CELESTIAL trial, which brand you mentioned, is a trial in this regard…

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where patients with CLL who had no prior therapy, but they needed treatment for this was their first treatment.

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They were randomized to receive venetoclax plus obinutuzumab, which is the current standard of care for one year duration and other half of the patients were given sonrotoclax and zanubrutinib...

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for one year. So that's a head-to-head comparison and this is the so-called CELESTIAL trial so I think eventually, the time will tell when that trial reads out if sonrotoclax with zanubrutinib, so two pills together,..

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is better than venetoclax plus obinutuzumab.

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And again, we are all eagerly waiting for that data when and if when that reads out.

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So again, that is an unanswered question right now, whether, and it's not just on sonrotoclax, there's another drug called lisaftoclax.

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So there are other new Bcl-2 inhibitors like venetoclax being developed in phase three studies and I guess in some sense, the time will tell if these will be better than venetoclax or if they will replace venetoclax. And I think that's something we are all eagerly waiting for the data.

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One of the questions a patient asked, and I think they make a good point here, is that they're on venetoclax and obinutuzumab...

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and for adenopathy being a big problem. And they had enlarged tonsils and…

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that actually significantly helps shrink their tonsils, which is lymphoid tissue. We think about the nodes in our neck or our groin, our armpits, interior nose...

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but there is other lymphoid tissue too, like the tonsils and stuff and they can respond to these therapies.

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And the question this person asks is, is there a role, if things have shrunk and gotten better for continuous venetoclax? When venetoclax was first approved…

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it was taken like you take the BTK inhibitors. So do you see a role of people staying on venetoclax maintenance therapy or, you know, so… first, if you want to comment on other lymphoid tissue in the body and then the second is…

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about continuous venetoclax. There was a number of patients who were asking about that, maybe wanting to avoid the immunosuppression effect from obinutuzumab.

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Yeah, so as Brian said, so yes, tonsils is one of the lymphoid organs, you know, so technically, I mean, there's a lot of other things we see which gets enlarged when patients have CLL is spleen and liver sometimes, and those also are the organs which regress…

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with adequate treatment of your CLL. So, these are other where the CLL resides in the lymph nodes, tonsils, liver, spleen, obviously blood and bone marrow.

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In terms of the treatment, yes. So as Brian said, when venetoclax was originally developed,..

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it was developed as a continuous monotherapy, daily monotherapy once a day you take it as you take currently an ibrutinib, acalabrutinib and you take it for a long, long time.

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And I have some patients who have been taking it for five, six years and still taking it. That's a small minority of patients.

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But then when venetoclax development occurred further, it was decided to combine it with either rituximab or obinutuzumab and a decision was made to shorten the duration of venetoclax…

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for patients who's relapsed refractory, it was two years of venetoclax, for newly diagnosed patients, it was one year of venetoclax.

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So having said that, I think that is an unanswered question in the field is that and especially it comes up for patients, some patients who have 17P deletion or P3 mutation, which is a high risk.

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Our current recommendation is to use a BTK inhibitor once a day every day continuously.

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Is that could I use venetoclax still with obinutuzumab and maybe I can continue with venetoclax not just for one year, as what the guidelines would say, but continue basically longer you know, uh, and I think those are the questions which are still kind of unanswered in the field in terms of…

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you know, long-term use of venetoclax for these patients. I would say, you know, some of the medical data which has been reported, there's not a concern for long-term toxicities per se with long-term venetoclax use. It's not that if you use venetoclax for five years or…

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four years, you will have really low blood counts or your bone marrow will be, like, suppressed forever or something like that.

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I think it's just how the field of clinical development has occurred that venetoclax development really focused highly, you know, after the initial trials on time-limited approaches of one to two years. So I think, yes, there could be a point of using long-term venetoclax use for some patients, and I have done that for some patients, especially in relapsed refractory setting.

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Where I'm hesitant a bit to stop after two years if a patient is MRD positive, thinking that patient would relapse, and I continue venetoclax longer.

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But those are, I would say, more individualistic kinds of decisions rather than maybe significantly data-driven decision.

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And to be clear, while many doctors prefer BTKi’s for the patients who have a TP53 aberration or 17P deletion, venetoclax works well in those patients, doesn't it?

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Yeah, absolutely. Absolutely. I think it's just like for a newly diagnosed patients if you use venetoclax plus obinutuzumab,..

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you know, for one year, the data from a trial called CLL14 trial so just that the long term, you know, it doesn't work as well and you may have to repeat it or things like that. So that's a concern. But yes, it works well.

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But could you need to use long-term venetoclax and that is somewhat unanswered.

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Well, here's another one, and I just want to get a sense of your thinking about this and how you're going to have this conversation with a patient…

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because odds are good, and we're all hopeful that acalabrutinib and venetoclax will be an approved option for patients, and already it's an off-label option for patients.

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And we have another great combination, limited duration therapy, venetoclax and obinutuzumab.

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How are you going to make these decisions with somebody in front of you saying,..

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if the patient, and also we have great continuous therapies, monotherapies,.

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how? How? This is the bread and butter of what you do, isn't it? Making these decisions.

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Yeah.

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Yeah. Yeah, so I think it adds in some sense a significantly new approach for the patient in the United States, because some of you may know ibrutinib plus venetoclax where most of the data is with this time limited approach of one year duration…

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is approved in Europe and Canada and many other countries, but not in the US.

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So, one based on the AMPLIFY study which I, which I showed in the slide deck, if this coming, this year I mean, one year of acalabrutinib plus venetoclax is approved, it does add in my mind a logistically, a much easier combination, right?

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Currently, the options are you take a continuous acalabrutinib with and without obinutuzumab or you take a continuous zanubrutinib.

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Obviously, you can take continuous ibrutinib as well, but it's less preferred.

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Or if you say, no, I want a one-year therapy, time-limited approach, which many younger patients like to do because they're done with it and it's just, you know, kind of we're done in one year…

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and they don't have to deal with the side effects of the BTK inhibitors.

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Now the only choice is when you talk venetoclax plus obinutuzumab for one year duration, but then adds a slight logistical complexity in terms of the tumor lysis monitoring, once a week labs for the first couple of months which sometimes can be tricky for treating physician's office to kind of manage and just giving a pill every day. It just seems logistically, just easier approach…

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for one year duration. I think logistically will make life easier because then you say, okay, you need to take two pills for one year and then you are done.

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There's no infusion of at least you're using the two drugs together.

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Now, for which patient, I may prefer that. You know, I think one thing would be if you look at the data.

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You know so, um, and then it's a bit of a tricky, I guess, explanation in a way or difficult maybe I think it may go down to the genomics of the patients.

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If someone has mutated IGHV, I think one year of venetoclax plus obinutuzumab does really well.

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But if you look at the one year of acala venetoclax, it also doing almost similarly well, maybe slightly lower, but also similarly well. So that's a group of patients I think I may favor that if you'd want to do one year of acala, ven, logistically much easier. I think that that would be fair. And I may use, and again that…

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it's just maybe my personal preference...

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some MRD-guided therapy, which again was not per se in the trial, I would say.

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But we have shown data that two years of therapy may be better when you combine ibrutinib plus venetoclax. We don't have that with acalabrutinib plus venetoclax.

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So I think, so that's one group of patients where I may consider it…

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or unmutated IGHV patient. The AMPLIFY data suggests that the triplet may be the best triplet of acala, ven and obinutuzumab.

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We also know that obinutuzumab may not be the best for unmutated patients for one year iteration. If you're doing a one-year treatment…

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for unmutated IgG patients, I may prefer a triplet regimen based on again on the AMPLIFY study. So, I think these will be the conversations with the patients because again, triplet regimen is much more risk of infection. Much more monitoring is needed. I should say infection list of…

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low blood counts, tumor lysis monitoring and whatnot. So, I think this at the end of the day,..

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we have many good options and it will come down to discussion with the patient to say logistically and how they want to do it.

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But I think at the end of the day, if you were to choose one of the regimens, many regimens we discussed, you won't be wrong. I mean, I think most of them are really excellent regimens really so but I think there are these fine…

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points which again many times it's really a discussion with the patient and see what exactly they want to do.

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And what I would add to it is, whatever decision you make today might be informed differently with data that comes out in a year from now or a different combination.

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Sure. Sure, yeah.

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So, we're constantly learning about this. Is it right? This is kind of a technical question, but patient A and O has really good results for progression-free survival, overall survival.

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But adding venetoclax, the AVO that we've talked about, is the benefit from that it gets more people into a deeper remission, a complete remission, uMRD?

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Maybe talk a little bit again, I know you touched on this, on the difference between a complete remission in uMRD and what the thinking is and maybe what the role of ven or adding another therapy is to get a deeper remission in is.

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Yeah, so I think, so complete remission definition is based on pretty much just thinking out is like your blood counts are normal and your lymph nodes are normal.

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That's pretty much under a specific definition, but in the big picture view, that's what the definition is. You feel well, your blood counts are normal, your lymph nodes are normal.

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The MRD definition, MRD is measurable residual disease or minimal residual disease is done traditionally by flow cytometry, either in the blood or the bone marrow,..

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which can pick up one cancer cell in 10,000 normal cells. So, we generally say 10 to power minus four sensitivity.

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Though there is a next generation sequencing assay by Adaptive which, this is the only FDA-approved assay at this time,..

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which can go to a minus six sensitivity, so a much deeper level of sensitivity. So, that's the MRD test.

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So those are the kind of the two flow cytometry and the next generation sequencing MRD testing which are currently kind of available and can be used for patients.

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Brian, remind me, just kept in my mind the question you were asking me. It just skipped my mind.

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Yeah. Oh, yeah.

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Yeah, just the differences between first,, um uMRD and CR, which the other is adding something in like venetoclax or might be adding in obinutuzumab in some circumstances.

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Yeah.

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All right. So, I think the good right, right, right. Right, so I think, and I remember the question, so the question was about the acalabrutinib plus obinutuzumab, which is already FDA-approved regimen based on the ELEVATE-TN study…

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which shows high rates of what is called progression free survival and survival overall. And in that study, if you look at it, about 30 to 40% of the patients achieved what is called undetectable MRD or uMRD…

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at ten to twelve minus four, which is a good number but when you add the triplet,..

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and I'm just quoting now from the AMPLIFY trial, because they did add venetoclax to make it a triplet regimen, acala and obinutuzumab.

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And if you look at the MRD data, that number rises up to like 70, 80% range, you know, so it doubles, almost doubles the uMRD rate.

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Now, I would expect, and most many studies have shown in CLL that the MRD eventually likely will correlate with PFS, progression free survival. So, if you are deep remission early on, intuitively also makes sense that your remission will last longer.

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So suddenly by adding the third drug, namely venetoclax to acalabrutinib, which is already FDA approved,..

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you do two things: one is when you add venetoclax, you also have to realize that if you're just using acalabrutinib, you're not doing acala for one year, you're doing acala forever…

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and obin is for one year or six months. But when you add the triplet of venetoclax,..

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you also cut down acalabrutinib from forever therapy to a one-year therapy, right? So, you just do acala for one year now.

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You'll give venetoclax for one year. And it looks like during that one year, you are achieving much deeper level of MRD.

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So certainly, I think, you know, and not just the AMPLIFY data which I showed, there's also data with ibrutinib, venetoclax and obinutuzumab. There's data with acalabrutinib with Matt Davids.

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The data with zanubrutinib, with Jake Soumerai. We reported data with pirtobrutinib, ven + obi, so basically there are a lot of data sets which are using triplets in investigational clinical trials and all are showing very high rates of uMRD remission.

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And our expectation is that that will correlate several years down the line...

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with high rates of patients remaining in remission. But again, kind of the time will tell you know what, what will happen.

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And we do know that across a number of different treatments, getting the disease driven down as low as possible seems to make a difference.

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In the chemoimmunotherapy you presented, your team at MD Anderson has shown that people who get into this undetectable measurable residual disease with FCR are the ones that can have these extremely durable remissions. So there's reasons.

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To be hopeful. I was asked about the monkey data and why is this important when these monkeys didn't even have CLL?

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And the point is, that the point is that the CAR T that was produced in the blood of the monkeys attacked the can't, would or can't attack the normal B cells in that monkey.

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The assumption is it would also attack the cancerous B cells because they have the identical the CD20 markers or the CD19 markers…

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depending on how you engineer it, that are also on the normal B cells.

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That's not proven, but there's no reason to believe that wouldn't happen. And that's why they're moving into human trials to see but to get a monkey model with an understanding, is to get a monkey model with a CLL type cancer is not an easy thing to do.

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So this was a step that was necessary. I just would like your, as a physician scientist, I would like your thinking on this in vivo CAR T. I mean, it seems, I remember when CAR T seemed like so space age and this seems…

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way out there. I mean, but what's your thought of this as a scientist?

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Yeah.

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It's actually, you know, Brian is fascinating. So you mentioned this and actually I've been, uh, involved with some of the pharmaceutical companies which have been working in the space for actually maybe six months or so or some time, similar to what, you know, there are some other…

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companies which also have now similar aspects of in vivo CAR actually from myeloma also for lymphomas.

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And the concept is very similar is that you inject these lentiviral particles into the patient but normally speaking, these lentiviral particles will go in and they can, they will infect or any cell and that's not good. Obviously, that's not allowed.

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But they have engineered these particles in a way that they will only go to the T cells, the patient's own T cells, and then they will basically make those T cells into the CAR in the patient himself like or herself to say. So,

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this is fascinating. And actually, we are also trying to work again with some pharmaceutical companies which have these CAR Ts…

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to bring it to MD Anderson to say. So, I think this is fascinating. I think this, if this works, this could change how we think of CAR T because right now,..

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CAR Ts, as you know, as the patients in the audience know, would collect your own cells take them out two, three weeks into the manufacturing, then infuse the cells back but here we are saying human body is the best to make the CARS.

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Just inject these, kind of raw material into the patient and let them find the normal T cells, make them CAR in the human body.

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And if it works out, then it will really make it easier,..

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really. And that we don't have to do all this look of pheresis and manufacturing units to be established. Patient body is the body which is making the CAR T or providing the milieu...

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to make the CAR T. So, it's fascinating. And I actually, am really looking forward and trying to see if we can open a trial at Anderson soon with similar concept for patients.

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People asked, and I know you went over this a little bit, but could you remind or give one more explanation of how a degrader works differently than an inhibitor because there were some questions on that.

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Yeah. So, the general thinking is that in terms of the degrader inhibitors.

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Inhibitors go attach to a specific protein or, you know, for example, in the context of ibrutinib they form this covalent bond with cysteine 481 residue on the protein itself and by forming the bond, they disrupt the functioning of the protein.

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Pirtobrutinib works in a slightly different way, but the basic concept is the same...

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is that you're inhibiting the functioning of the protein. And that's how these inhibitors work. And besides CLL, there are many approved in different cancers. The degrader is a new class of drugs and they are being developed not just for CLL, where this seems to be one of the most advanced, but they're also being developed for other targets…

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in heme malignancies as well as in solid tumors. And the concept here is that you basically degrade the entire protein itself, the entire BTK protein gets degraded in the cytoplasm of the cell…

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by this ubiquitination pathway and it just gets kind of gobbled up completely so there's not present in these cells anymore.

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And it does seem, and again, this is an area of active research, but it does seem to be somewhat independent…

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of the known mutations, for example, cysteine 481S mutation or other mutations which have been described in the context of pirtobrutinib resistance.

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Non-cysteine 481S mutation, L528W and others. Again, that's again an area of active research where so seems to that mutations don't matter because you just gobble up the entire protein. Again, that's a very simplistic way of maybe explaining it.

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So, and the data, you know, a couple of trials I mentioned, which were at ASH and some other trials which are being done and not public yet really are showing very encouraging results…

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with these degraders. And again, I won't be surprised if the degraders continue to work the way they are, the efficacy and we see in the next year or so the data is maintained in terms of the safety and efficacy that there will be very soon…

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being used in patients or maybe trying to replace inhibitors. Because of, they're very specific. They just deplete the protein, the BTK protein, they don't deplete anything else.

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And again, I think the safety and efficacy so far to me seems quite promising.

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They don't have the off-target effects because these kinase, they inhibit other kinase, which is an enzyme.

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Correct.

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All right.

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And it's those off-target effects that lead to issues. So along that line,..

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where are you using degraders? Obviously, they're only available in trials right now, versus where do you use pirtobrutinib or nemtabrutinib, which is like pirtobrutinib but only available in trials,

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because it seems both of those are for people who develop resistance to a BTK, the covalently binding BTK, acala, zanu, and ibrutinib. Yeah.

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Yeah, right. So, I think certainly these are the patients who have so called, what we call double exposed patients. And again, just that terminology we use…

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in medical term, but it means patients who have failed or have used, they may have stopped it for toxicity.

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Co and BTK inhibitor, so ibrutinib, acalabrutinib, or zanubrutinib and have also failed venetoclax or for that matter now any Bcl-2inhibitor. Once you have failed these two classes of drugs, those are the patients where practically lots of these therapies are being developed right now. Certainly pirtobrutinib got approved. So that is one approved. CAR T-cell therapy got approved.

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But degraders are in the same class. So, I think certainly I think if a patient is eligible for a greater study and they have failed ibrutinib, they have filled venetoclax. I think it's certainly, if they're interested in participating in the degraders,..

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knowing some early safety data and efficacy data, I think is pretty worth it. On the other hand, if they want to start standard of care pirtobrutinib because that's FDA approved, I think that's, that's absolutely perfect. And CAR T cell therapy. So, think we have..

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CAR T-cell therapy, pirtobrutinib, and there's investigational clinical trials. And I think those are the options we present to the patient.

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And there are patients who may want to participate in the trial.

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Obviously, some of the early data with degrader specifically looks pretty promising, so they may derive benefit from that.

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Will degraders be used as continuous therapy or limited duration or we don't know yet?

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So right now, the trials are only in phase one, so they are being used as a continuous therapy. I think eventually it's possible, we may start using them as a time-limited approach, but I think that's still, I think, it's sometimes away.

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So, here's a question you're going to like, and it's about the C word, cure.

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So, this is a person who's, and you can talk a little bit about this, who's MRD negative. Does that mean I'm cured? And the quick answer to that is no, but maybe.

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You know, maybe better. Do I still have CLL? When I was at a doctor's visit, I don't know what to say, and you're going to like this.

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Right.

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The patient had iFCG in 2018-19, so maybe you can tell people what that is. She's been in remission since finishing this12 months of treatment.

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I have no maintenance drugs. We're all interested in being cured, Dr. Jain, so talk to us a little, and you have to pass uMRD to get to cure. You're not cured unless you're uMRD. But if you're uMRD, you're not necessarily cured. Usually, you are.

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Yeah.

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So, help us with that and maybe answer this lady's question, yeah.

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Yeah.

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Correct. Sure. Yeah. I mean, first of all, I mean, iFCG is actually the trial from which I'm the principal investigator. So, thank you for participating in the trial for the iFCG study.

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So, and I will maybe talk about that in a second, what that study was just for everyone to know.

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But coming back to your question about cure. And I think this is a question which is, is a question, you know, so there are a few kind of, you know, I think maybe philosophical question, like, do you need to be cured to live a normal life expectancy with CLL, right?

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If you have one in a 1 million, I'm just again for the sake of argument, I'm making it one in one million cancer cell, which no one can detect except sophisticated lab techniques,..

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you won't know it. Your doctor won't know it. Your blood counts won't show it. Your lymph nodes won't show it but you have one in one million cancer cell in your blood of CLL.

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You will live a normal life. I mean, you can just continue to live a normal life.

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So, I think there's a question of what is, what is cure? Some patients say, okay, if you are 10 years and out from the last therapy and you're not on any therapy…

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for the last 10 years and we don't find any evidence of disease, maybe if you have cured your leukemia.

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But you know actually, even from FCR studies, actually, we had some patients who have had late relapses 15, 16 years later. So, it can happen that even late patients can relapse.

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So, I think it's a, you know, I always say that I think one thing we know, I think for patients who are diagnosed in today's era with CLL,..

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with the kind of therapies we have now, kind of therapies which are coming,..

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I think for a majority of the patients, I think we'll have a normal life expectancy for their disease, for their age and match control to say.

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Whether they will be cured of their CLL, whether, you know, I think it remains to be seen. So, I will just make in the interest of time, one quick example that, you know, we treated patients with ibrutinib and there was a study published last year…

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where they looked at the outcomes of patients who got ibrutinib as a first-line therapy. This was their first therapy.

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And then they ask the question, what is the survival of these patients…

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compared to their age match control? Like so if someone is 60 or we say, okay, 60-year-old healthy person or whatever the same medical issues, what is their life expectancy as you ask that question.

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And it was the same. Patients who got ibrutinib had CLL. They lived the same duration for controlling for the same person of their age who didn't have CLL.

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Now, as you may know, with ibrutinib, you never cure CLL.

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You will still have disease present, but they are living their normal life expectancy so I think it's a bit of a tricky kind of thing to say that if I'm cured of your leukemia.

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There are some therapies like CAR T-cell therapy where there are some really excellent examples for a small number of patients who maybe we can say they are cured.

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FCR therapy, which Brian mentioned, Dr. Keating at our center established it many years ago.

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There are patients with that. iFCG study was a new version of FCR, which we developed back in 2014, 2015. We started the study in 2016, stopped accruing in 2019.

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Where we replaced some aspects of FCR to make it better, which I certainly think that it is better than FCR.

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And now we have many, many patients long term as the person you're seeing, the patient who kind of alluded to her history.

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So, I think whether they can say cure, I think now what we're trying to do for these patients, I think we are checking the new assay, the MRD assay,..

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the one in one million assay to see if we can still detect the disease.

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But I think, you know, I think it's a difficult question to kind of answer. But in my opinion,..

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you don't need to be cured per se to live a normal lifespan for patients with CLL, though for some patients, it may be a difficult different issue.

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Well, we're running up against the end of this, and this has been incredibly useful. I know this is one of our more advanced topics, for sure.

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And this is… this is an area that demands sophistication. So, I'd say to the people who've hung on to the end, good on you.

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And it's an iterative process learning about this. I mean, listen to it again, go over it again. Dr. Jain and myself may have used language that you weren't comfortable with.

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But please spend a little time with it, learn it, because this is the cutting-edge stuff.

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If it's over your head now, it won't be a year from now. I can guarantee that. You'll learn from this.

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And it can be a very worthwhile to be on top of what's happening in the latest science.

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Any final thoughts about ASH or anything you want to share with the community?

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No, I would say I think as we kind of discussed, I think, you know, the CLL field, you know, has advanced tremendously in the last 10 years, right? Since ibrutinib approval,..

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a decade of progress in the context of CLL. And you know the outcomes, which were 10, 12 years ago and now are dramatically different.

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But I'm very, very optimistic and hopeful about the new drugs which are coming along. We talked about the BTK degraders,..

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we briefly talked about bispecific antibodies, we talked about CAR T cell therapy. We talked about some new ways of in vivo CARs which are still, you know, really investigational, but we'll see how those pan out.

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We talked about some new techniques of measuring deep levels like MRD testing at minus six. So, I think all these coming together, I think we will further continue to improve the outcome of patients with CLL. And again, as I said, patients who come to see me here…

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I tell them routinely that it's my really strong belief that though you're diagnosed today and if you're diagnosed today or you know in this era that you will have a normal life expectancy for the most part with the therapies we have now.

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Certainly, there will be patients who may have a tougher course with genetics or their high-risk features and whatnot and may not respond. But for most part, most patients, I think we can have a normal life expectancy and deliver really good care. And these therapies are much, much safer than what used to be with chemotherapy. So I think…

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we're continuing to make significant progress. And I think this year ASH certainly show some of the new, you know, kind of continued progress for these many of these drugs.

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Well, Dr. Jain, I'm so grateful for you and your colleagues are doing, the research that you're doing, the care you're giving to patients at MD Anderson and a lot of these researchers are collaborations not only across the US but internationally and…

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you've led a lot of that. So, I want to thank you for that. I want to thank the participants in this. I want to thank for the great questions we had, I do want to thank Lilly for, um, their sponsorship in making this event possible.

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There will be an event survey and I would like to, you to provide your feedback for future events. It was recorded and our IT team will get that up for you very quickly.

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We have a fun event coming up, which is an Ask Me Anything event…

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which is going to feature a CLL patient, Doreen Zetterlund, and Dr. Jackie Broadway-Duren, whose an advanced practitioner, a nurse practitioner, and she's going to be answering any practical or other questions you have about CLL. And if you haven't attended any of these Ask Me Anything events,..

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they're really… a fun event really fast and a lot happening with them.

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So, I'm going to ask you again to ask you to remember that the CLL Society is invested in your long life.

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Please invest in the long life of the CLL Society by supporting our work.

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Stay strong. We are all in this together. Thanks to everyone.