The Future of CLL Treatment: What's Next?

Operator
Greetings, and welcome to "The Future of CLL Treatment: What's Next?" a live telephone and web education program. At this time, all participants are in a listen only mode. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

Lizette Figueroa-Rivera
Hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Adam Kittai for volunteering his time and sharing his expertise with us today. For this program, we'd like to acknowledge and thank our supporters, AbbVie, BeiGene, Genentech and Biogen, and Lilly. Over the past 10 years, The Leukemia & Lymphoma Society has invested more than $52 million to accelerate pioneering research in chronic lymphocytic leukemia. Our investment has unlocked knew insights on CLL

disease mechanisms and advanced new therapies to improve outcomes and care for patients. The therapeutic landscape for CLL has evolved significantly in the past decade. Next-generation sequencing has expanded our knowledge of the molecular underpinnings of the disease, ushering in promising precision medicine approaches.

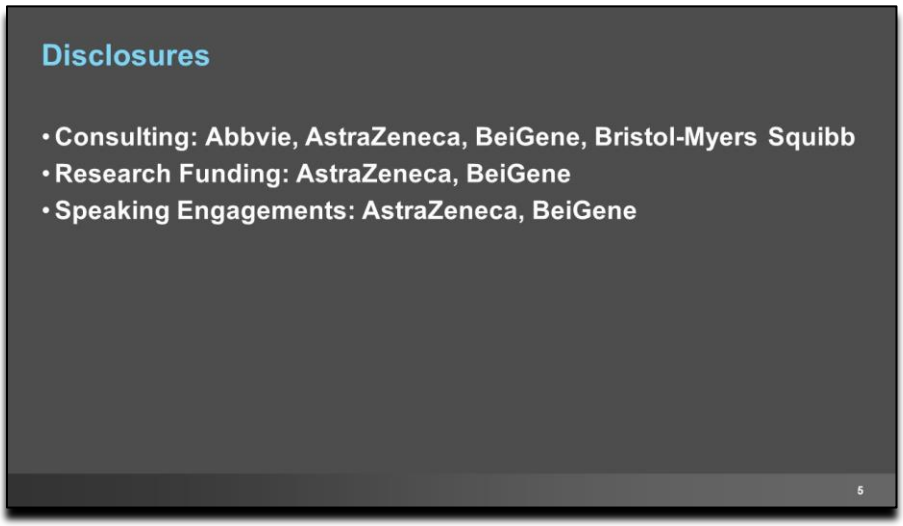
LLS has been at the forefront of CLL treatment innovation and continues to invest in cutting edge research to find cures. LLS is laser-focused on advancing novel therapies and optimizing the best combination and sequence of treatments so more patients with CLL can experience long-term disease control and improved quality of life. As the leading source of free blood cancer information, education, and support for patients, survivors, families, and healthcare professionals, LLS helps patients navigate their cancer treatment and ensures they have access to quality, affordable, and coordinated care. Research will help us achieve an end to cancer. In the meantime, patients need help before, during, and after their diagnosis and treatment. Thank you for participating in our program today and allowing us to be here for you.

Disclosure Slide

The Future of CLL Treatment: What's Next?

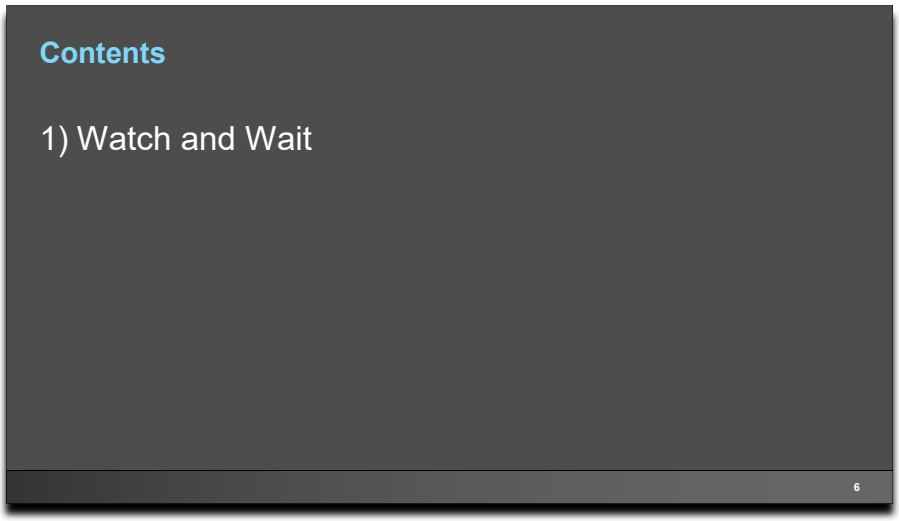
I am now pleased to introduce our speaker, Dr. Adam Kittai, Hematologist Oncologist, Associate Professor, Assistant Director of Lymphoma Clinical Research and Leader of the CLL Clinical Research at Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Kittai, I am privileged to turn the program over to you.

Dr. Adam Kittai
Hi, everybody. Thank you for having me here to discuss CLL, the future of CLL treatment, and what's next. I just want to say thank you to LLS for inviting me to give this seminar. And I'm looking forward to an engaging question and answer session at the end of this talk.



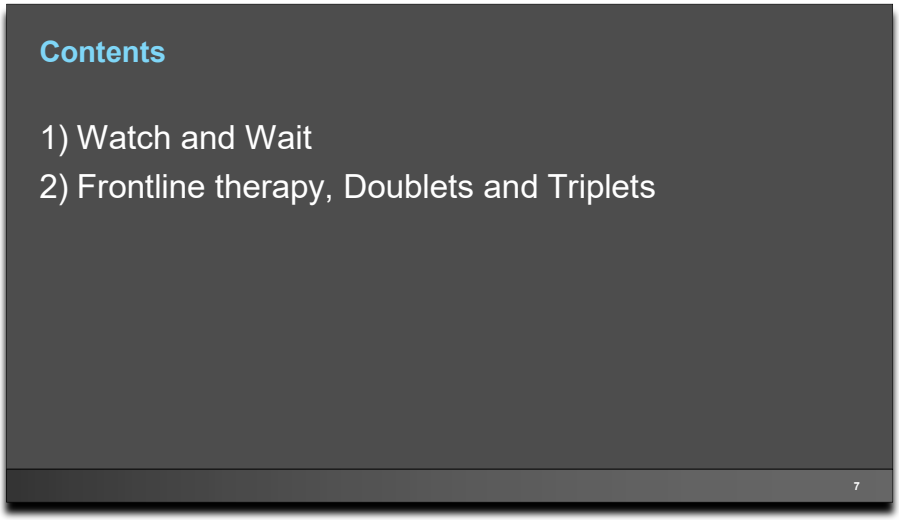
Disclosures

Here are my disclosures again.



Contents

So, today, we'll talk about watch and wait.



Contents

Followed by frontline therapy, doublets and triplets.

Contents

We'll talk about refractory disease, Richter transformation, and future therapies. And as I'm walking you through all of these different phases during someone's treatment and disease course, I hope to highlight all the exciting new things that have come out recently in the CLL space because, as Lizette had said, really in the last 10 years, we've really revolutionized the way we treat CLL, leading to improved survival for our patients compared to chemoimmunotherapy and not only improved surviva,l but also improved adverse events where I can truly say to all my patients that we can find the medication that works for them, that they'll be able to tolerate, that will help them remain in the state where their disease is controlled for a very long time. So, it's a really great time in the world of CLL as we have a lot of treatment options that work really well for all of our patients.

Watch and Wait

So, first, we're going to start by talking about watch and wait. So, for all of you that are unfamiliar, watch and wait is the time between getting diagnosed with CLL and the time that treatment starts. And so, oftentimes, a lot of patients will refer to this as being watch and worry because ultimately, we're not treating their disease and we're just watching them closely to wait until we need to start treating their disease.

Active Surveillance

Now, I recently had a conversation with a friend of mine, Dr. Lamanna at Columbia. And she likes to refer active surveillance as watch and wait. And the reason why she likes to refer to it as being active surveillance is because when we think about watch and wait, it doesn't mean that we are actually doing anything for somebody, where in reality, we are actively surveilling them for disease progression. We are actively making sure that our patients are getting the best care that they deserve from a standpoint of vaccinations, from a standpoint of making sure that they are getting treated for infections and giving IVIG. But ultimately, there's a lot that patients can do during this time of active surveillance that can improve their lives and improve their outcomes.

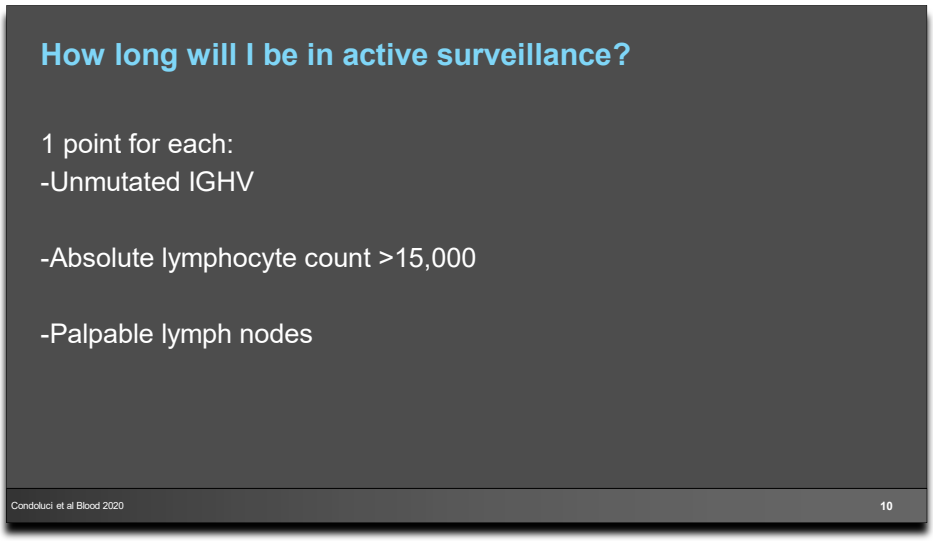
Lastly, one thing to mention here and one thing that I like to mention is that as someone is in active surveillance or watch and wait, really, we're kind of buying time. We're buying time for us as investigators to come up with new and novel therapies that might benefit you better, meaning that the longer that you wait to start treatment, means the longer that we have to develop new and novel therapies that might be more effective and safer for the treatment of your CLL.

Active Surveillance – When should we treat my disease

So, typically patients get diagnosed with CLL incidentally, meaning that they come in for some other reason, and they're found to have a high white blood cell count. And ultimately through diagnosis we can figure out that they have CLL, but they may not have known that they had CLL or been asymptomatic when they came in to see their clinic. And so, ultimately, we wait until one of these indications are met to be started on treatments. So, one is marrow failure [low blood cell counts], and that's going to be a low hemoglobin or a low platelet. One is going to be massive or progressive splenomegaly [enlarged spleen]. And what we define that as being as a spleen that's bigger than six centimeters below the left costal margin. So, if you feel the left side of your abdomen and feel the lowest part of your left rib, you can measure six centimeters down, and if it's bigger than that, then that would be an indication to treat. Massive or progressive lymphadenopathy. And we define massive lymphadenopathy [swollen lymph nodes] as being greater than 10 centimeters, which is quite, quite big.

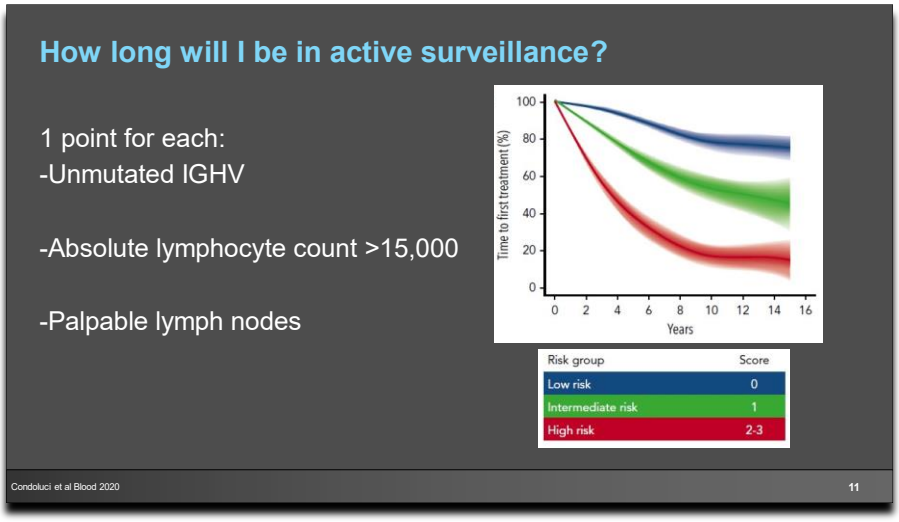
We also consider progressive lymphocytosis as an indication to treat. But typically, that's quite controversial in that, the way that the guidelines define that as having a lymphocyte doubling time that's less than six months. So, ultimately, we think about ALC [absolute lymphocyte count] doubling time as an indication to treat. But it really is a sign that treatment is imminent. And so, it really depends on what the other factors of your disease are if that's going to be the reason that someone decides to treat.

We also think about autoimmune cytopenias [low levels of blood cells] such as autoimmune hemolytic anemia and ITP [idiopathic thrombocytopenic purpura] not responding to other treatment as an indication to treat organ-threatening disease, as well as progressive B-symptoms. And so, a lot of my patients have B-symptoms, which are fatigue, drenching night sweats, fevers, chills, and weight loss. But typically, we wait to start treatment until these symptoms are impacting their ability to enjoy life. I don't typically wait for that moment because I feel like once these symptoms are impacting the ability to enjoy life, that's a little bit too far. So, I like to catch patients right before that. And typically, we also see that the B-symptoms get worse as some of the objective symptoms get worse, meaning that these B-symptoms get progressively worse as your white count starts to rise, as your hemoglobin or platelets start to fall. So typically B-symptoms alone are not necessarily an indication to treat and should be a conversation between you and your doctor about the severity of the symptoms you're feeling as well as whether or not we think those symptoms are related to your CLL.



How long will I be in active surveillance?

So, a common question that I often get is: How long will I be in active surveillance? And there was a recent publication that came out that looked at these three factors as a way to predict when first treatment will happen. So one factor is unmutated IGHV [immunoglobulin heavy chain variable]. One is absolute lymphocyte greater than 15,000. And one was palpable lymphadenopathy. And all three of these factors are easy variables for any clinician to test.



How long will I be in active surveillance?

And ultimately, what they found was that if you had zero of these risk factors, you were in the lowest risk group, represented by the blue line. If you had one risk factor, you were intermediate. And if you were high risk, you had two to three risk factors, you were in the red line and you were high risk.

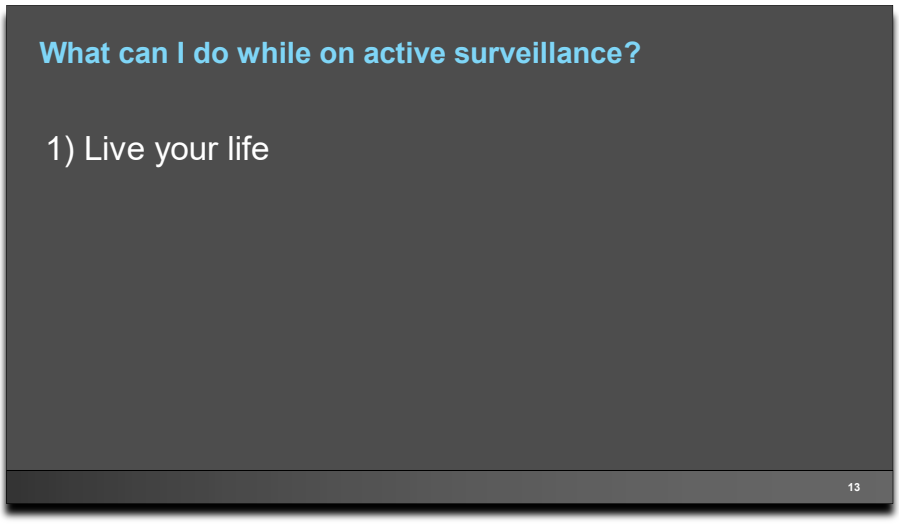
Now, if you look at this curve -- and we're going to see a bunch of curves today -- this is called a Kaplan-Meier curve. And you can imagine that day zero is on the left, and it goes forward in time. And you can see that when basically the line moves an event occurs. So, how I interpret these graphs is -- let's take a look at year 10. You go to year 10, and then, you look up, and then you cross over to the left. You can see that on the

blue line that, at 10 years, patients with zero risk factors -- 80 percent of those patients did not require treatment. Whereas at 10 years, about 50 percent of those at intermediate risk require treatment, and at 10 years, the majority of those patients who had high risk disease required treatment.

And so, usually when I look at these curves and I'm counseling patients, I usually tell them that if they have zero of these risk factors, the chance of them needing treatment at around 16 years is only about 20 percent. In general, the median time to first treatment for intermediate risk disease is going to be about six to eight years. And then, for high risk, the median time to first treatment is probably somewhere between two to four years, looking at these curves. So, this helps keep expectations together and allows patients to maybe rest a little bit at ease while they're in active surveillance knowing that they have a lot of years to go before they might require therapy.

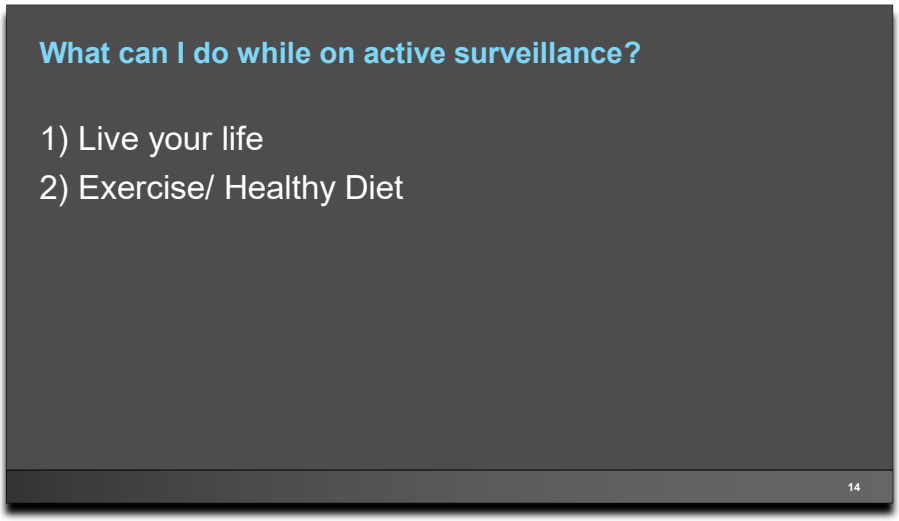
What Can I Do While on Active Surveillance?

Now, another common question I get is: What can I do while on active surveillance? What can I do now that might change my treatment course or at least change my life?



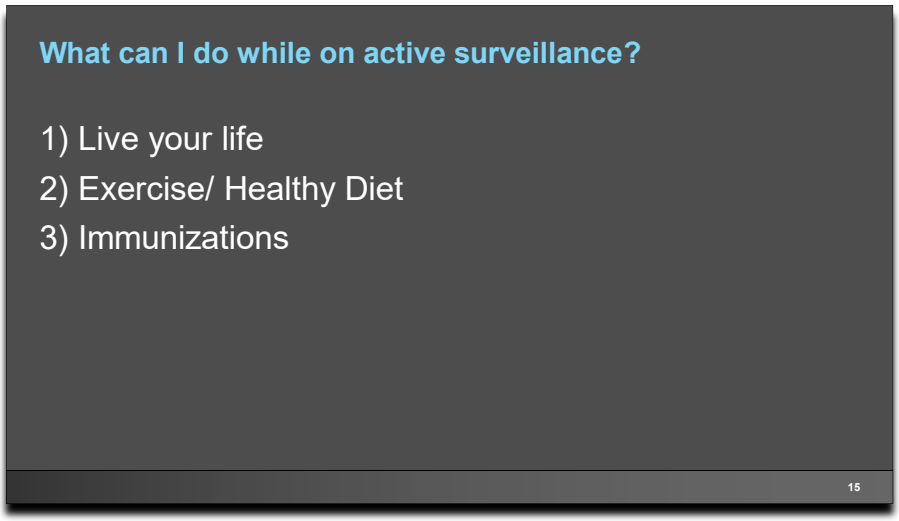
What Can I Do While on Active Surveillance?

And the first thing I always recommend is to live your life. Most likely while on active surveillance you're going to not need treatment for many, many years. So, it's important to keep that in perspective in that you really need to enjoy your life as best as you can and try not to worry about your disease so much. I know it's easier said than done, but it's something to focus on, knowing that you might have many, many years before we even start treatment.



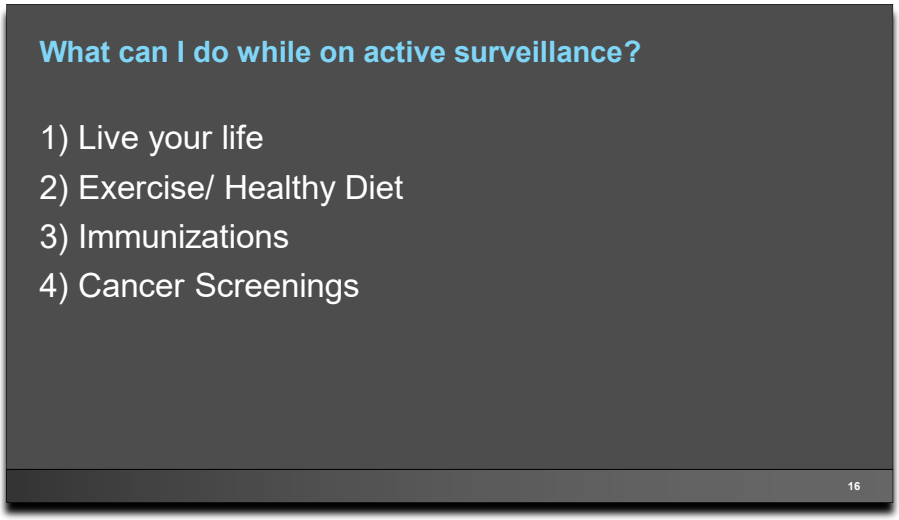
What Can I Do While on Active Surveillance?

Next, is I also would recommend exercise and healthy diet. I don't recommend that someone all of a sudden start training for an Iron Man or go on a heavily restricted diet like the Keto diet or something like that, mostly just eating a nice, well-rounded diet like the Mediterranean diet and keeping up with the exercise that you're currently doing, and if you're not doing any exercise, I do recommend to try to get in the habit of doing so. And the reason is that we know that the healthier somebody is going into treatment from another comorbidity standpoint, the better outcomes that they have, especially when our BTK inhibitors are associated with cardiac risk. And so, decreasing your cardiac risk as much as possible while you're in this active surveillance phase is integral for successful outcomes later on.



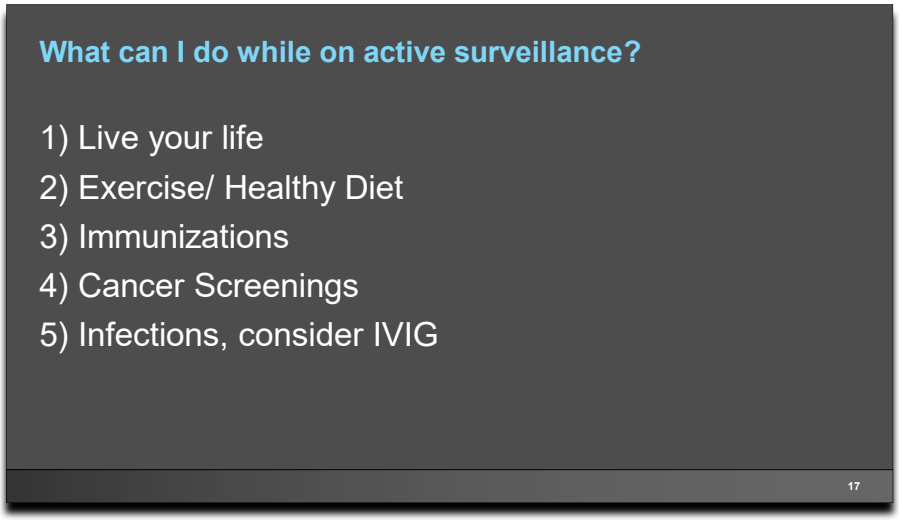
What Can I Do While on Active Surveillance?

The next thing I recommend is to make sure that you get your immunizations. We recommend a flu shot every year. We recommend a pneumonia shot every five years. There are some updates on the RSV vaccine. You should ask your doctor about the shingles vaccine and of course the COVID vaccine. But in general, flu and pneumonia for sure and making sure that you're up to date per the CDC guidelines on RSV, shingles, and COVID. And the reason why we recommend this is that, as we know, patients with CLL are more prone to infections. So, making sure that they're up to date on their immunizations is integral.



What Can I Do While on Active Surveillance?

Next is to make sure that they're up to date on their age-appropriate cancer screening. CLL is associated with secondary malignancies. So, making sure that if you're a female, that you get your mammograms, making sure that if you're a male, you get your prostate cancer screening, everyone should be getting their colonoscopies and colon cancer screening. And the number one thing that we see in CLL patients is secondary skin cancers. So, I recommend all my patients see a dermatologist at least once a year to get screened.

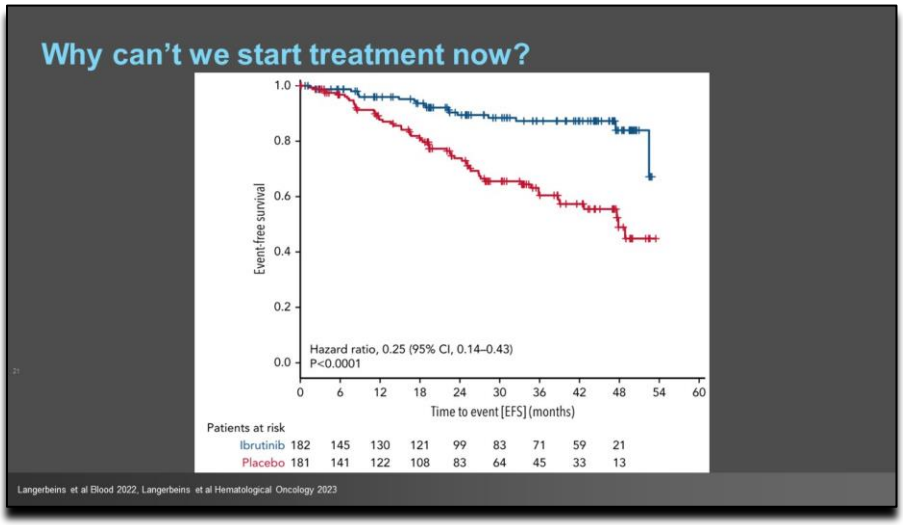


What Can I Do While on Active Surveillance?

Last but not least is if you are experiencing multiple respiratory infections a year or infections in general, talk to your doctor about intravenous immunoglobulin. So, intravenous immunoglobulin is antibodies pooled from the community and then given to patients. And what it does is it boosts your immunity to fight those infections. And it's indicated for anybody who has over two infections per year who have an IGG less than 500.

So, if you're having multiple infections, talk to your doctor about IVIG. It may totally change the rate of infections that you're receiving.

Of note, IVIG is typically given once per month. And so, it is something that you have to understand is something that you're going to have to buy into. Oftentimes I treat my patients with IVIG for one full year and then give it a pause during the summers and then monitor IGG from there. So, once for a whole year, and then, I give them a break during the summer because typically during the summer we don't get upper respiratory tract infections.



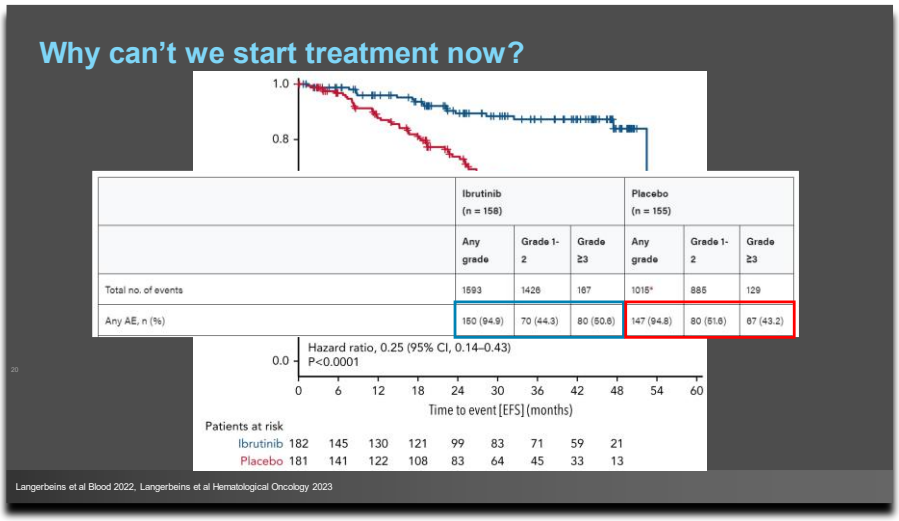
Why Can't We Start Treatment Now?

So, moving forward about why we don't treat patients with watch and wait or active surveillance. And the reason originated back in the 1990s where they looked at use of early chemotherapy for patients who did not meet indications to treat. And they found that basically patients who were treated with chemotherapy had worse overall survival than patients who treated in the placebo arm who did not meet indications. So, this led to the era of watch and wait.

Now that we have our new therapies, we are rechallenging this perspective, and this study, the CLL11 study randomized patients who were in watch and wait who received placebo in the red line versus ibrutinib (Imbruvica®) in the blue line. And you may look at this and say, "Wow, the ibrutinib patients look better than the patients who had placebo, as the ibrutinib line is above the placebo line." But in fact, when we are thinking about early intervention, what's important is not event free survival, which I'm showing you here, but what's really important is how long patients are living and if ibrutinib made an improvement in how long patients are living. And in fact, there was no improvement it seemed.

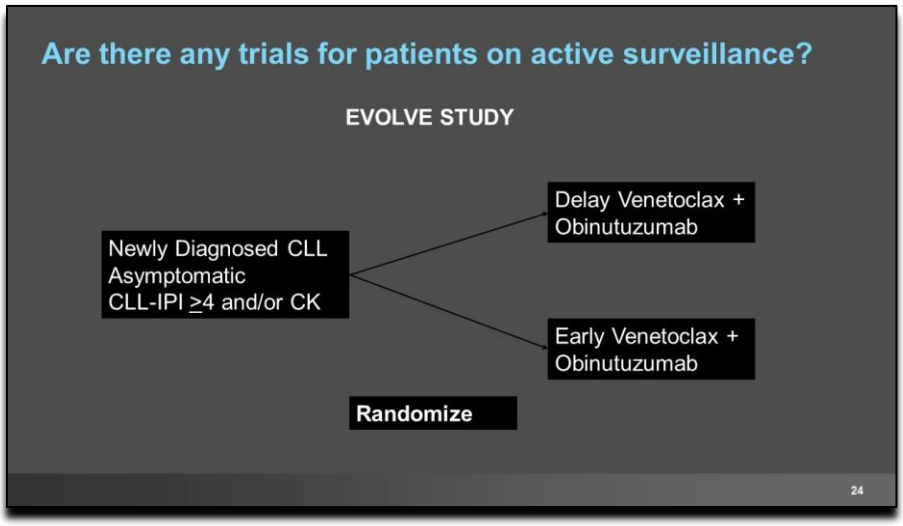
Why Can't We Start Treatment Now?

Ibrutinib did not lead to an extended overall survival for this group of patients, and so therefore, it did not change our watch and wait active surveillance treatment paradigm. Now, what I found really interesting in this specific study is this chart here.



Why Can't We Start Treatment Now?

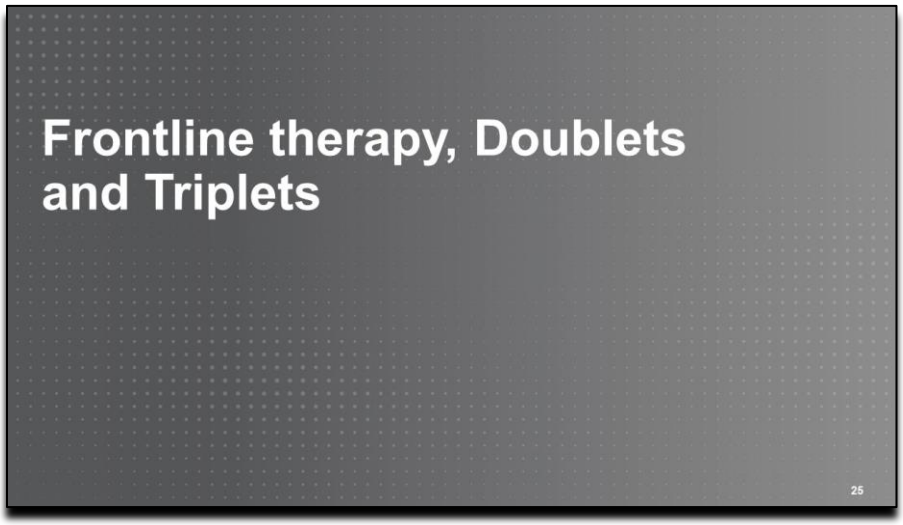
And so, this is our toxicity chart. And highlighted in red are the toxicities observed by those patients who got placebo. And grade three toxicity is the classic severe toxicity. And what we're showing here is that 43 percent of patients treated with placebo had grade three or higher toxicity. That to me is a really high number, and it was surprising. It shows us that our patients with CLL are really struggling from fatigue, from infections. And we really need to use active surveillance appropriately to get them the intervention that they need. So, I just want to use this data to highlight that if you are struggling in active surveillance, you need to talk to your doctor about it, talk about the symptoms that you're experiencing because there are things and there are ways that we can be better physicians to tackle this problem, to make our patients better, especially when they're in this active surveillance timeframe.



Are there any trials for patients on active surveillance?

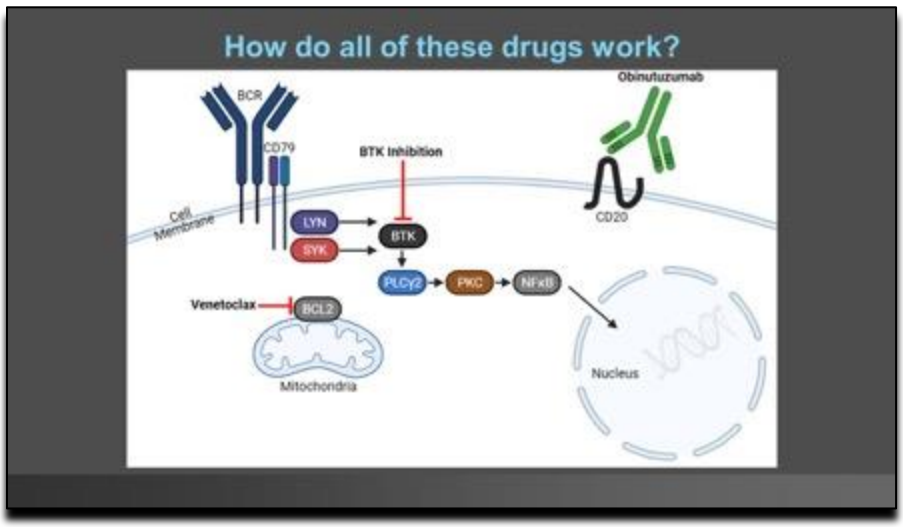
So, in terms of what's coming next, we have the EVOLVE study. So, the EVOLVE study is a cooperative group study, and a cooperative group study is a clinical trial that was created with a lot of academic doctors as opposed to the pharmaceutical companies where we decide what we think is the most prevalent issue within various diseases and we work together to get the clinical trial done. So, this is available nationwide. And so, if you're interested, you should talk to your doctor about it. And basically, what it does is it randomizes patients with high risk CLL to either early treatment with venetoclax (Venclexta®) plus obinutuzumab (Gazyva®) for one year versus delayed venetoclax plus obinutuzumab. And so, similar to the trial I just showed you with ibrutinib but using venetoclax instead.

The reason why we're so interested in this is because venetoclax does tend to induce deeper remissions than ibrutinib. And so, therefore we think that maybe this is the drug to use in the watch and wait setting. So, this is a really interesting study available for most patients who are newly diagnosed with CLL who are in the active surveillance watch and wait setting. And if you are interested, I would totally reach out to your doctor to see where this might be available in your region.



Frontline Therapy, Doublets and Triplets

So, moving on, let's chat about frontline therapies, doublets and triplets. And I'm going to start by talking about what is available currently for patients with treatment-naïve disease because I think it's important to understand what is currently available for us to speak about what will be available in the future.



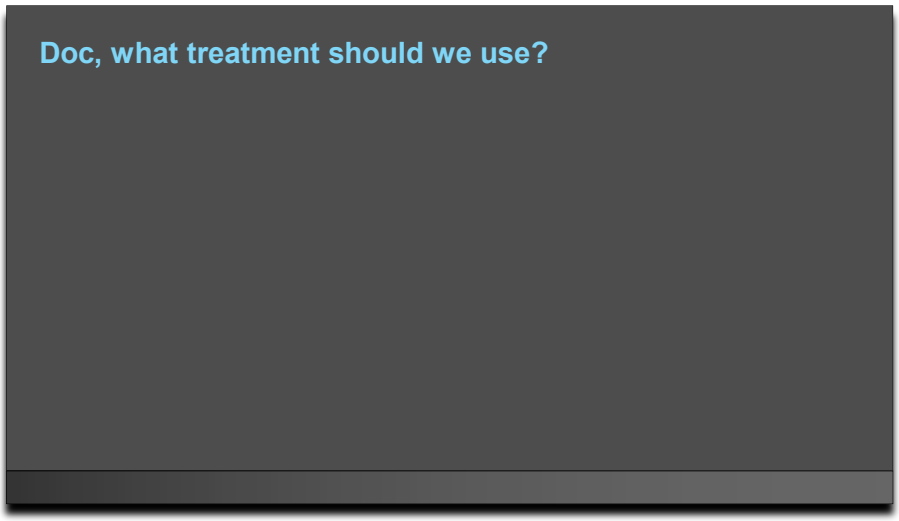
How Do All of these Drugs Work?

So, this is our mechanism of action chart highlighting the three ways our three main drugs target CLL cells. So, first we have the BTK inhibitors, which target something called Bruton's tyrosine kinase, which is an essential kinase or signaling protein that signals from the surface of the cell down to the nucleus and in CLL cells specifically, this BTK acts aberrantly, over-signaling, causing the cell to divide faster and live longer than it should. And so, BTK inhibitors specifically target BTK and inhibit it.

Next is venetoclax, and venetoclax targets the mitochondria by being something called a BCL2 inhibitor. So, imagine at any point, any one of your cells is deciding if it should undergo cell death or be alive. And basically, cells decide this based off of how much stress they're under. And the cell that's more under stress will undergo cell death versus one that's functioning nicely will stay alive. And so, you can imagine cancer cells like to

upregulate those signals that lead to cell prolongation and not death. And so, what venetoclax does is it allows the cell to rebalance itself and undergo cell death like it should if it's under stress.

Lastly is obinutuzumab, which is a monoclonal antibody that targets CD20, which is located on the surface of the cell and is present on all B cells. So, as you see here, all three of our drugs -- they don't overlap in their mechanism, which typically means that they don't overlap in their toxicity, allowing us to combine them together. And that's exactly what we've been doing.

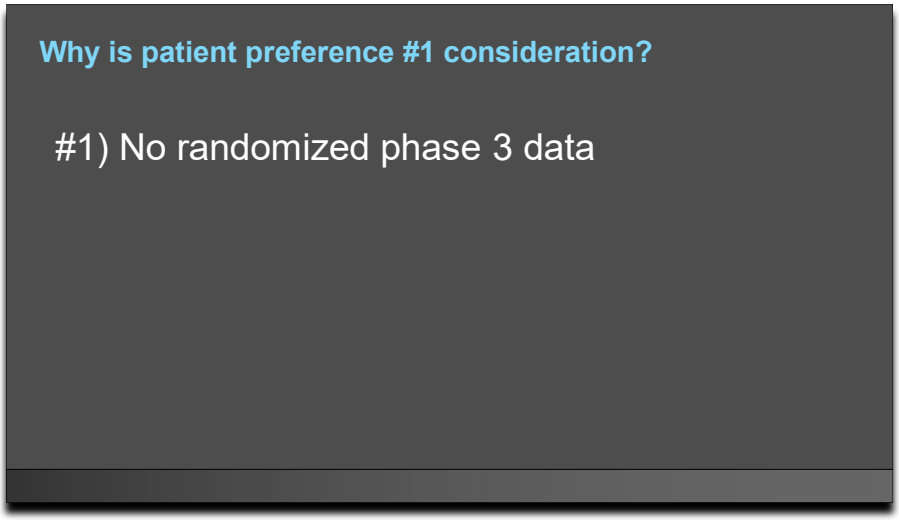


Doc, What Treatment Should We Use?

So, the classic question I get, once we decide treatment is indicated, is, "Doc, what treatment should we use?" And ultimately how I perceive this question is that it should be a patient-physician conversation, and the number one thing that I use to help my patients and guide them on what treatment that we should pick as a team is actually patient preference.

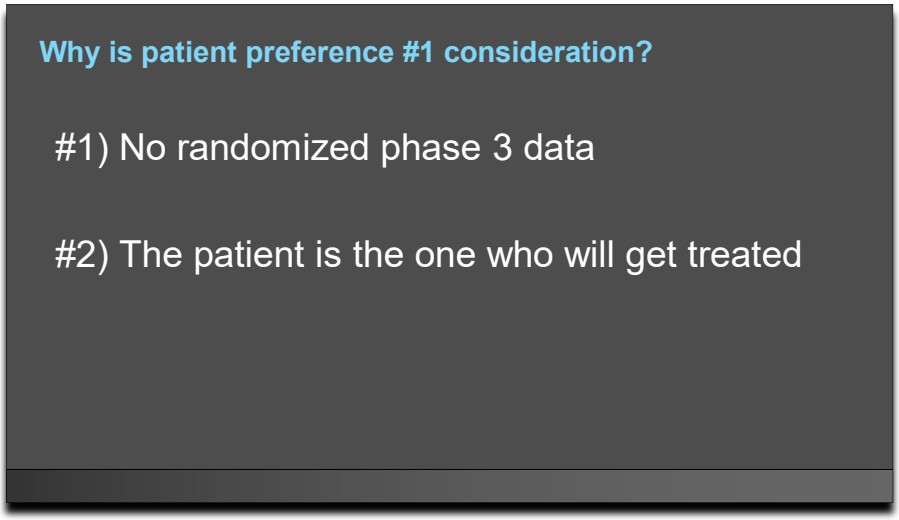
Doc, What Treatment Should We Use?

And the reason why it's patient preference is that all of our drugs that are currently approved in the treatment use setting of CLL have never been compared to each other in the gold standard, a randomized phase three clinical trial. And so, we don't have a randomized phase three clinical trial to tell us that one might have superior efficacy versus another, then we really don't know which one's best for the patient in front of us. So, ultimately, we have to rely on patient preference to decide what to do. So, next I'm going to kind of go over how I favor continuous versus time-limited therapy.



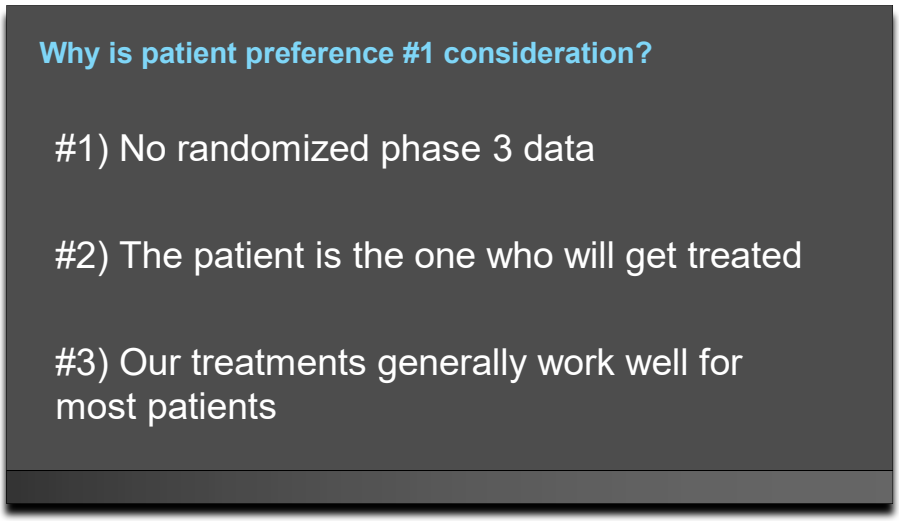
Why is Patient Preference #1 Consideration?

So, once again, we talked about why patient preference is number one, and that includes no randomized phase three data.



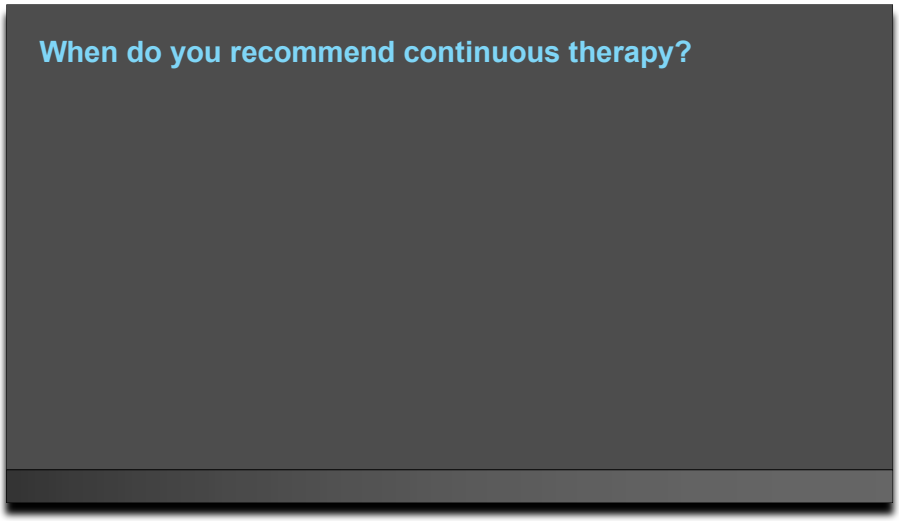
Why is Patient Preference #1 Consideration?

The patient is the one who will get treated, so therefore, it should be a patient-focused conversation. Additionally, when we're using all of these oral therapies, if the patient is not interested or is worried about a side effect of one particular therapy, it's very unlikely that they'll take it and be compliant with it.



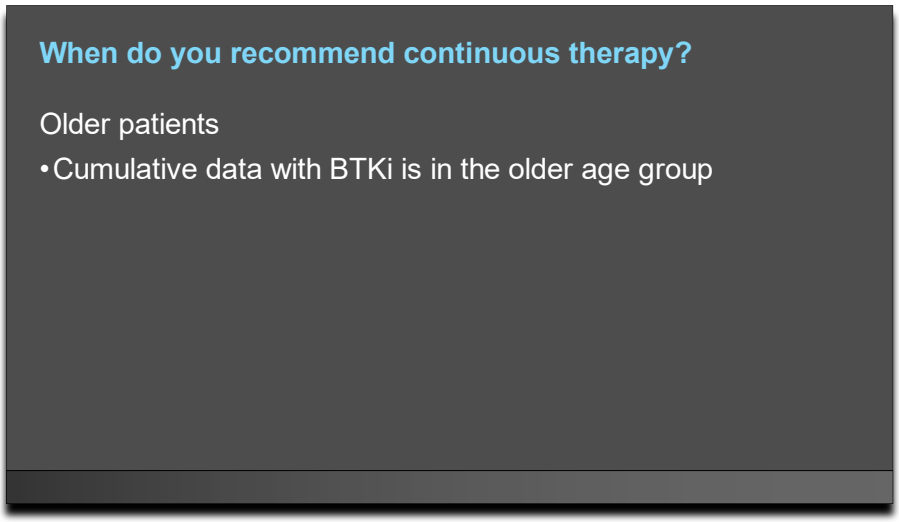
Why is Patient Preference #1 Consideration?

So, that's why it's important for me to have a conversation with you and decide what treatment is best for you and your lifestyle. And last is a great point -- and I mentioned it earlier -- but all of our treatments in the treatment setting work really well and the majority of patients can find a drug that works really well for them and makes the time for CLL treatment now to be so good in that we could typically find a drug that works for everybody and works well for everybody.



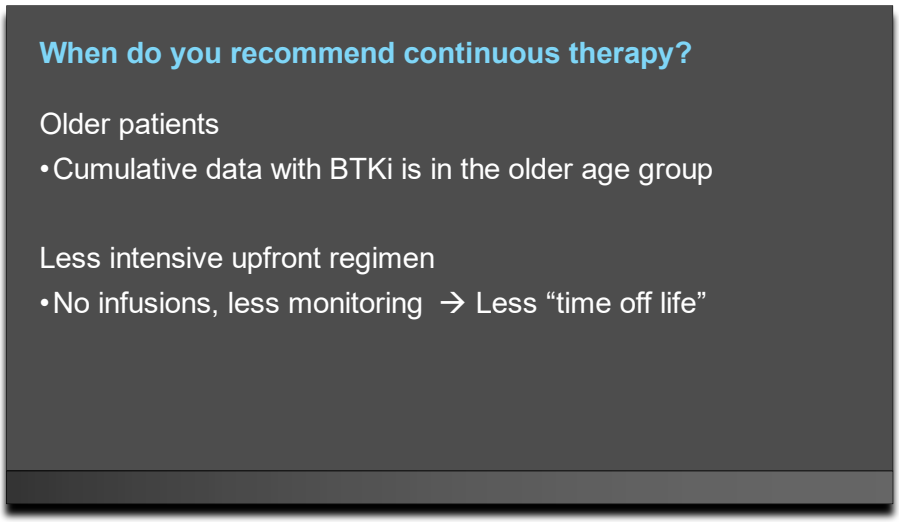
When Do You Recommend Continuous Therapy?

So, when do I recommend continuous therapy? And so, when I talk about continuous therapy, I'm meaning single agent, BTK inhibitor therapy.



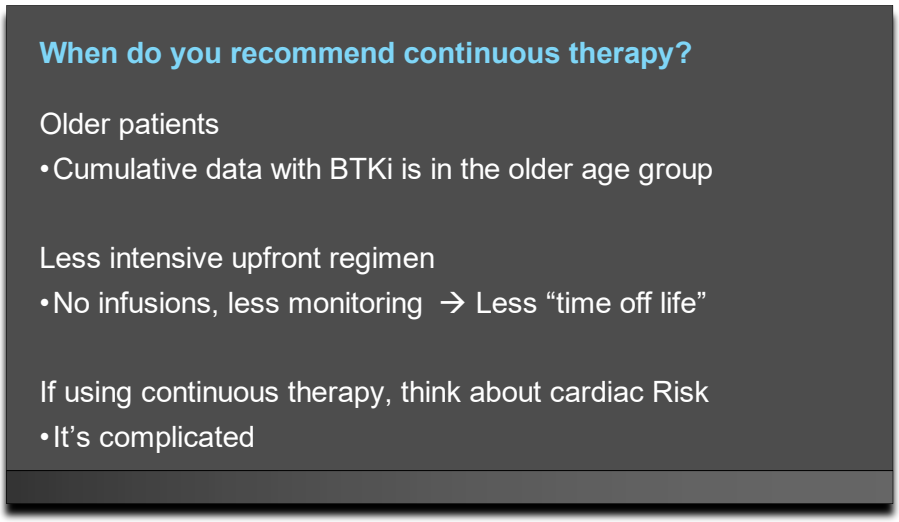
When Do You Recommend Continuous Therapy?

And I typically favor it for older adults. And the reason that is, is that the trials that led to the approval of BTK inhibitors was mostly done in older adults. And so, there's just ample amount of evidence that supports their use in older adults. It doesn't mean that I don't give time-limit therapy for older adults. I'm just saying when I would favor it. And so, in general, the BTK inhibitors are well tolerated and just very well studied in older adults.



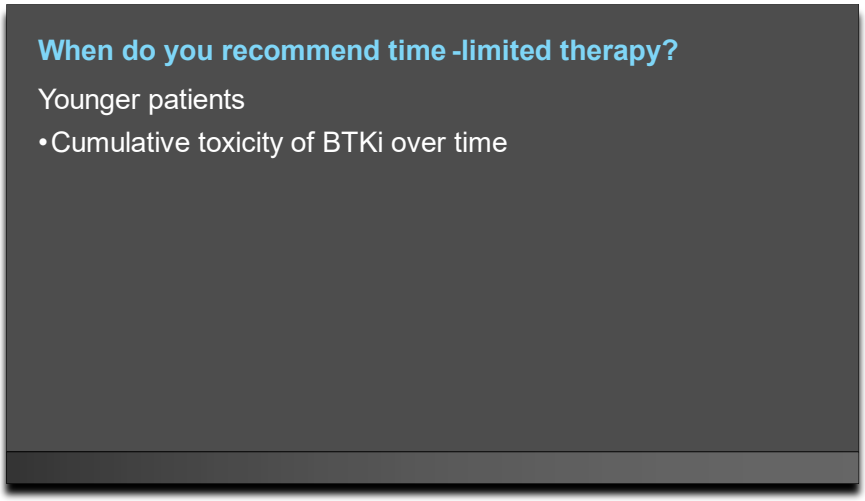
When Do You Recommend Continuous Therapy?

Next is that BTK inhibitors are associated with less intense upfront regimen. So, when I start somebody on a BTK inhibitor, I usually see them two weeks after start, a month after that, and then three months after that, so only three times in the first three months. That's really easy for our patients. And so, if we have somebody with a really active lifestyle who can't take off work to come in, starting a BTK inhibitor is just really super easy and simple, especially for our patients that live far away from us. So really, in the beginning, there's really not so much time off life. That being said, when you get started on time-limited therapy, you do get the time off therapy at the end. So, that's the trade-off that we're dealing with.



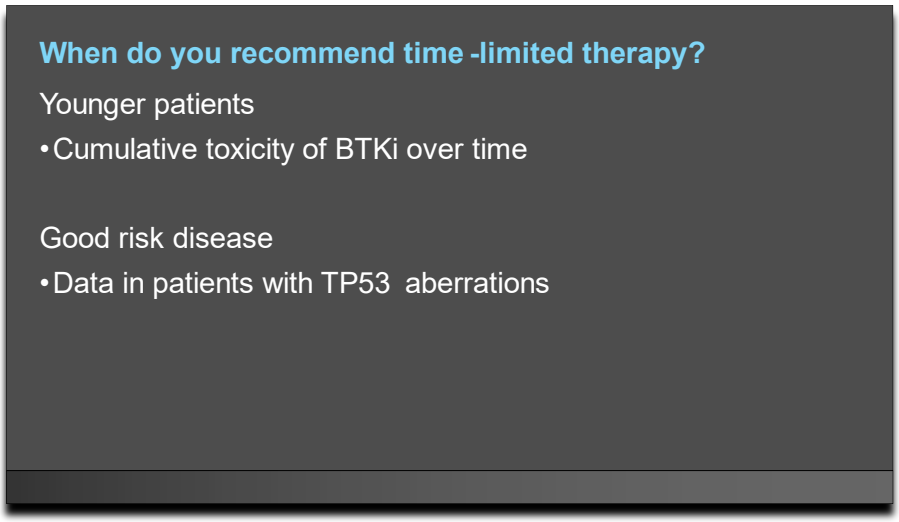
When Do You Recommend Continuous Therapy?

Lastly, when I'm thinking about continuous therapy with BTK inhibitors, I think about cardiac risk as well. And so, in general, we know that the BTK inhibitors come with cardiac risk. And so, if I have somebody who has cardiac comorbidity, I make sure that that cardiac comorbidity is optimized by their cardiologist. And if your provider has access to cardio-oncology, they can be of great benefit to our patients as well. So, it's just something to think about. It doesn't mean, once again, that they don't give BTK inhibitors to patients with heart disease. I do, but I just make sure that they're optimized prior to their initiation, and I make sure that my patients understand the risks and what I'm worried about.



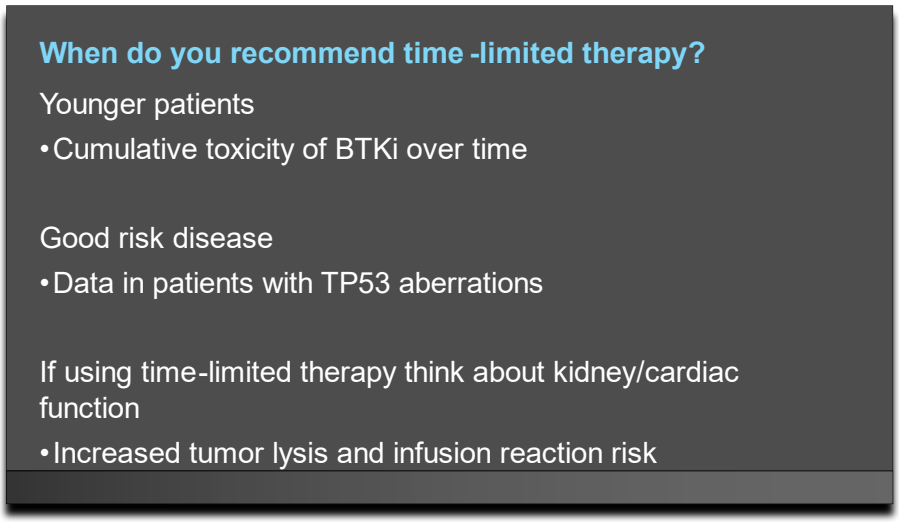
When Do You Recommend Time-Limited Therapy?

In terms of time-limited therapy, I generally think about it for younger patients. And the reason why I think about it for younger patients is because when we're giving continuous therapy, patients are on continuous therapy over a long time. And specifically, as we know, it has cardiac risk. That's a lot of cardiac risk to put on a younger patient. And so, if I can get away with time-limit therapy for younger patients, that's typically what I choose. But in general, once again, I don't necessarily, not use BTK inhibitors for younger patients. I just prefer time-limited therapy.



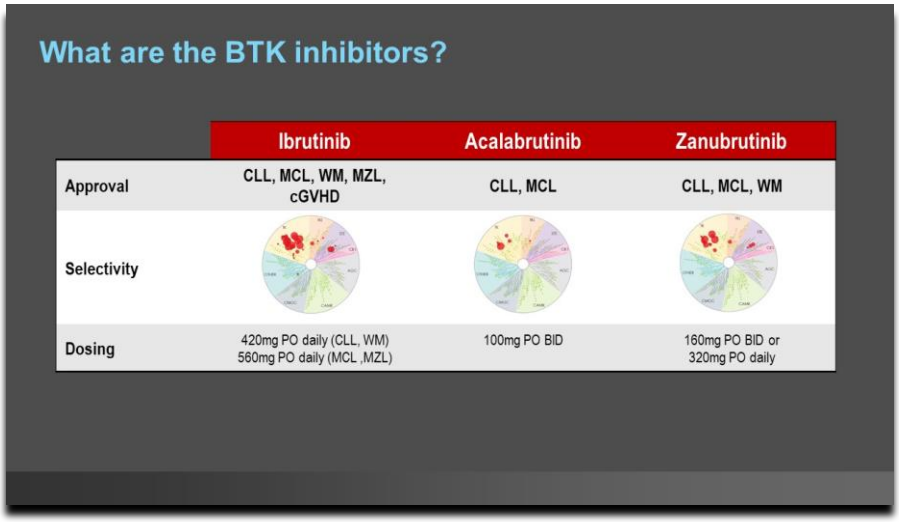
When Do You Recommend Time-Limited Therapy?

Next, I tend to prefer time-limit therapy for patients with good risk disease. And that's because there's some good data out there that shows that patients who have high risk disease defined as deletion 17P or TP53 typically have worse outcomes with time-limited therapy. And that factor has not been shown to be significant when we're using continuous therapy. Once again, it doesn't mean I don't give time-limited therapy to patients with higher risk disease. It's just something to think about and make sure that our patients are aware of.



When Do You Recommend Time-Limited Therapy?

And lastly, if I'm using time-limit therapy, I make sure that their kidney function and cardiac function are optimized because the biggest risk with time-limit therapy is something called tumor lysis syndrome, which can put a lot of pressure and stress on the kidneys, and an infusion reaction risk with the obinutuzumab. And so once again, I kind of consider these things, kidney and cardiac risk. I make sure that they're optimized prior to starting therapy. I make sure to consider giving them fluids before starting therapy, and now I've been giving more steroids just to debulk and de-enflame a little bit before therapy as well.

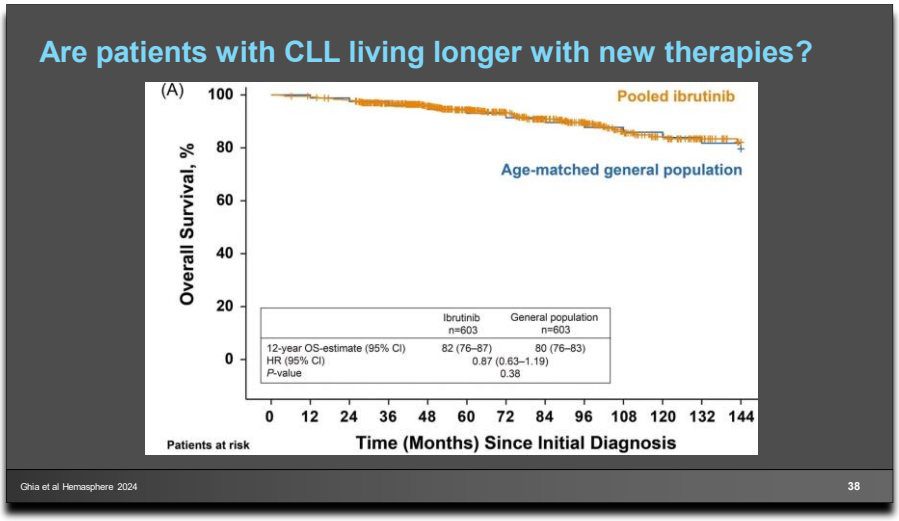


What Are the BTK inhibitors?

So, let's talk about the BTK inhibitors. So currently there are four BTK inhibitors approved. These are the three that are currently approved in the treatment-naive setting. The fourth one is pirtobrutinib, and I'll show you that later. These are what we call covalent BTK inhibitors, meaning they bind to BTK in a covalent manner. Pirtobrutinib (Jaypirca®) is noncovalent. It binds differently than these drugs. Ibrutinib is generally considered the first targeted therapy ibrutinib. And then, acalabrutinib (Calquence®)and zanubrutinib (Brukinsa®) are the second generation. And here I have the approvals for each drug in the United States. As you see here, ibrutinib has the most approvals, probably because it has been around for the longest amount of time.

And then the second part is the selectivity. So, what these little maps are -- they're called kinome maps. BTK is a kinase and what we're showing here -- these are all the kinases that we are aware of in science. And those little red dots are basically where the BTK inhibitors inhibit. So unfortunately, our BTK inhibitors are not perfect. They don't just inhibit BTK. They have off target effects hitting other kinases. So, the more red dots means the more off-target effects. And so, ultimately what we think is -- the reason why we found safety improvements with acalabrutinib and zanubrutinib is because there are less off-target effects than ibrutinib. Lastly is the dosing. Ibrutinib is given once per day. Acalabrutinib is given twice per day. And zanubrutinib can be given either once or twice per day, but typically, we prefer that twice per day because that is how it was studied in CLL.

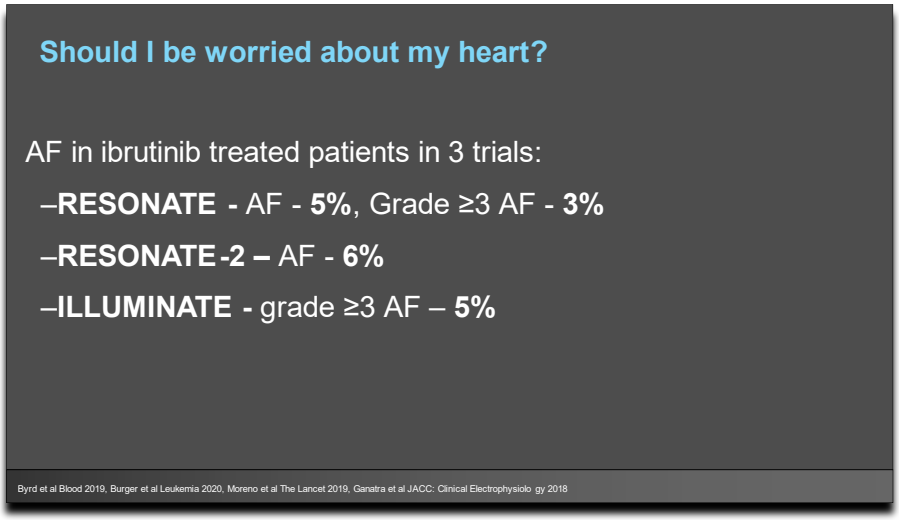
So, moving forward about BTK inhibitors, I want to show you some exciting data that was just published.



Are Patients with CLL Living Longer with New Therapies?

So, this was a recent publication by Dr. Ghia, et al., that was published over the last week. And what they did was they took all the patients treated on clinical trial in the original ibrutinib study. And they got age matched controls from the general population, and they looked to see whether or not overall survival differed between those age-matched controls and ibrutinib. And as you see here, the lines are overlapping, meaning that patients treated with ibrutinib on clinical trials had equal outcomes to patients who were aged-matched controls of the general population. So, what that's telling me is that these patients had the same life expectancy. This is great, right? Our drugs are working so well that the life expectancy changes that we see with CLL are basically negated with our new therapies. This is great news.

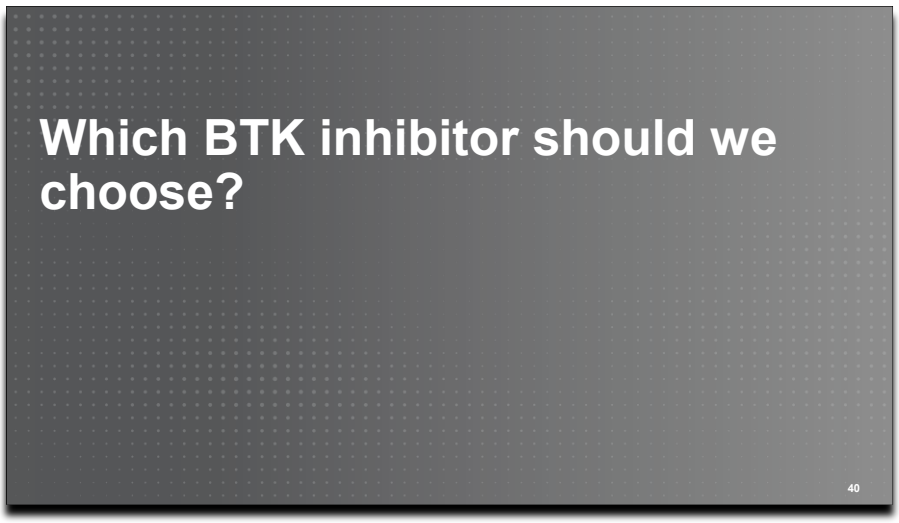
And interestingly enough, when they mapped chemoimmunotherapy on here – and I don't have this slide for you -- those patients did have worse overall survival than the general population. And so, really our new therapies are bridging this gap, making our patients live longer and similar to the overall population.



Should I Be Worried About My Heart?

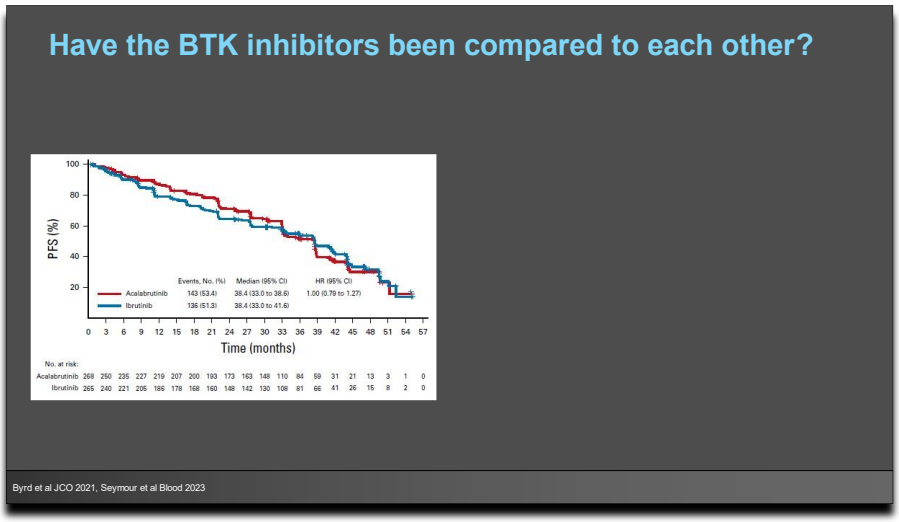
So, when ibrutinib was developed, there was note that there was significant cardiac adverse events, specifically in hypertension, atrial fibrillation, ventricular fibrillation and bleeding. And so, when these side effects occurred, basically our patients started to ask, "Should I be worried about our heart?" And that's why I generally recommend patients who are being treated with BTK inhibitors to see a cardiologist -- or I should say if they have cardiac comorbidity -- to make sure they have their cardiac comorbidity optimized prior to starting a BTK inhibitor therapy.

So, here I show you the atrial fibrillation rates in the clinical trials that led to ibrutinib approval and the atrial fibrillation rates were higher than expected at around five percent. And this is high specifically because these patients typically had good hearts. In order to enroll onto a clinical trial, you need to be healthy enough. And so, typically these patients had good hearts if they were still experiencing high rates of atrial fibrillation.



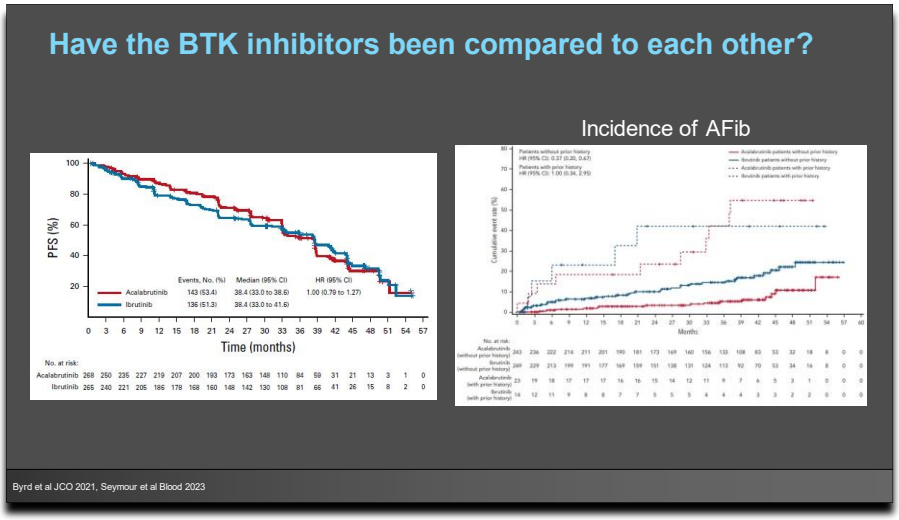
Which BTK Inhibitor Should We Choose?

And because of these high rates of cardiac toxicity, that's why the second generation BTK inhibitors were studied, and they were studied specifically as compared to ibrutinib. And I'm about to show you those two studies now that have now helped us decide which BTK inhibitor is the one of choice.



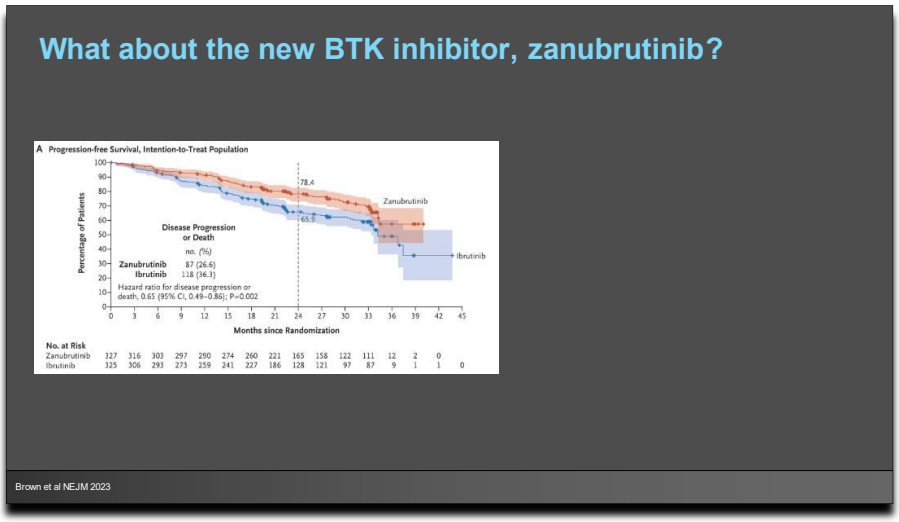
Have The BTK Inhibitors Been Compared to Each Other?

So, the first study talked about is the ELEVATE-RR study, which compared acalabrutinib versus ibrutinib in the relapse setting for patients with high risk CLL with deletion 11q or deletion 17p. Once again, you see these lines are overlapping each other, so acalabrutinib had equal efficacy to ibrutinib and high-risk patients with relapsed/refractory disease.



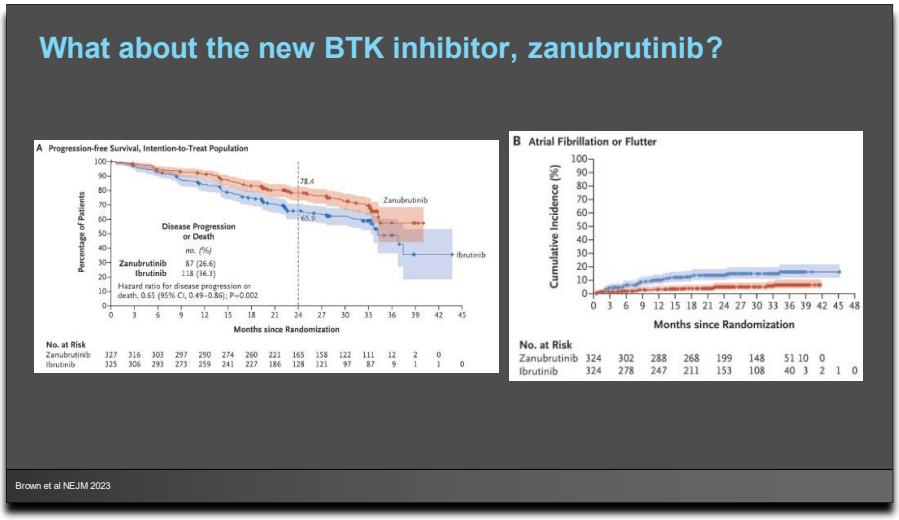
Have the BTK Inhibitors Been Compared to Each Other?

And then when they looked at toxicity, there was a significant reduction in atrial fibrillation for those patients treated with acalabrutinib as seen by the solid red line. And for patients who had pre-existing cardiac comorbidity, there was also a reduction, but it wasn't as prominent as those patients who had no prior cardiac comorbidity. I don't have this graph on here, but there was also an improvement in rates of hypertension when patients were treated with acalabrutinib versus ibrutinib as well.



What About the New BTK Inhibitor, Zanubrutinib?

The second study is the ALPINE study, which compared zanubrutinib to ibrutinib, also in the relapsed/ refractory setting in all comers. So, this wasn't high-risk patients, and actually what they found was zanubrutinib led to an improvement in efficacy compared to ibrutinib, which I was certainly surprised by, but also happy to see.

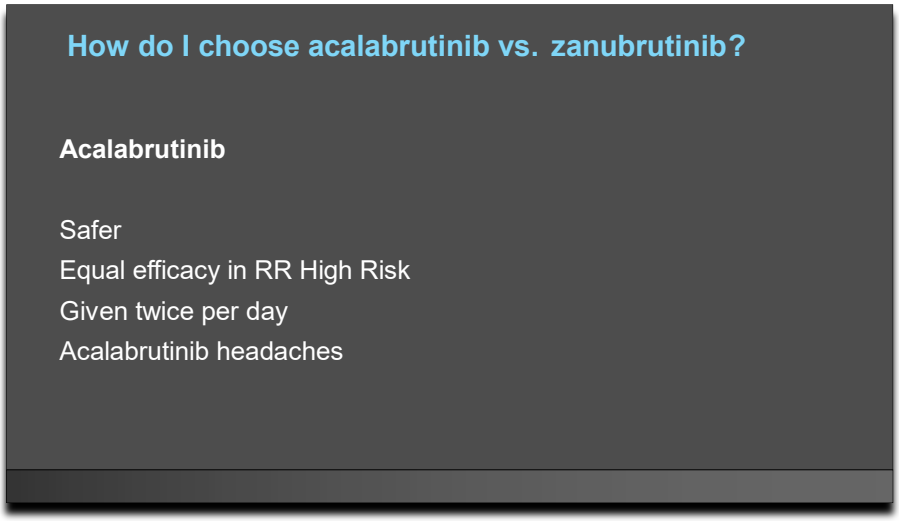


What About the New BTK Inhibitor, Zanubrutinib?

And when they looked at atrial fibrillation, they found that atrial fibrillation was also significantly improved compared to ibrutinib in the red line versus the blue line. But when they compared hypertension from zanubrutinib to ibrutinib, there was no improvement, meaning that zanubrutinib did not improve hypertension rates compared to ibrutinib.

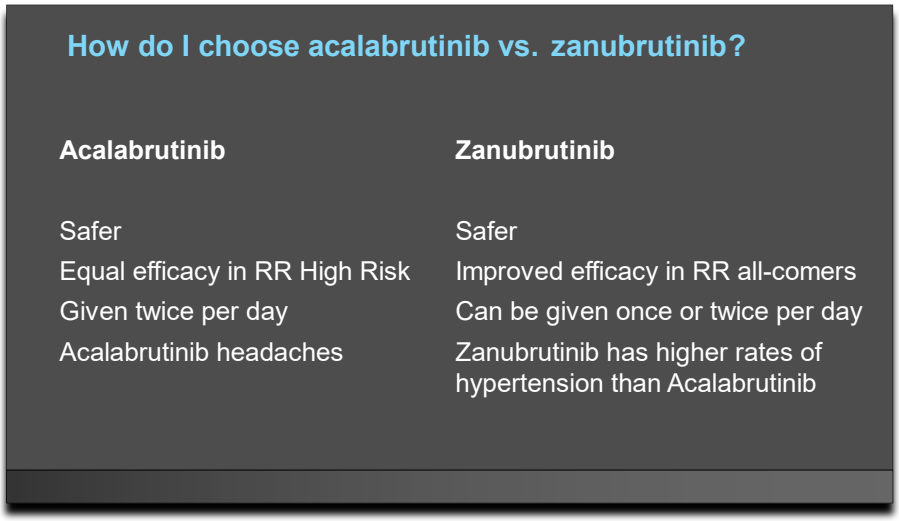
Now, we have two studies. We have acalabrutinib, the same efficacy as ibrutinib in relapsed/refractory patients with high-risk disease but led to an improvement in AFib [atrial fibrillation] as well as hypertension. And then we have zanubrutinib, which led to an improvement in efficacy compared to ibrutinib, but for all

comers-not just high-risk disease-that led to an improvement in atrial fibrillation, but no improvement in hypertension. So ultimately, where does that lead us.



How do I Choose Acalabrutinib vs. Zanubrutinib?

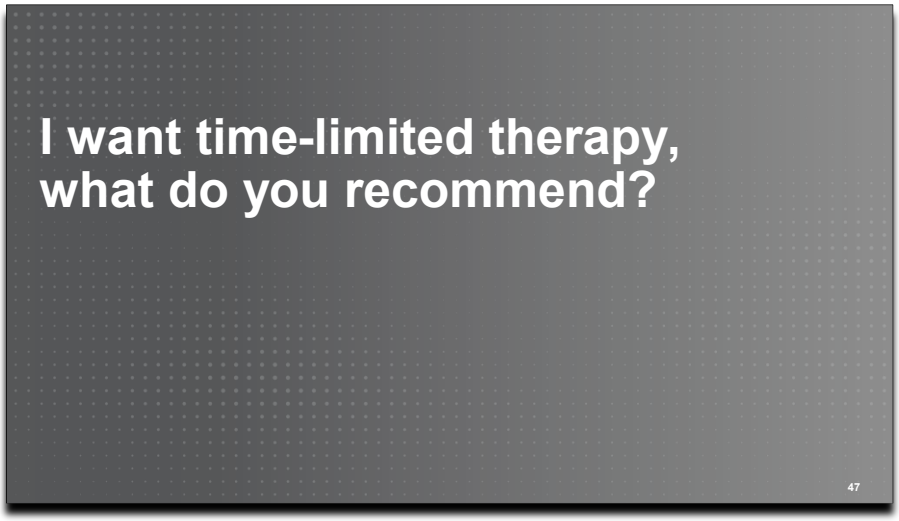
Because we don't have a randomized phase three study comparing acalabrutinib to zanubrutinib. So, ultimately this is how I view it. I know acalabrutinib is safer than ibrutinib. I know it has equal effects efficacy in relapsed/refractory patients with high-risk disease. It can be given twice per day versus once per day. And we also know -- and I didn't mention this earlier -- that acalabrutinib is associated with headaches, usually in the first two months and usually resolved with Tylenol or caffeine and is therefore self-limited.



How Do I Choose Acalabrutinib vs. Zanubrutinib?

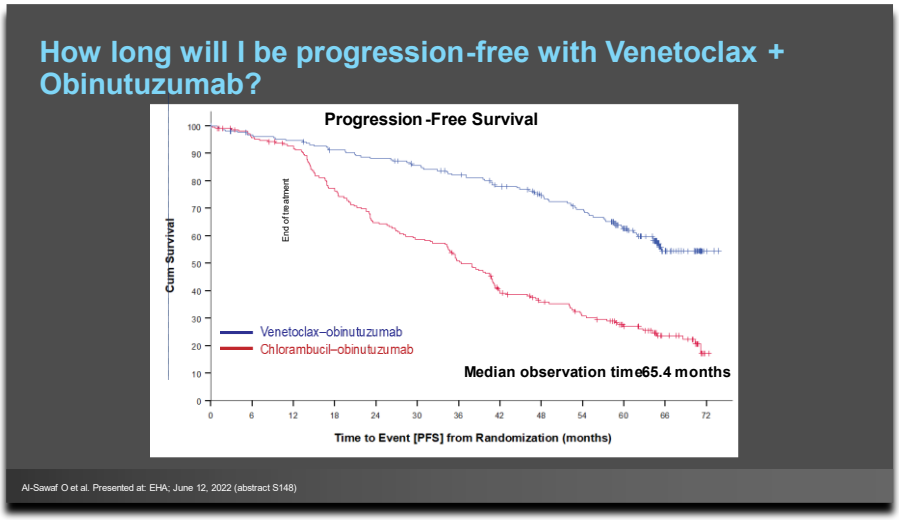
For zanubrutinib, we also know that it's safer. It led to a reduction in atrial fibrillation, but it had improved efficacy in relapsed/refractory all comers, not just high-risk disease, can be given once or twice per day. But zanubrutinib has a higher rate of hypertension most likely than acalabrutinib. And so, when I'm thinking about these two drugs their efficacy is probably pretty similar, and that in general I'll use the zanubrutinib for a patient with a history of headaches and I might use acalabrutinib for someone with a history of hypertension

and cardiac comorbidity. That's how I kind of view these drugs. I think they're probably more alike than dissimilar. And so, I think if you are on one of these drugs currently, they're great drugs. They're really safe. And the differences between the two -- I think we're just splitting hairs at this point. But in general, what I encourage my friends who are providers and physicians is to get used to one of these drugs and know their side effect profile so that way you can adjust their doses and do treatment holidays as are needed.



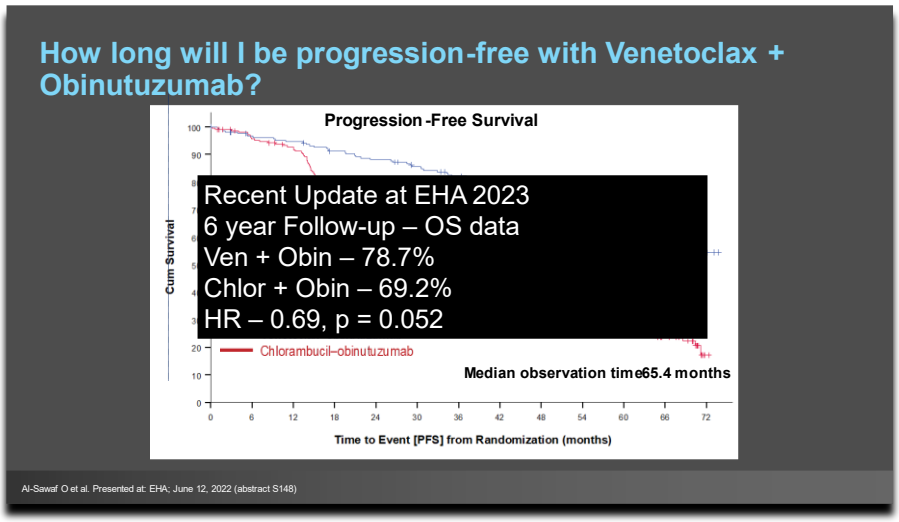
I Want Time-Limited Therapy, What Do You Recommend?

Next up, let's talk about time-limited therapy. So, I like how I phrase this because most often patients come into me saying, "I want time-limited therapy," for various reasons and we'll talk about why you may or may not want time-limit therapy in a second.



How Long Will I Be Progression-Free with Venetoclax + Obinutuzumab?

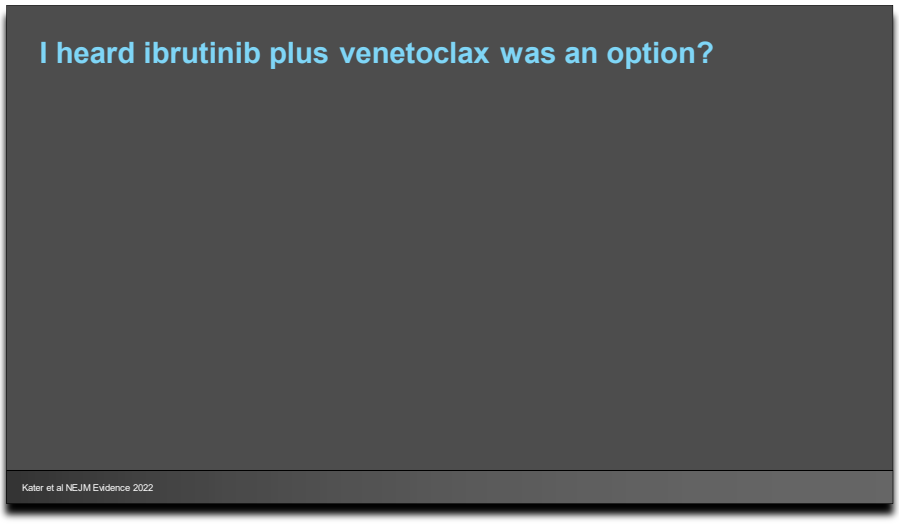
So, first off, let's talk about the CLL14 study. So, this trial led to the approval of venetoclax plus the anti-CD20 monoclonal antibody obinutuzumab for frontline treatment of CLL. And we had recent results, presented by Dr. Al-Sawaf, of patients that showed a continued improvement of progression-free survival as compared to chemoimmunotherapy.



How Long Will I Be Progression-Free with Venetoclax + Obinutuzumab?

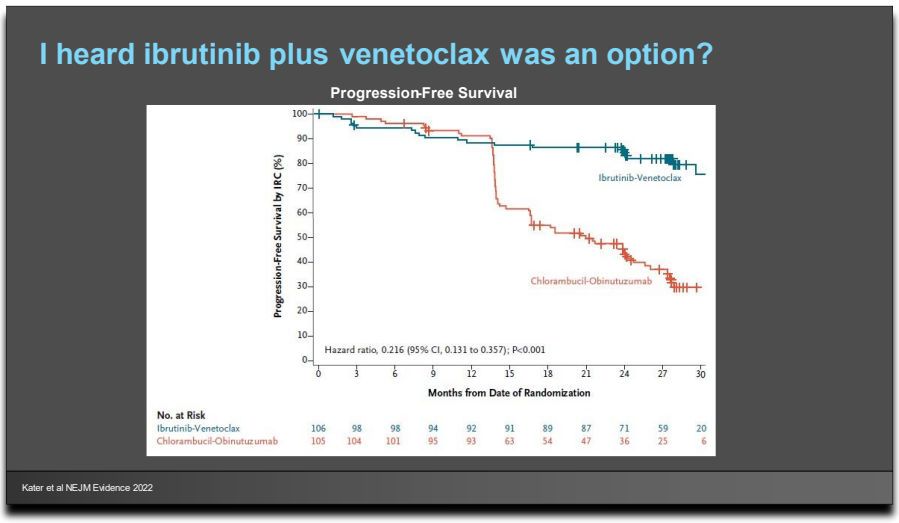
And there was recent data published at the EHA [European Hematology Association] Conference in 2023 that actually showed that venetoclax plus obinutuzumab might lead to an improvement in overall survival. We're not there yet, but we're getting really, really close, which is also exciting to see. So, for time-limited therapy, just to remind you all, we often monitor patients weekly for the first two months. Number one is because they get infusions on day one, day eight, and day 15, and then on day 22, they start the venetoclax and we have to monitor labs for tumor lysis syndrome every time we up dose the medication. So, it's like we up titrate the drug until we get to its max dose of 400 milligrams. So, that's a really big barrier for some patients.

So, I recently had a patient who came into clinic who was really interested in time-limited therapy, but he was a construction worker who couldn't take time off work because if he took time off work, he couldn't afford to take care of his family. So, ultimately, we decided to use BTK inhibitor therapy just because the time off work aspect of things was much more easier for him. And so, ultimately comes down to patient preference. It comes down to which drug suits your lifestyle cause both of these classes of the drugs work really well [and] in general are very well tolerated.



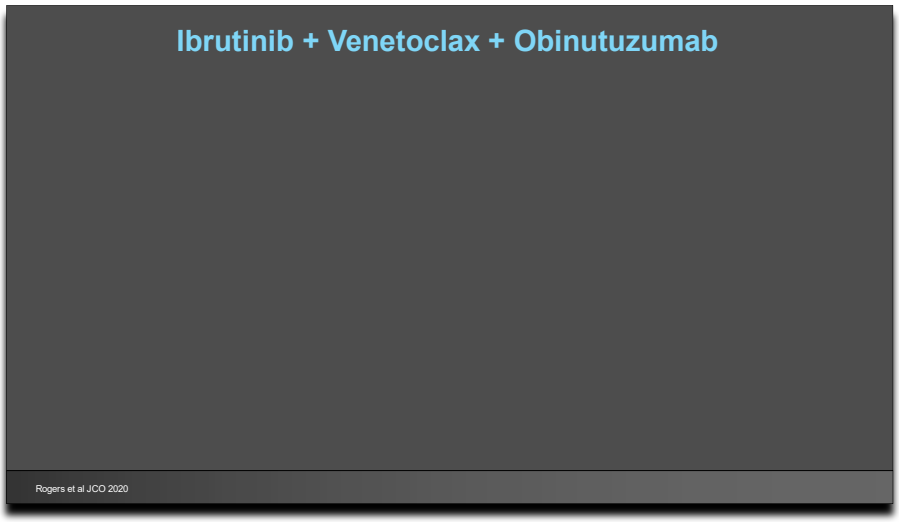
I Heard Ibrutinib Plus Venetoclax Was an Option?

So, the next thing that comes up often is the combination of ibrutinib plus venetoclax. And so, unfortunately, it's not currently FDA approved in the United States, but it is on our NCCN [National Comprehensive Cancer Network] guidelines. So, you may be able to get this combination.



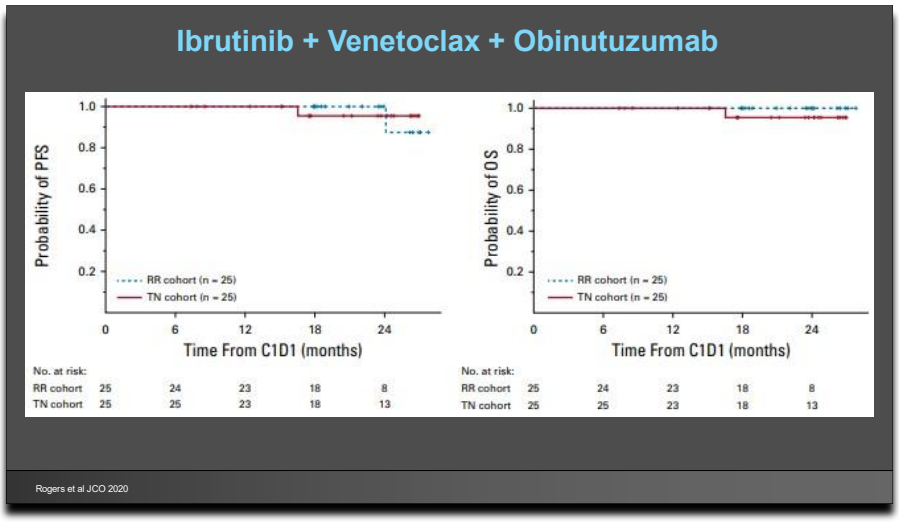
I Heard Ibrutinib Plus Venetoclax Was an Option?

So, this combination was studied in the phase three randomized control trial called GLOW, which randomized patients to either ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab. And as you see here, it led to a significant improvement in progression-free survival. This combination is given for 15 cycles. And it's all oral. So, that's why it's attractive because patients don't have to come in for the infusion of obinutuzumab like they would with venetoclax plus obinutuzumab. Patients are given three cycles of ibrutinib, three months of ibrutinib and then started on the venetoclax which helps decrease the risk of tumor lysis syndrome as well. Unfortunately, even though the study met its primary endpoint of extending progression-free survival, there were some early deaths at the beginning of treatment with ibrutinib plus venetoclax, and that's what led the FDA decide not to approve this combination. It is approved in Europe and Canada, which is one of those rare situations where international groups have approved a combination that we have not approved. So, it is a combination that you could potentially get because insurance companies usually reimburse things that are on the NCCN guidelines. But do note that it's not FDA approved. But it's something for you to talk to your doctor about and see what they think. Personally, I'm not currently using ibrutinib venetoclax because it's not FDA approved. I am using venetoclax plus obinutuzumab. But if it were FDA approved, I would totally talk about it as an option in the frontline of CLL.



Ibrutinib + Venetoclax + Obinutuzumab

The next up is if ibrutinib plus venetoclax works, why not add obinutuzumab? As I showed you all, it has a non-overlapping mechanism of action and typically has non-overlapping toxicity.

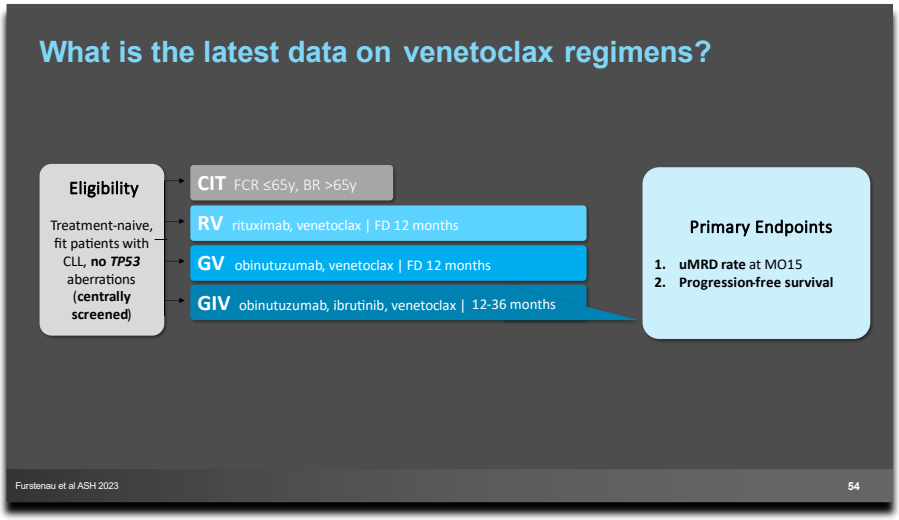


Ibrutinib + Venetoclax + Obinutuzumab

And this study was presented by my colleague Dr. Rogers at the Ohio State University also given for 15 cycles. And as you see here these lines are flat. There's nothing better than looking at a flat line on a Kaplan-Meier curve because it tells you that nothing happened, no one died, and no one had a progression event. So, these are wonderful curves to see.

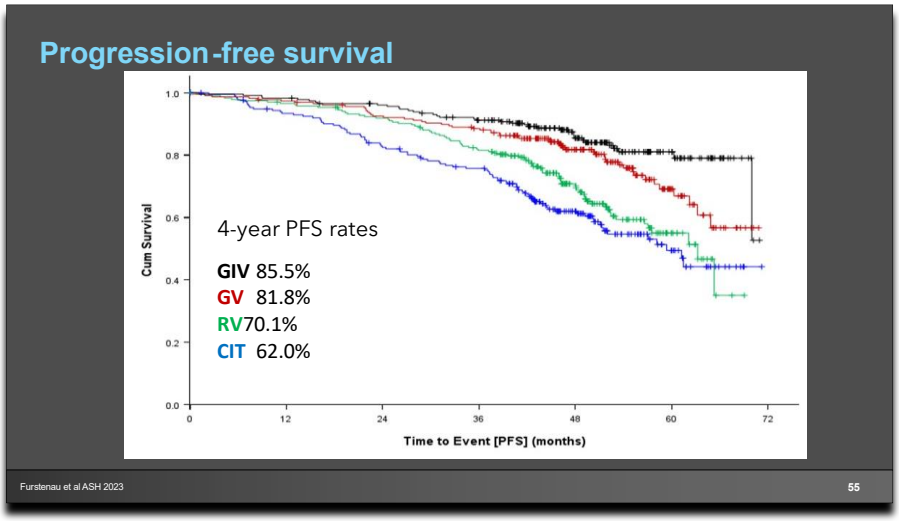
Now, there was the update, and it was the ALLIANCE study which compared ibrutinib plus venetoclax plus obinutuzumab to ibrutinib plus obinutuzumab in older patients. And what they found was that patients who got the triplet, the I plus B plus O, actually had more deaths in that arm than the ibrutinib plus obinutuzumab, which was surprising. But it turned out this study was primarily done in the era of COVID, and unfortunately this triplet therapy was really toxic for patients with COVID. And so, ultimately, I think that once this combination is approved, because I think it will be approved eventually, I would probably reserve it for

younger patients who can tolerate the toxicity associated with it, who is interested in receiving all three drugs instead of two. And now we have some clinical trials are currently underway that also might be informative to tell us which regimen is the best for our patients.



What is the Latest Data on Venetoclax Regimens?

Next is the GAIA study, the CLL13 study. And this trial was really a surprise and gave us a lot to chew on in the treatment of CLL. In this study, patients were treated with venetoclax regimens as time limited versus chemoimmunotherapy. Patients either received FCR [fludarabine, cyclophosphamide, rituximab], if they were less than 65, BR [bendamustine and rituximab] over 65, or venetoclax plus rituximab (Rituxan®) or venetoclax plus obinutuzumab given for 12 cycles or venetoclax plus obinutuzumab plus ibrutinib.



Progression-free Survival

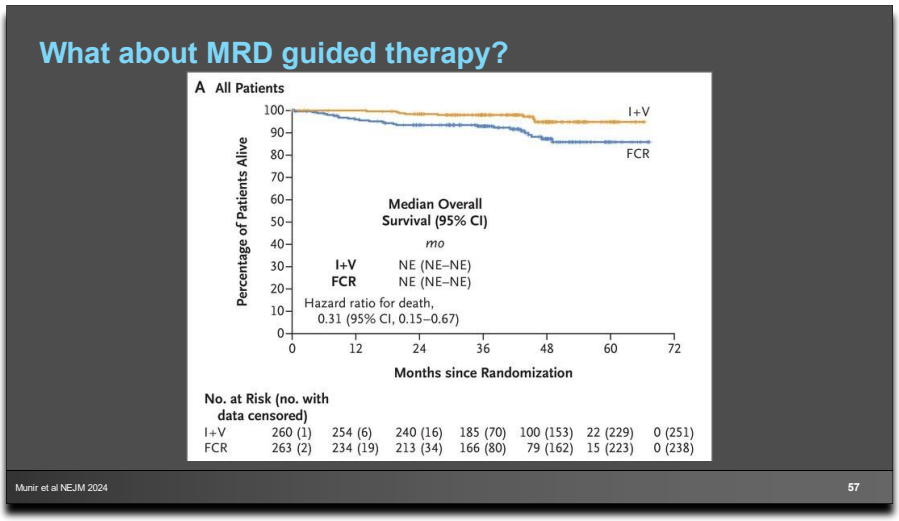
And the interesting thing on this study, which everyone was surprised about, was that patients who were treated with venetoclax plus rituximab in the frontline as represented by the green had inferior outcomes to those patients treated with venetoclax plus obinutuzumab. And ultimately, this is the study that basically solidified obinutuzumab as being our favored anti-CD20 monoclonal antibody for patients with CLL.

So, just to acquaint you with this slide, because there's a lot of lines, the black is the triplet, ibrutinib plus venetoclax plus obinutuzumab. The red is venetoclax plus obinutuzumab. The green is venetoclax plus rituximab and the blue is chemoimmunotherapy. And as you see here, the triplet did the best. But it was associated with toxicity. And so, once again I have to see more follow up to decide if I feel like the toxicity is worth it. But for a four percent gain in PFS [progression-free survival] and not much different in the overall survival, I'm not sure it is. So, I think we need longer follow up, but I think I would probably reserve that triplet for younger patients who could tolerate it if they want it in the future.

What About MRD Guided Therapy?

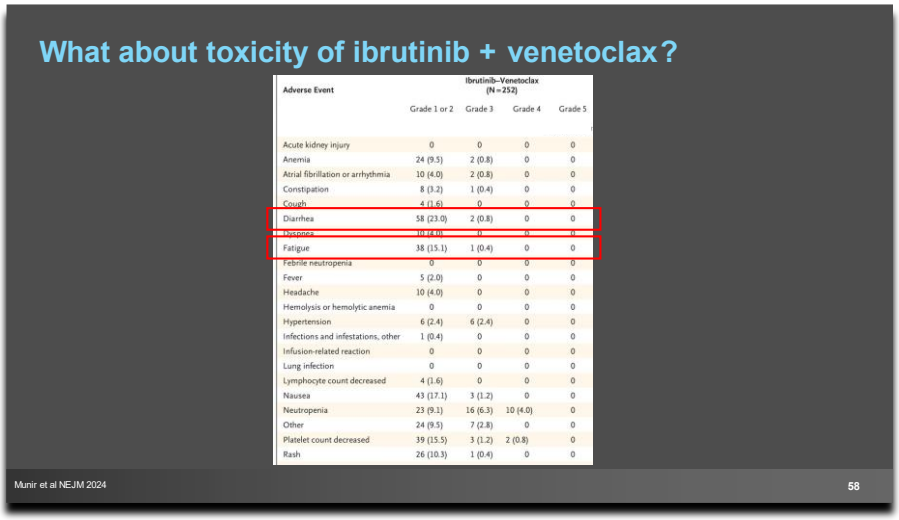
Oftentimes I get asked about MRD guided therapy. So, what's MRD? MRD is minimal residual disease or measurable residual disease, depending on who you ask. And what we're trying to do is see at what level can we detect your CLL using the most modern day technologies. And in general, I only use MRD guided therapy to be informative for patients being treated with venetoclax regimens. And so, if patients get into a deep MRD, meaning we can't detect the CLL with modern day regimens, it tells us that their time to next treatment after completing time-limited therapy is going to be really long. So, that's how I use it.

Now, there was this study, which was interesting, that used MRD as a guidance tool, meaning that if someone attained MRD or didn't attain MRD, they would decide how long to treat somebody for.



What About MRD Guided Therapy?

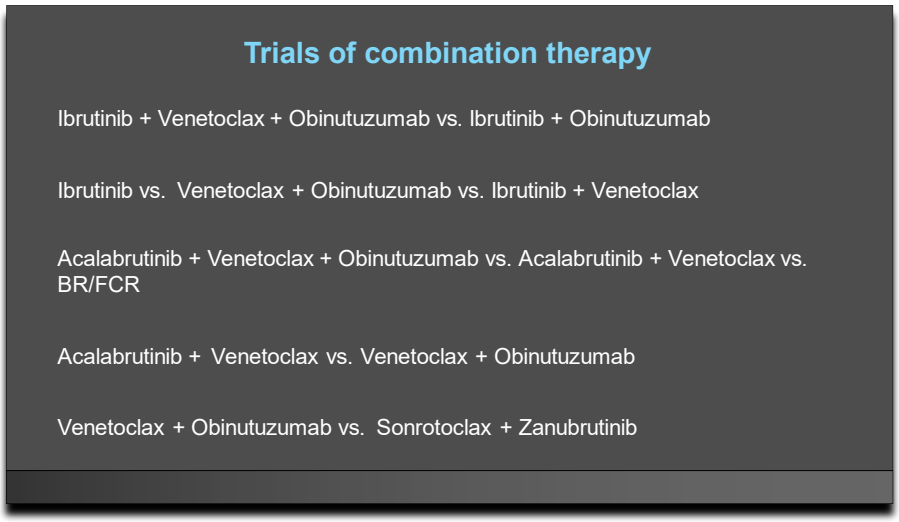
So, in this study, the FLARE study, they compared ibrutinib plus venetoclax versus FCR and they found that, first off, it improved overall survival. Great. Second off, how they did it was that they would treat until someone had reached undetectable disease and they would then extend the treatment by two-fold. So, let's say they waited, and they got MRD after one year. They would get two more years of therapy after that. So, it's a way of doing MRD directed therapy using our modern-day therapies. So right now, this is not ready for prime time. I think we need to see more data. In general, I use MRD as a way to predict when the time to next treatmentwill occur in patients who are getting time-limited venetoclax-based therapy.



Adverse Event	Ibrutinib–Venetoclax (N = 252)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Acute kidney injury	0	0	0	0
Anemia	24 (9.5)	2 (0.8)	0	0
Atrial fibrillation or arrhythmia	10 (4.0)	2 (0.8)	0	0
Constipation	8 (3.2)	1 (0.4)	0	0
Cough	4 (1.6)	0	0	0
Diarrhea	58 (23.0)	2 (0.8)	0	0
Dyspnea	10 (4.0)	0	0	0
Fatigue	38 (15.1)	1 (0.4)	0	0
Febrile neutropenia	0	0	0	0
Fever	5 (2.0)	0	0	0
Headache	10 (4.0)	0	0	0
Hemolysis or hemolytic anemia	0	0	0	0
Hypertension	6 (2.4)	6 (2.4)	0	0
Infections and infestations, other	1 (0.4)	0	0	0
Infusion-related reaction	0	0	0	0
Lung infection	0	0	0	0
Lymphocyte count decreased	4 (1.6)	0	0	0
Nausea	43 (17.1)	3 (1.2)	0	0
Neutropenia	23 (9.1)	16 (6.3)	10 (4.0)	0
Other	24 (9.5)	7 (2.8)	0	0
Platelet count decreased	39 (15.5)	3 (1.2)	2 (0.8)	0
Rash	26 (10.3)	1 (0.4)	0	0

What About Toxicity of Ibrutinib + Venetoclax?

So, moving forward about toxicity, generally the combination of ibrutinib plus the venetoclax -- we're seeing the same toxicities as you'd expect if you've got each drug individually. We haven't seen cumulative toxicity or anything new. But in general, there was a high rate of fatigue and diarrhea observed with this combination. So, it's something to note to counsel patients on.



Trials of Combination Therapy

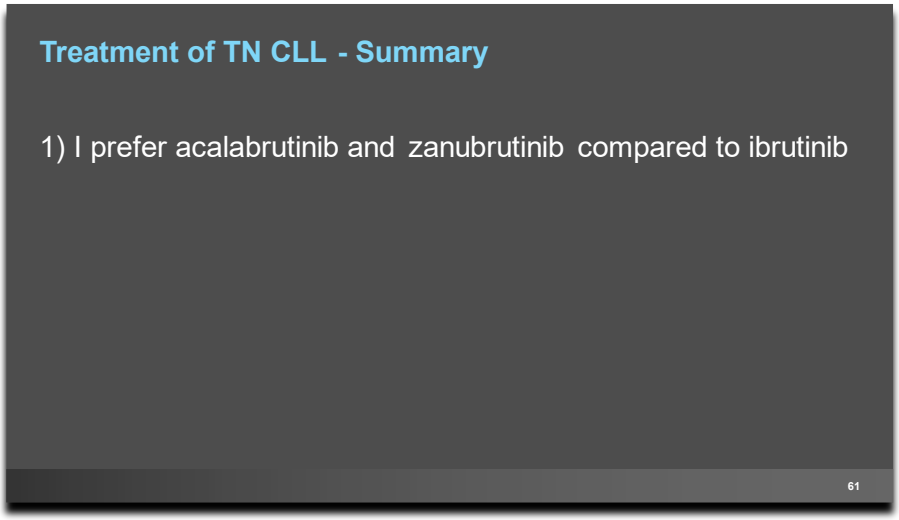
Moving forward, we have a bunch of randomized 3x3 clinical trials that are either fully enrolled or almost fully enrolled that will answer some of these lingering questions. Should we be using a triplet? Should we be using ibrutinib plus venetoclax or venetoclax plus obinutuzumab or continuous therapy in the frontline? So, we have the ALLIANCE and the ECOG study. ALLIANCE is over than 70 and ECOG is less than 70. Both of these trials have been fully accrued, and we should see more data from them. That's ibrutinib plus venetoclax plus obinutuzumab versus ibrutinib plus obinutuzumab.

We have the CLL17 study, which we're all really excited about, which is ibrutinib versus venetoclax plus obinutuzumab versus ibrutinib plus venetoclax to see which is the best regimen to use in the frontline setting. Next, we have the AMPLIFY study, which hopefully will read out soon as well -- it's fully accrued -- which subs in acalabrutinib for venetoclax.

We have the MAGIC study, which is also fully accrued, which is acal plus venetoclax versus venetoclax plus obinutuzumab. And lastly, we have the just opened venetoclax plus obinutuzumab versus sonrotoclax, which is a new BCL2 inhibitor, which I'll talk about in a little bit, plus zanubrutinib. So, we have a lot of trials coming up that hopefully will help us answer these questions.

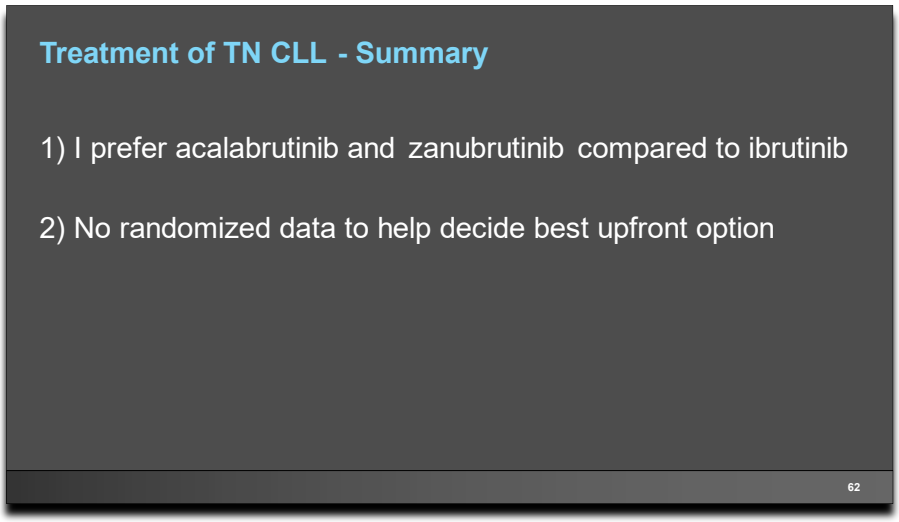
Treatment of TN CLL – Summary

So in summary, how do I approach treatment of CLL?



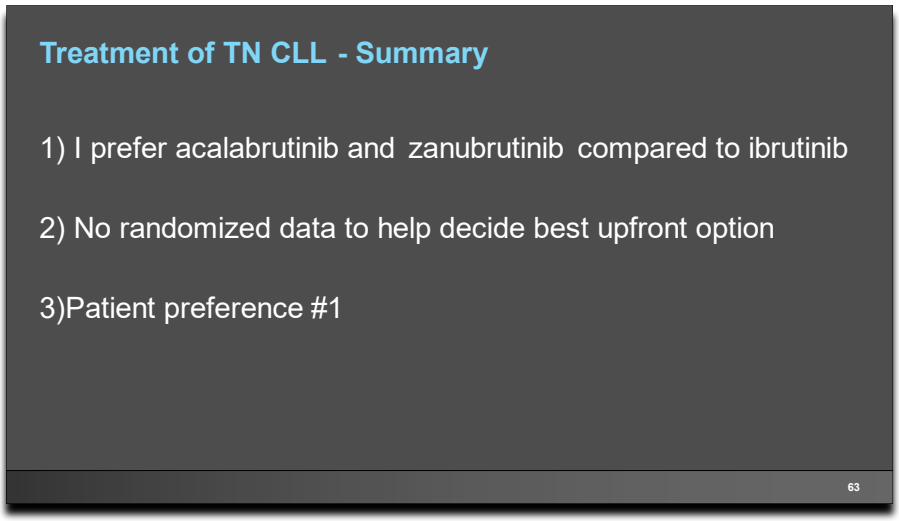
Treatment of TN CLL – Summary

For one, I prefer acalabrutinib and zanubrutinib compared to ibrutinib.



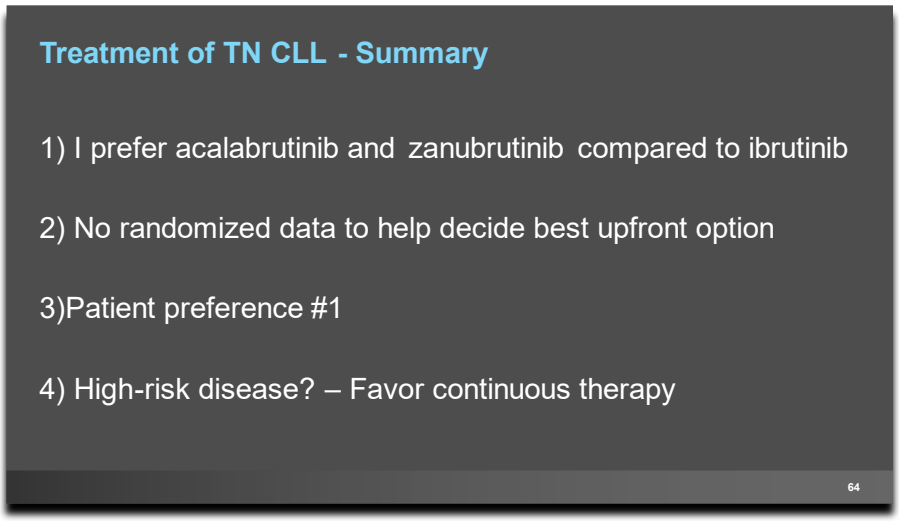
Treatment of TN CLL – Summary

There's no randomized data to help us decide what's the best upfront option.



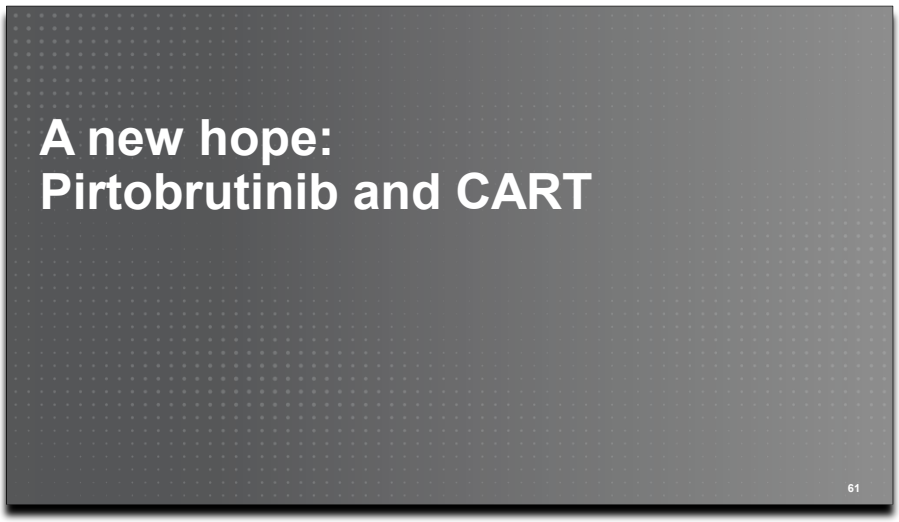
Treatment of TN CLL – Summary

So therefore, I rely on patient preference to help decide what to treat patients with.



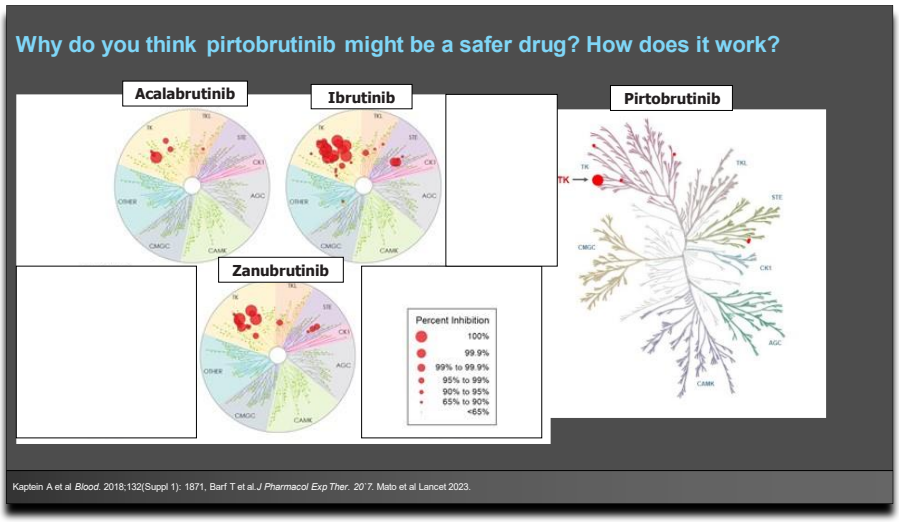
Treatment of TN CLL – Summary

And lastly, for high-risk disease, I typically favor continuous therapy, but that's also a debatable thing.



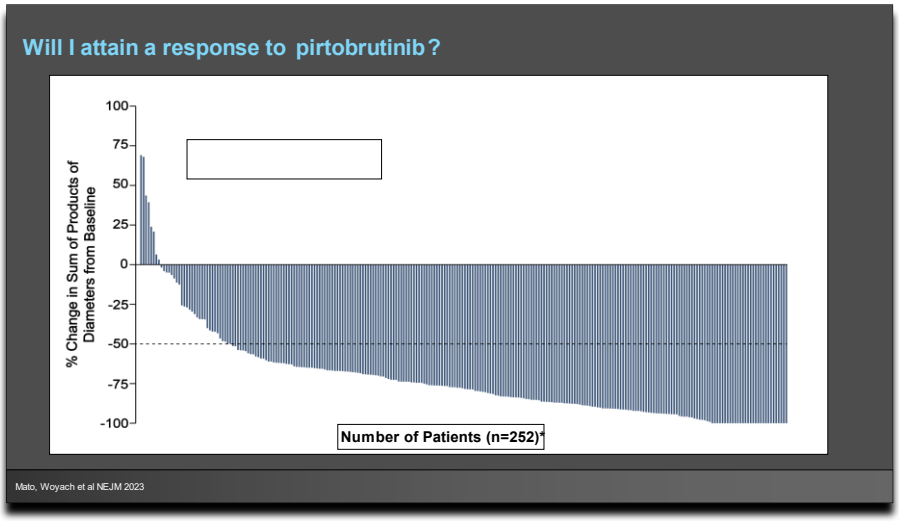
A New Hope: Pirtobrutinib and CAR-T

So moving forward for the last 10 minutes of our talk, I'm going to talk about pirtobrutinib and CAR-T. I'm also going to talk about Richter transformation. So pirtobrutinib and CAR-T are both now approved in the U.S. for relapsed/refractory CLL after patients progress or are refractory to covalent BTK inhibitors and venetoclax, which is really exciting news.



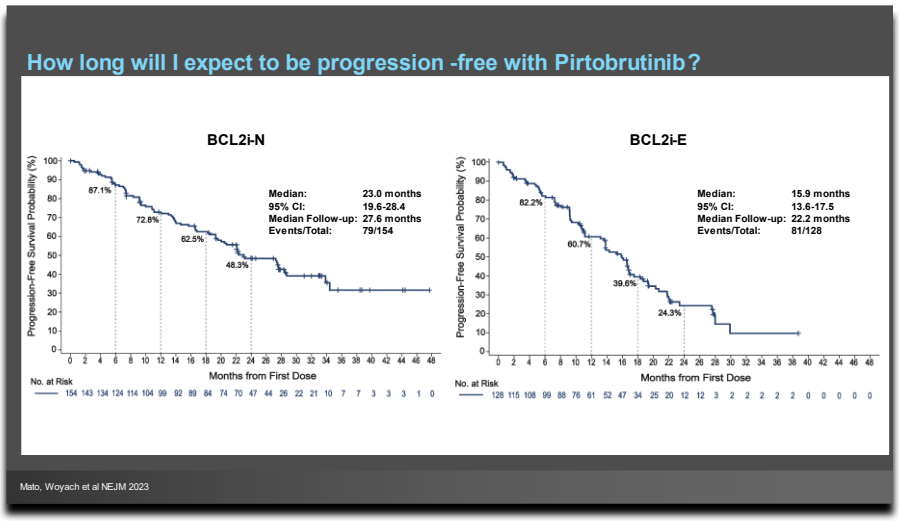
Why Do You Think Pirtobrutinib Might Be a Safer Drug? How Does it Work?

Pirtobrutinib is a noncovalent BTK inhibitor. Remember how I told you earlier how it binds a little bit differently than the classic covalent BTKis. And specifically, pirtobrutinib was designed to work in patients who had resistance mutations to our covalent BTK inhibitors. And here again we have those kinome maps. And once again you can see that there's very few red dots with pirtobrutinib. So, it really is very specific to BTK inhibitor inhibition. And so, therefore we're hopeful that it will have a good safety profile.



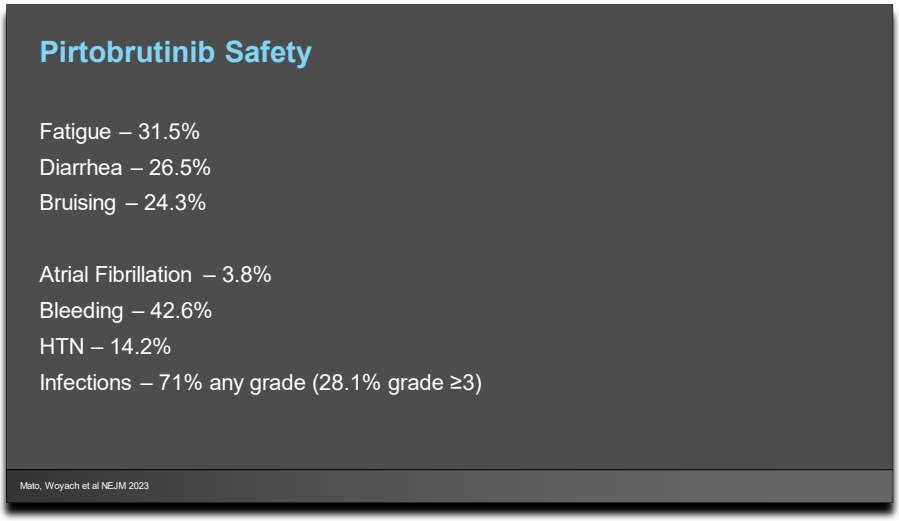
Will I attain a response to pirtobrutinib?

So, these are the results of the BRUIN study, which was a single arm study of pirtobrutinib in patients who had received prior covalent BTK inhibitor. And this is what we call a waterfall plot, it's self-explanatory, that looks kind of like a waterfall. But anyone who falls below zero -- and those little lines are a patient -- that means that patient responded. And so, the response rate on this trial was upwards of 80 percent, which is really great for patients who previously had gotten covalent BTK inhibitor and a BCL2 inhibitor.



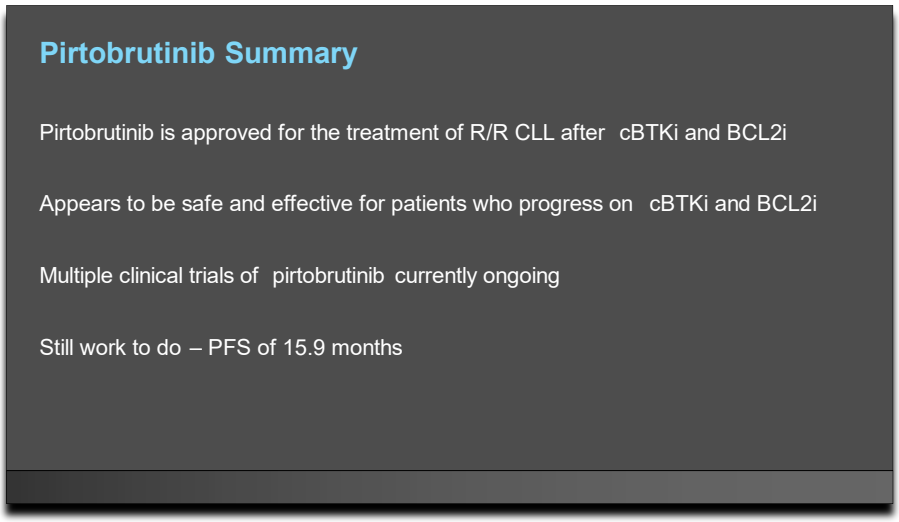
How long will I expect to be progression-free with Pirtobrutinib?

And now, when the investigators split, those patients who were BCL2 inhibitor-naive versus those who were exposed, E, they saw that pirtobrutinib worked better in patients who were BCL2 inhibitor-naive versus exposed. Now the question then becomes should we be sequencing patients from a covalent BTK inhibitor to pirtobrutinib to venetoclax? And really, this doesn't really answer that question because we don't know how those patients did who were BCL2 inhibitor-naive who then got venetoclax later on. So, we need to see more data on it. I think, which is really nice to see, that we saw good outcomes regardless of whether or not they got both the covalent BTK inhibitor and BCL2 inhibitor or they just got one.



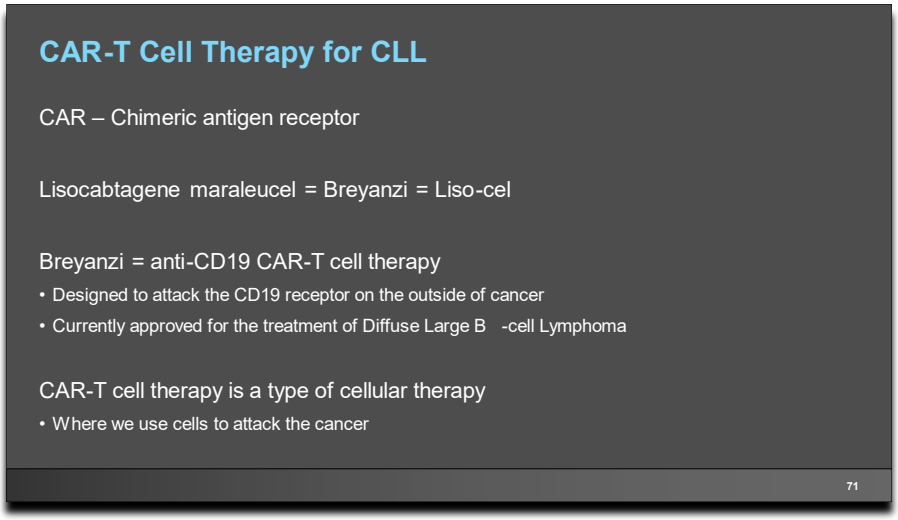
Pirtobrutinib Safety

So next is safety. So this is the safety profile of pirtobrutinib. In general, this looks pretty good, especially when we're considering relapsed disease. That being said, we really need to see how it works in the frontline setting. There is a clinical trial that is fully accrued. So hopefully we'll have data soon of ibrutinib versus pirtobrutinib. And that will be a better assessment of safety than in these patients who were heavily pretreated.



Pirtobrutinib Summary

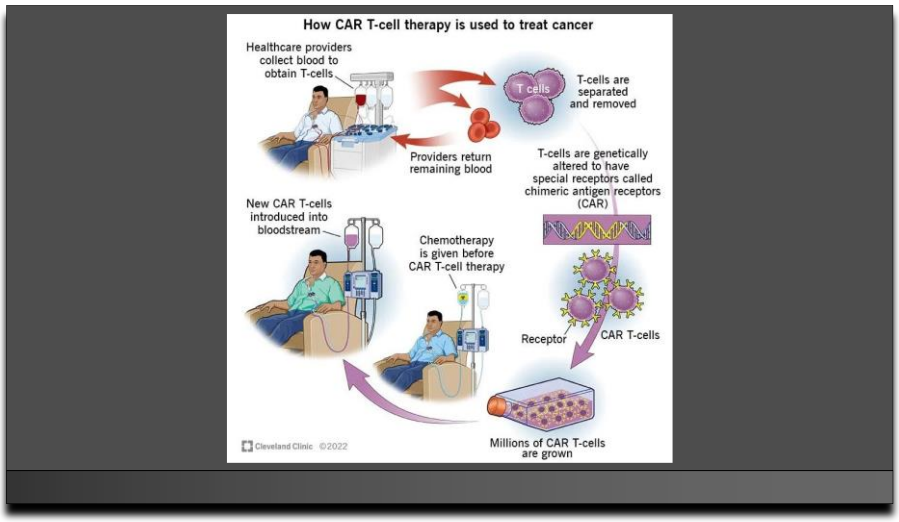
Lastly, pirtobrutinib is approved for the patients with relapsed/refractory CLL after covalent BTKi and BCL2 inhibitor. It appears to be safe and effective for patients who progress on both, and there are now multiple clinical trials that are currently ongoing, and the progression-free survival is about 15 months for patients who are treated with pirtobrutinib.



CAR-T Cell Therapy for CLL

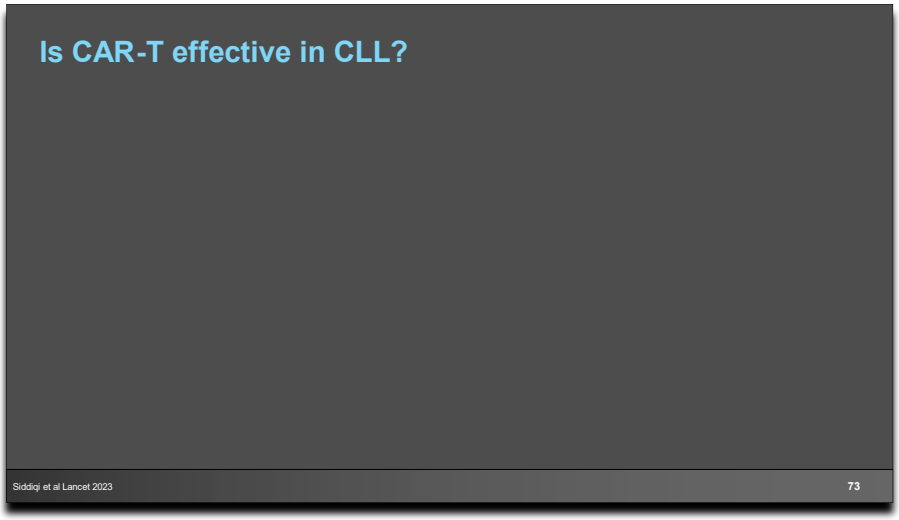
Let's move on to CAR-T. So, there's a lot of linguistics and various words that are associated with CAR-T. So, let's get this out of the way. So, CAR stands for chimeric antigen receptor, lisocabtagene maraleucel -- say that 10 times fast -- is also Breyanzi®, which is also Liso-cel. And that's the drug that's currently approved for the treatment of CLL in patients who progress after covalent BTK inhibitor and BCL2 inhibitor.

Breyanzi/Liso-cel is an anti-CD19 CAR-T cell therapy. So, just like our monoclonal antibodies target CD20 on the outside of B cells, these link T cells with CD19 B cells in a similar effect and all B cells express the CD19. And then once again CAR-T cell therapy is a type of cellular therapy. So, it's a way that we use our own immune system to attack our cancer.



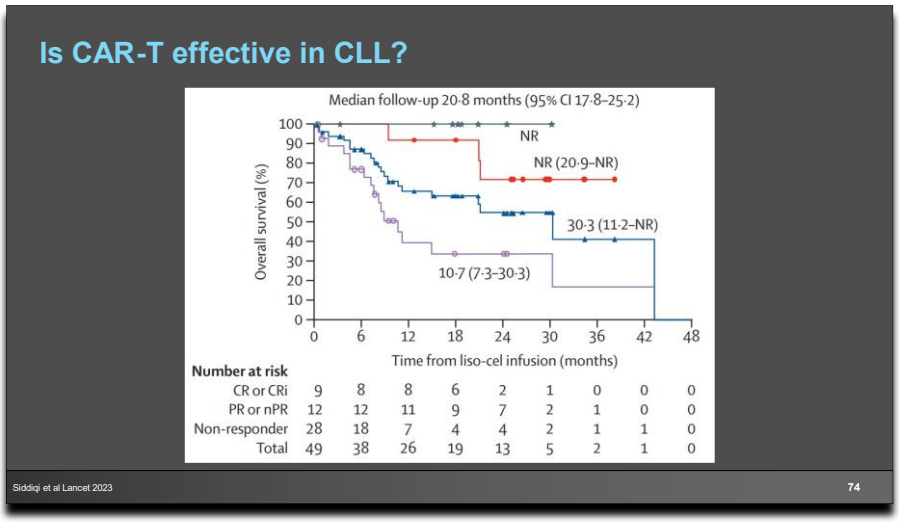
How CAR-T cell therapy is used to treat cancer

This is how CAR-T cell therapy is performed. First, our patients get apheresed. We take out their T cells from their body. We then shift those T cells to get altered in the lab. So, this is called the manufacturing process. It could take close to three weeks for this to happen. And then the T cells are genetically modified to express the CD19 so that way your T cells, which are like the soldiers of your body, have homing beacons directly to the cancer. So that's how these work. Basically, the soldiers are modified so that way they can better identify the cancer cells and destroy them. Once the CAR-T cells are made, they're transferred back into the patient. And so, this is a three-to-four-week process where apheresis occurs, three to four weeks happens, patients then get a couple of days of chemoimmunotherapy to prime their body, and then they receive the CAR-T cell therapies. So how did they do in CLL?



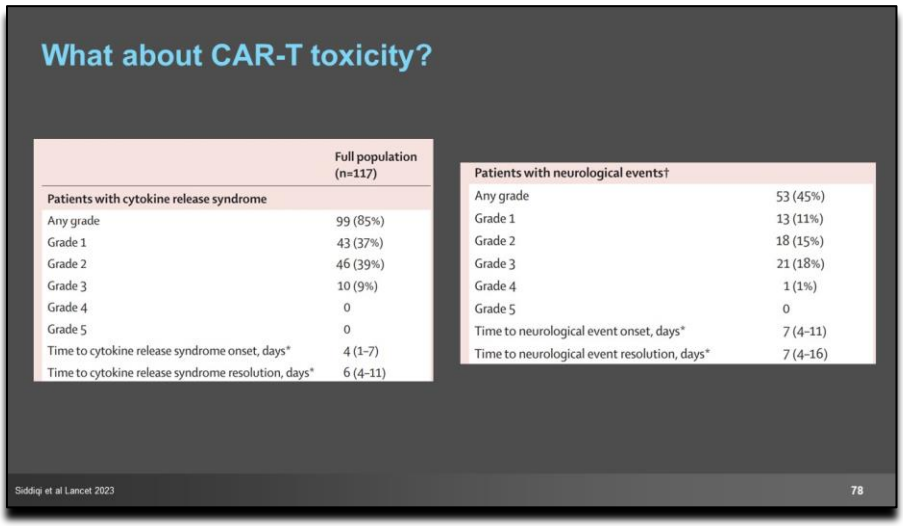
Is CAR-T effective in CLL?

So, this is the results of the TRANSCEND 004 study.



Is CAR-T effective in CLL?

And ultimately CAR-T cell therapy did work in a minority of patients. So, on the top is those patients who had a complete response, and that was nine patients. And the red is those who had partial response, and that was another 12 patients. But unfortunately, the majority of the 49 did not respond to therapy. Once again, this is a one-time deal. So, they get chemotherapy for just three days before the CAR-T and then they get the CAR-T and then they're done. So ultimately, some patients are finding these CAR-T cells to be quite beneficial as they get this one-time therapy and then could be in a complete remission for many years afterwards. But really, their role in CLL is still questionable. And I think most of us would use pirtobrutinib before CAR-T cell therapy. But there are some patients who I would think about CAR-T cell therapy in. So, talk to your provider about whether or not you are a candidate for CAR-T cell therapy after you've progressed on a covalent BTK inhibitor and venetoclax.



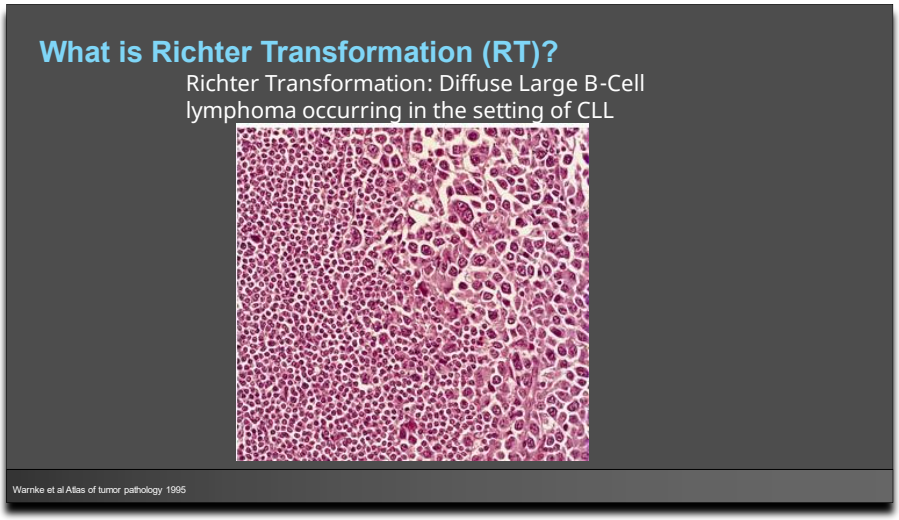
What about CAR-T Toxicity?

So, the specific toxicity for CAR-T cell therapy is something called cytokine release syndrome and neurotoxicity. Cytokine release syndrome is basically the T cells working. They release all these inflammatory cytokines that can lead to fevers, chills, hypotension, and infection. And then, interestingly, CAR-T cells can

cause neurotoxicity where patients can get confused. So, it is associated with significant toxicity. So, it's important to note this in that CAR-T isn't for everybody because you have to be understanding that you may have toxicity from this drug that may be significant and may lead to hospitalization. Fortunately enough, no one died from these toxicities during this trial, and so that was a good thing that we saw. And as we become more familiar with CAR-T moving forward, we're getting better and better at treating these toxicities and giving prophylactic medications to mitigate these toxicities from ever happening.

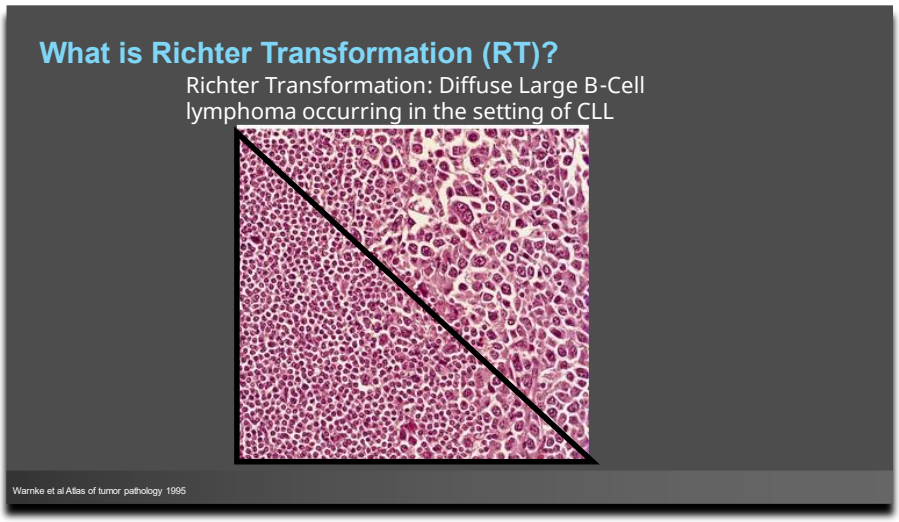
Richter Transformation

The last part of the talk -- we'll talk about Richter transformation and then we'll touch a little bit on some future meds.



What is Richter Transformation (RT)?

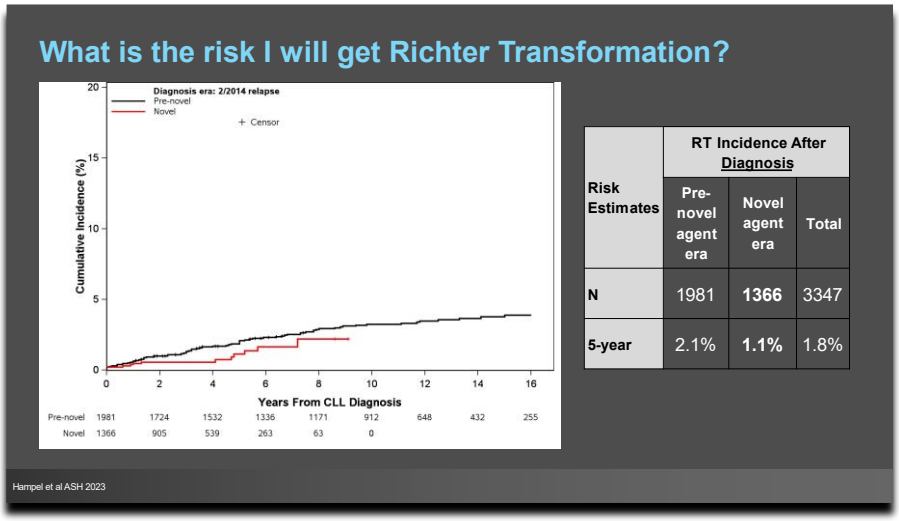
For those of you that don't know, Richter transformation is when CLL literally turns into diffuse large B cell lymphoma. And on this slide, you'll see really small cells on the left and really large cells on the right.



What is Richter Transformation (RT)?

Those little, small cells are CLL, and those large cells are diffuse large B cell lymphoma. So, it kind of gives you an idea of what they might look like underneath the microscope.

And in general, anything in cancer when something literally turns into one thing into the other, it's not a good sign. And unfortunately, patients with Richter's transformation are associated with an overall survival that's less than one year. So, it really is an area of unmet need that we really need to do more research in. But thankfully, there's been some research recently that shows that there's hope on the horizon.

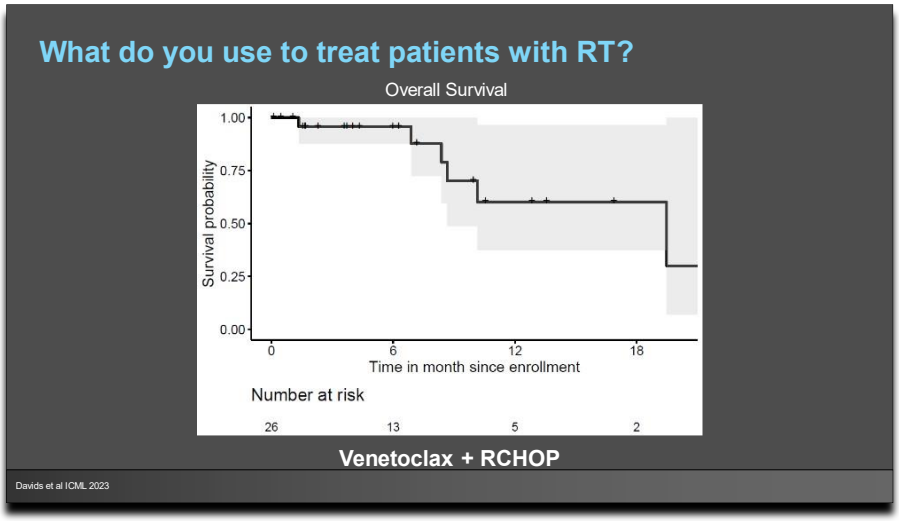


Risk Estimates	RT Incidence After Diagnosis		
	Pre-novel agent era	Novel agent era	Total
N	1981	**1366**	3347
5-year	2.1%	**1.1%**	1.8%

What is the Risk I Will Get Richter Transformation?

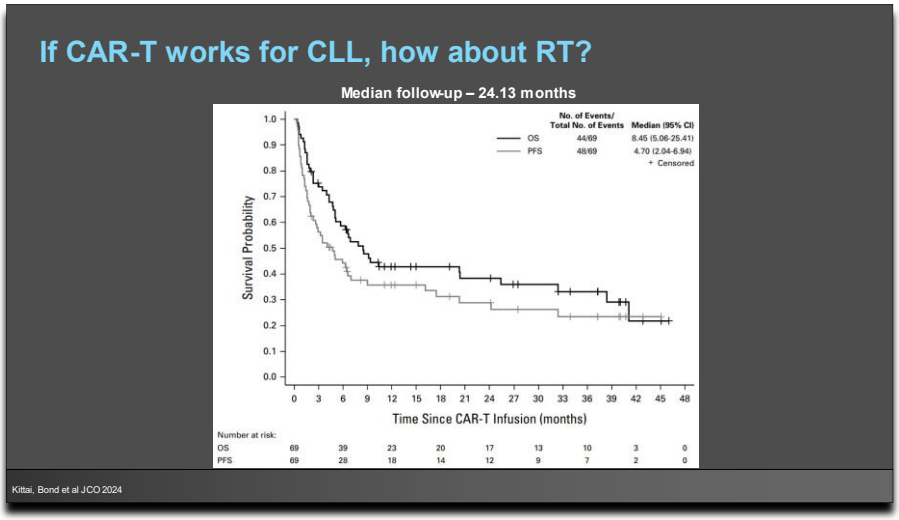
For one, it looks like the incidence of Richter's transformation is decreasing. So, this is data from the Mayo Clinic that looked at incidence of Richter's since the development of our new therapies. And it showed that the five-year incidence of Richter's dropped in this Mayo Clinic database from 2.1 percent down to 1.1 percent. I'm not sure why they saw this, but I'll take it as a win. And I think it might be something to do with our new therapies in and of themselves. But overall, the risk has dropped. I would say that I think that this instance is

a little lower than what I experienced in the clinic, but in general the risk is not so high for patients with CLL. It's somewhere between one and probably five percent over the lifetime of the disease.



What Do you Use to Treat Patients with RT?

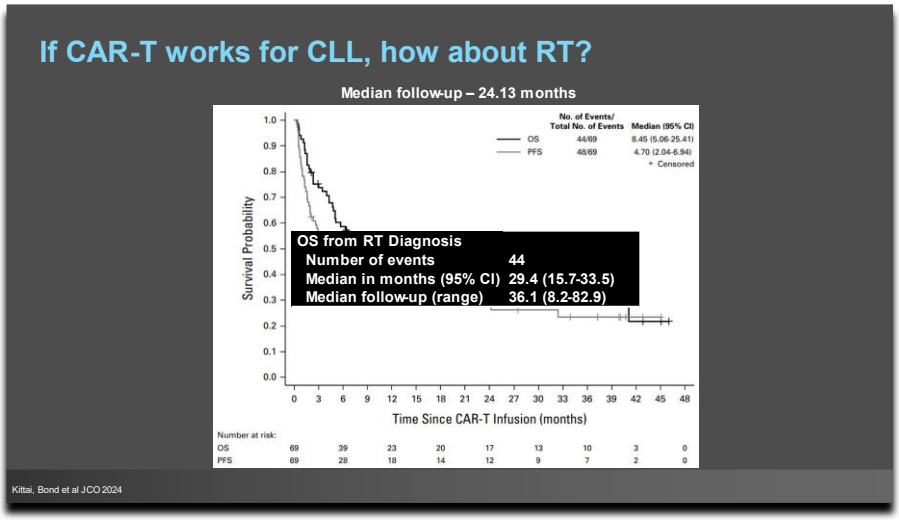
Classically, we use chemoimmunotherapy to treat Richter's transformation. We use R-CHOP or R-EPOCH, which is the classic therapy we use for diffuse large B cell lymphoma. But recently Matt Davids from Dana Farber Cancer Institute presented this data that showed that with the addition of venetoclax, patients did pretty well where their overall survival looked like it was greater than one year. So, in general, because of this data, I've now adopted this as my frontline go-to for patients with Richter transformation. And so, something to think about and talk about with your physician if you do have this. But there is hope on the horizon.



If CAR-T Works for CLL, How About RT?

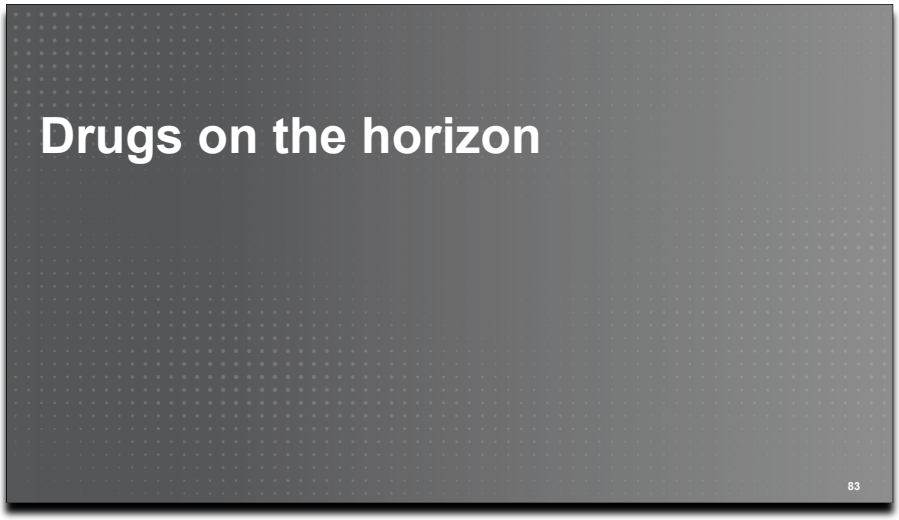
Lastly, I recently published our experience using CAR-T cell therapy for Richter's transformation and these were patients who were heavily pretreated. And what this curve shows is something we like to call a tail. So, you can see that's flattened at the end. That means that we're probably curing some subset of patients of

Richter transformation with CAR-T, which is great. But unfortunately, the overall survival for this cohort of patients was only nine months from the date of CAR-T. But interestingly, when we looked at overall survival from the date of Richter transformation, we have these patients doing quite well where they live close to three years.



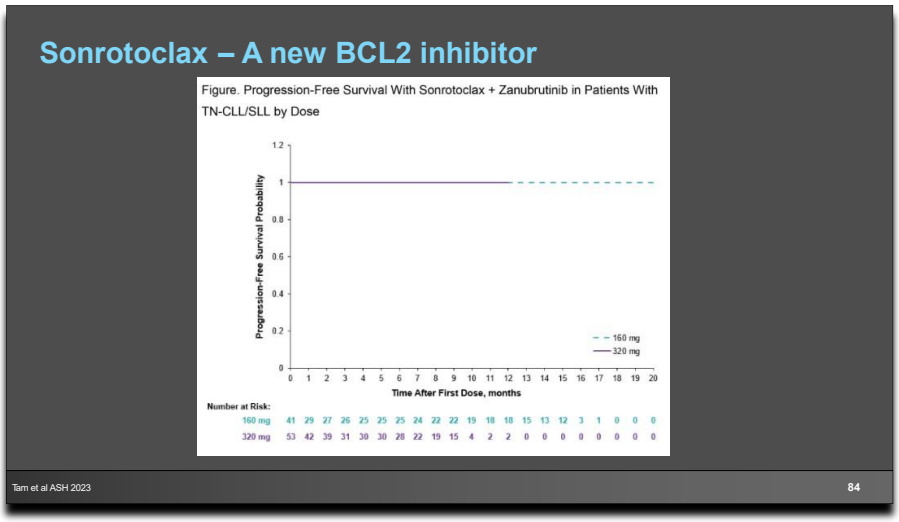
If CAR-T Works for CLL, How about RT?

This is great compared to what we've seen previously where the overall survival for patients with Richter's transformation is really less than one year. So, I think there's hope on the horizon for patients with Richter transformation and we're really trying to do our best to open novel clinical trials to make an impact for patients who struggle with this disease.



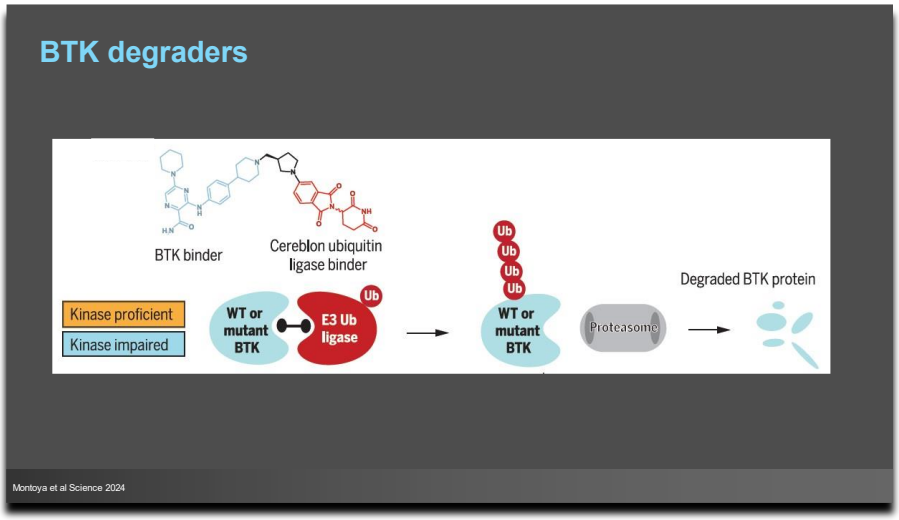
Drugs on the Horizon

Let's talk about drugs on the horizon.



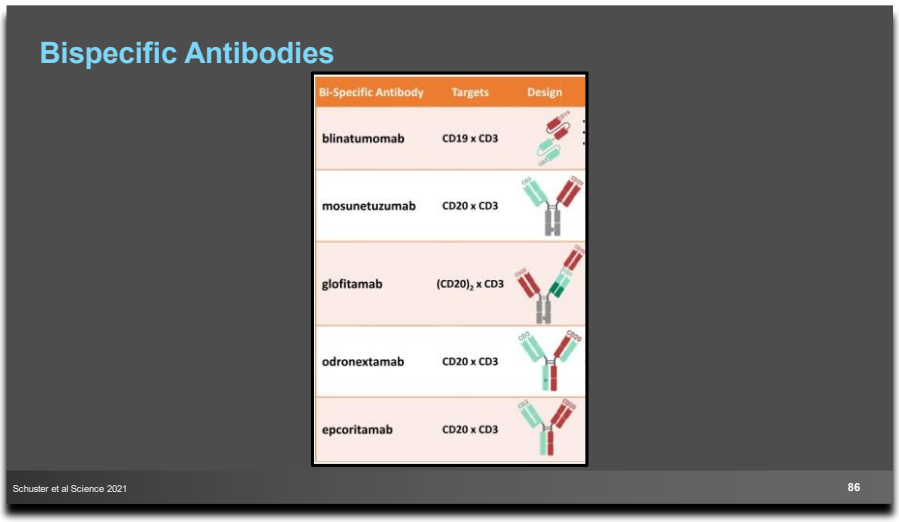
Sonrotoclax – A New BCL2 Inhibitor

So, first off, we have sonrotoclax. I mentioned this earlier. It's the new BCL2 inhibitor that in the lab looks really good. And so far, we have this phase one study. Once again, I remind you that we love flat curves because it means nothing happened. It means no patients died or progressed. And so, this was combining sonrotoclax with zanubrutinib for patients with treatment CLL. And so, you can't get better than this curve, but obviously there's a short amount of follow up. This only goes out to 20 months. Now there is a clinical trial that's examining this combination that we're looking forward to, sonrotoclax plus zanubrutinib versus venetoclax plus obinutuzumab.



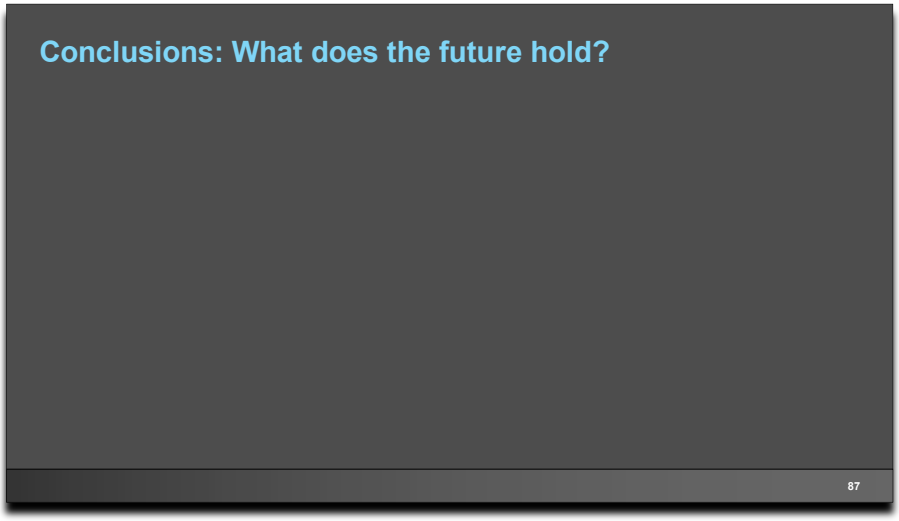
BTK Degraders

Next is something called BTK degraders. So, these don't just inhibit BTK, they literally degrade them using our own ubiquitin proteosome system, which is what we use to break down proteins in our bodies. So, really interesting drug that's currently being available ~~with a lot of~~, with a lot of uses. And might be good for patients who progress on our currently available BTK inhibitors.



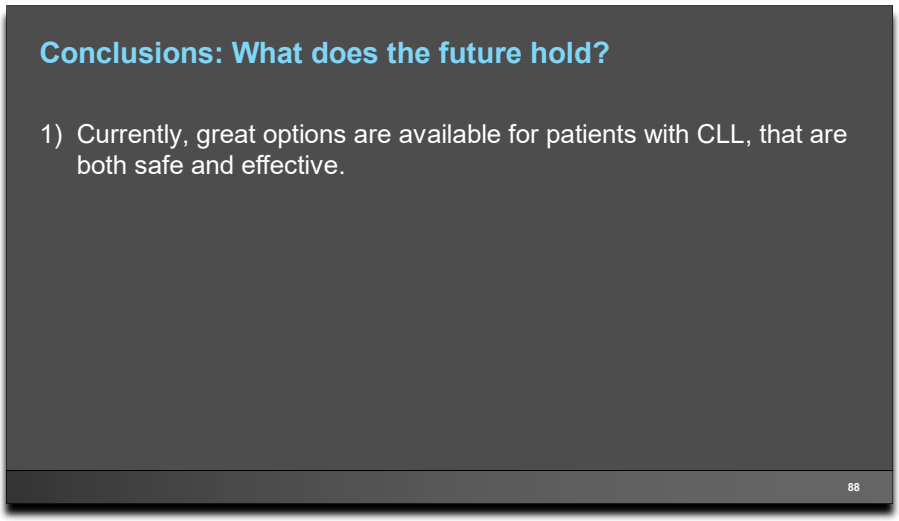
Bispecific Antibodies

Last are the bispecific antibodies. These are currently mostly approved for various other lymphomas. We don't have an approval for CLL just yet. I will note that epcoritamab (Epkinly®) patients can get for Richter's transformation because [it's] approved for transformed indolent lymphoma which Richter's transformation is. But bispecific antibodies -- basically what they do is they link the T cells to your cancer. And so, it's a little bit different than CAR-T cell therapy because there is no manufacturing time with these drugs. They're off the shelf, so you can use them immediately, which makes their use really attractive. So, these are currently being studied in CLL. And so hopefully we'll have an approval soon for our patients.



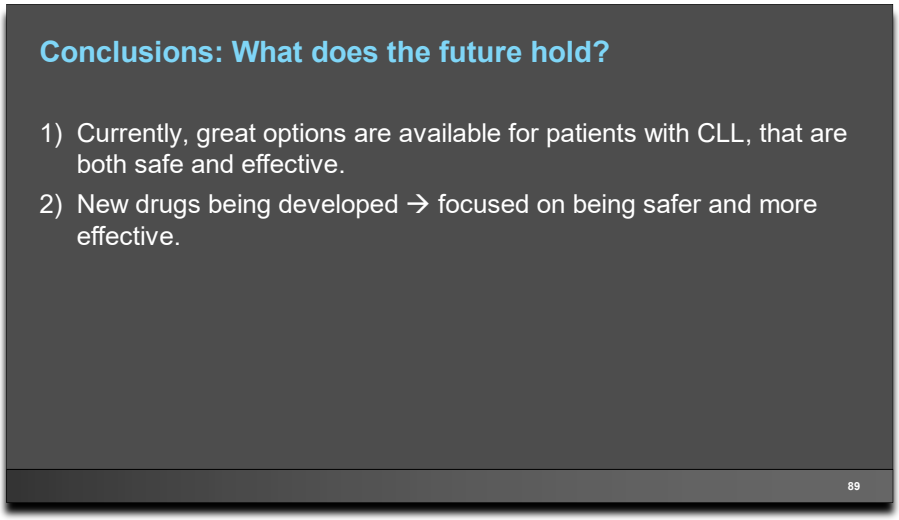
Conclusions: What Does the Future Hold?

So, conclusions -- what does the future hold?



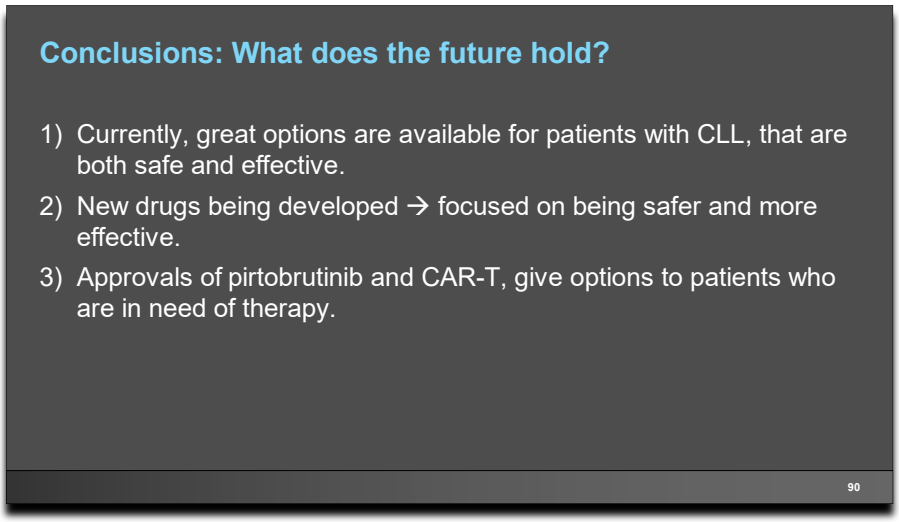
Conclusions: What Does the Future Hold?

First off, currently there are great options for our patients with CLL that are both safe and effective. And so, as I tell my patients with CLL is that I expect them to live a really long life that's as good or as close to normal life expectancy as possible given the new data that I showed you. And so, for the most part we can find a drug that really works for you.



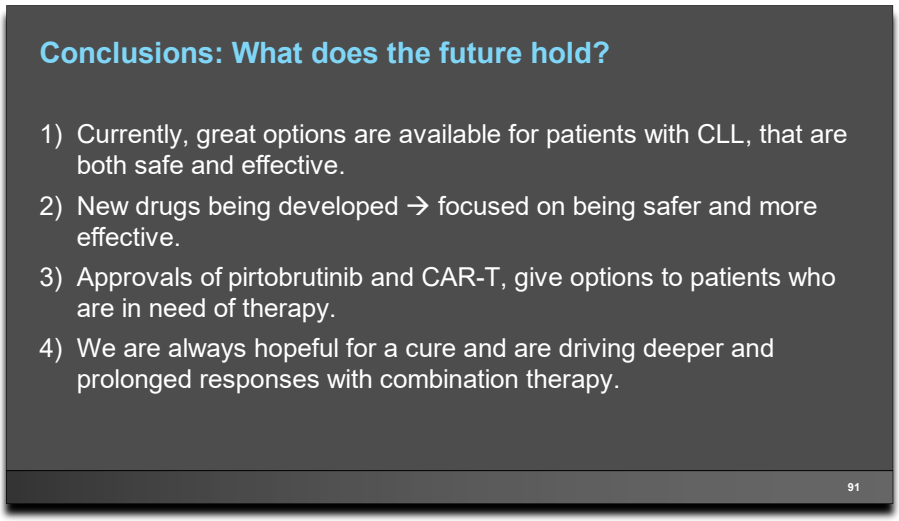
Conclusions: What Does the Future Hold?

New drugs are currently being developed that are focused on being safer and more effective. I showed you data for pirtobrutinib that appears to be very safe and may be more effective. We'll have to see based off of phase three clinical trial data.



Conclusions: What Does the Future Hold?

The approvals of pirtobrutinib and CAR-T give patients who progress on covalent BTK inhibitors and BCL2 inhibitors an option, which is really the area of unmet need currently and so exciting to have these two drugs.



Conclusions: What Does the Future Hold?

And lastly, I'll end on a point of hope is that we're really hopeful that we are hopefully attaining a cure in patients by driving deeper and prolonged responses, especially with these combination therapies. And, so, that's the end of my talk. I'm really looking forward to hearing your questions. Thanks for coming and listening in.

Thanks! Questions?

Lizette Figueroa-Rivera
Well, thank you so much, Dr. Kittai, for your very informative presentation.

Question & Answer Session

As you mentioned, it's time for the question and answer portion of our program. We'll take our first question from our web audience. Doctor, many participants today are asking a very important question. Can you define what you mean by older adults and younger adults?

Dr. Adam Kittai
Yeah, it's a great question. So, in the phase three clinical trials that led to the approval of BTK inhibitors and BCL2 inhibitors, they were defined as over 65 or younger than 65 with comorbidity. That being said, it really is a continuum. I don't define my patients by how old they are. I really define them by their comorbidities and what their health status is. So, a really healthy 70-year-old really can act very similar to a very unhealthy 50-year-old. And ultimately it comes down to the comorbidities that you have, including cardiac disease, kidney function. But once again, I want to highlight that all of these drugs have been studied in both older patients

and in younger patients. And so, I don't really limit what I use to treat patients based on age. It's just what I favor based on the data in front of me. But once again, every patient is an individual. It requires a detailed conversation between you and your doctor, and ultimately, I don't limit my treatment based off of someone's age.

Lizette Figueroa-Rivera
Thank you, doctor. And we'll take the next question from our telephone audience please.

Operator
Our first question comes from Carol calling from New York. Please state your question.

Carol
My mother died from CLL 30 years ago. I'm 83, and I have it and my son, who is a physician in Buffalo, he also has it now. I want to know, is this genetic?

Dr. Adam Kittai
That's a great question. So, the answer is that typically CLL is not genetic, but it can run in families. And so, if I see somebody like you who has multiple first-family relatives -- first degree family relatives who have CLL, I do refer them to a genetic counselor because it may impact you and your family into the future and is mostly informative, so that way you can tell future generations that they're at higher risk for CLL. There is a genetic mutation that is associated with CLL, but you have to get advanced genetic testing to get it done. And I really reserve it for those patients who have multiple first-degree relatives.

That being said, patients who have CLL -- their children are more likely to get CLL, just like if you have cardiac disease, your children are more likely to get cardiac disease. But it's not necessarily a genetic link. It's just you are more likely to have it if your parents were to have it. But for somebody like you or other patients out there who have multiple family members who are affected, I do send them to a genetic counselor to see if they have that high-risk genetic feature. And it's not high-risk genetic feature for outcomes of CLL. It's high risk for getting a CLL.

Lizette Figueroa-Rivera
Thank you so much for the question. Our next question comes from Vic. Vic is asking about the role of stem cell transplantation in CLL.

Dr. Adam Kittai
So there still is a role for stem cell transplantation in CLL. However, it's very rare that we actually need it anymore. And the reason why it's very rare is because -- number one is that CLL typically affects a median age of 65. And so, if you look at all of our drugs that we currently have, most of our patients don't need to get a transplant because they have a lot of good, safe drugs that will get them to the end of their life. Stem cell transplant can be considered in younger patients because younger patients have more life to live, and we might get through our BTK inhibitors and BCL2 inhibitors faster and then may need to get stem cell transplant to make sure that patient stays in the remission. But that's pretty rare. And the reason why it's rare once again is because there's a lot of toxicity associated with stem cell transplant. So, ultimately, we reserve it for younger patients and because there's so much toxicity, we generally avoid it with patients with CLL, because our drugs are so safe and effective. So, there is a role for some patients, but in general, it's very rare that I send somebody to get transplanted in CLL anymore.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our telephone audience please.

Operator
This question comes from Jackie calling from North Carolina. Please state your question.

Jackie
Has there ever been any thought or consideration given to a clinical trial for the use of ivermectin (Stromectol®) in a CLL environment?

Dr. Adam Kittai
Excellent question, Jackie. Unfortunately, ivermectin has no effect on cancer, and so there hasn't been a clinical trial for the use of ivermectin for CLL.

Lizette Figueroa-Rivera
Thank you so much. And our next question comes from Storm. Storm's asking does cardiac risk for BTK also apply to stroke patients?

Dr. Adam Kittai
The cardiac risk does apply to everybody, and so the issue that usually comes up with patients who had a prior stroke and cardiac comorbidity and CLL that we've seen is that oftentimes patients with strokes, if it's embolic stroke and cardiac comorbidity need to be on blood thinners. And so, we know that patients who are on blood thinners, especially if they're on aspirin, Plavix® [clopidogrel] and a DOAC [direct-acting oral anti-coagulant] like apixaban (Eliquis®), they have a very high risk if they have to go on a BTK inhibitor. And so, that really does require multidisciplinary care. And so, if you've had a stroke or you're on blood thinners and you want to go on a BTK inhibitor for CLL, it's a conversation that you have to have with your physician about really which blood thinners that you need to be on because BTK inhibitors do have antiplatelet effects, and so they can overlap, leading to risk of serious bleeding. So, something definitely to consider if you have prior stroke, because it definitely affects our consideration for concurrent meds that patients are on if they were to get a BTK inhibitor.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our telephone audience please.

Operator
Our next question comes from Anita calling from Pennsylvania. Please state your question.

Anita
Hi. I'm 78 years old and have CLL for about 18 years and I've been on Imbruvica® (ibrutinib) 280 milligrams for about seven years and I'm doing really well with it. But I need some clarification about the risk, the cardiac risk and Imbruvica® because a year ago I got angina upon exertion and had a stress test that showed a small blockage, and they treated it with pravastatin (Pravacol®) and metoprolol (various brands), and I've been fine with it. But now just a couple of months ago, I started with severe fatigue and shortness of breath. But my iron was eight, so I received three iron infusions and I'm feeling better. But my cardiologist, because of the shortness of breath, wants to send me for a bunch of tests because he's concerned. But when I asked him if he thought it was from the Imbruvica®, he said that's not his expertise. So, what do I do?

Dr. Adam Kittai
You bring up a lot of good points, so I'm going to kind of tackle them one by one. So, number one is that there was a recent study that showed patients who need dose reductions of their ibrutinib actually do just as well if they don't need dose reductions, if they dose-reduced to an adverse event. So, that's one thing to not worry about. I know that's not related to your question, but just wanted to point that out.

Number two is that ibrutinib is associated with arrhythmias like atrial fibrillation, ventricular fibrillation, chronic hypertension. There is a risk of congestive heart failure there, but it's not so strong for that specific cardiac issue. So, your issue of having a blockage in your heart is a little bit different than the classic cardiac issues that we see with ibrutinib.

Lastly, your shortness of breath -- from what you're telling me it probably was due to the iron deficiency anemia, and I wouldn't necessarily worry about your heart if your heart tests all come back okay, especially if your fatigue drastically improved with your IV iron infusions. But in general, another thing to note is that if after conversation with your hematologist, oncologist, and your cardiologist, you decide to stop the ibrutinib because you are -- they are worried that it might be affecting your heart too much at this point, patients who stop ibrutinib with good disease control can go years without needing new treatment. So, there was a recent study presented at one of our major conferences that patients on ibrutinib after six years who had good disease control stopped and they're already at two years of follow up with not many patients relapsing. So, there's many times in between that you can have off therapy potentially if you have to stop because of toxicity. In general, I don't typically stop just randomly for my patients. But for your case, if you all decide that the ibrutinib is contributing to some heart disease, I can assure you that at least your CLL likely will be controlled for a few years if you're under currently good disease control.

Lizette Figueroa-Rivera
Thank you. And our caller does bring up another question that Graham was asking. Graham was asking, "Should I have a conversation about cardiac risk with my oncologist or my cardiologist?"

Dr. Adam Kittai
Both. So, your oncologist should know about the cardiac risks associated with BTK inhibitors. Discuss it with your cardiologist too before starting to make sure that you are optimized in general. I would pick a second generation BTK inhibitor. I would likely pick acalabrutinib most likely because it has less cardiac risk. But certain patients will go on zanubrutinib, and that's okay too. It has good cardiac risk. But it's just a conversation to make sure that you are optimized before starting therapy. And certainly, I have started a lot of patients with cardiac comorbidity on BTK inhibitors who generally had their disease under control.

Lizette Figueroa-Rivera
Thank you. And William is asking, does decreased red blood cell count impact the ability to exercise during watch and wait?

Dr. Adam Kittai
Yes, red blood cell count being decreased is usually associated with the low hemoglobin and low hematocrit as well. And so, if your hemoglobin is low, it might decrease your exercise tolerance. Oftentimes when I see somebody with a low hemoglobin and if the other signs of the CLL look good, I make sure that they don't have something called autoimmune hemolytic anemia. So, that's something to talk to your doc about. And just like the last patient who called in, I always check iron studies because I found a lot of patients are actually iron deficient and can really greatly improve with iron infusion. So, the short answer to your question is yes, low hemoglobin can cause poor exercise tolerance and to check your iron studies and move forward that way.

Lizette Figueroa-Rivera
Thank you. And Russell is asking -- he was diagnosed with CLL in 2019, but with low white blood counts before and continually after the diagnosis. How atypical is a low white blood count with CLL?

Dr. Adam Kittai
Great question. So, I've seen it in a few patients and the reason that is, is because CLL not only affects your bloodstream, but it also affects your lymph nodes and your bone marrow. And so, you need to have a healthy bone marrow to create white blood cells -- normal white blood cells. And so, some patients will have a lot of disease in their bone marrow but not have much of it in their blood or their lymph nodes. And similarly, some patients have a lot of disease in their lymph nodes, but not having their blood or the bone marrow. It kind of depends. The majority of patients certainly have a high white blood cell count. But I have seen it predominantly affect the bone marrow, which can make it difficult for your bone marrow cells to be produced if you have a lot of disease there.

And so, it comes with some special considerations. In general, when someone has a lot of bone marrow disease, giving them venetoclax plus obinutuzumab can get a little complicated because it's associated with low cell counts also. And so, it does require a little bit more nuance than the classic patient with a high white blood cell count. But typically, once their CLL is treated, we do see improvements in their white blood cell count because we're treating the CLL and the bone marrow as well. And one thing to make sure of too is that -- I don't get bone marrows [biopsies] in most of my patients. I do get bone marrows when the CLL isn't reading the textbook and isn't presenting like classically it does. So, patients who are presenting with predominantly low cell counts, I do get a bone marrow biopsy to make sure that we're just dealing with CLL and not another cancer like a different type of leukemia, which I've also unfortunately seen as well.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our phone audience please.

Operator
Our next one comes from Karen calling from Minnesota. Please state your question.

Karen
Yes, I heard mention of shingles at some point in his talk. I don't know if you're supposed to have the shingles shot or not to have it. It seems like I've heard both directions if you have CLL. Should you get the shingles prevention shot?

Dr. Adam Kittai
So, the old shingles shot used to be a live virus and we don't like to give live vaccines to patients with CLL because patients with CLL are immunocompromised. But the new shingle shot called Shingrix is perfectly safe for patients with CLL. And so, in general, I give Shingrix to my patients with CLL, especially if they're older and meet the other indications for Shingrix. So, talk about getting the Shingrix vaccine with your oncologist as well as your primary care doctor and it should decrease your risk for shingles.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Barbara. Barbara is asking, "What can I do to combat fatigue?"

Dr. Adam Kittai
So, this is probably the most difficult thing to deal with in my clinic. Patients come in with fatigue, which we presume is due to the CLL without having any other objective signs that their CLL is progressing. And it's really

difficult because some people are more sensitive to the CLL in their body than others. So, the first thing I do when someone comes in with a presenting sign of fatigue without other objective signs of CLL progression is I test for other things. So, I always test for thyroid dysfunction. I've caught a lot of hypothyroidism. I always test for obstructive sleep apnea, especially for patients who are overweight or if their partner reports that they are snoring a lot. And I also test for depression. And so, these three things are chronic things throughout society that go unnoticed, and people classically don't ask about. And I've caught a lot of all three of these things in my patients.

If we can't find an alternative diagnosis to their fatigue, we think about treating their CLL. And one of the things that we think about doing is we try giving a steroid burst, and if the steroid burst does not improve the fatigue, then it likely is not the CLL that's causing the fatigue. Similarly, you can try a monoclonal antibody just to see if it works, and if it doesn't work, it likely isn't the CLL that's causing fatigue. If we see improvements with steroids, I then would consider going on full blown CLL treatment, which hopefully will help with the fatigue.

But every patient is a little different and ultimately if you don't want to go on CLL treatment and you don't meet any other objective signs for CLL, I think the classic things that you can do is making sure that you keep a sleep diary, make sure your sleep hygiene is up-to-date. Make sure you're optimizing your diet, making sure you're eating healthy, and trying to get exercise. Those things have all been associated with fatigue, even in patients -- improved fatigue, even in patients who don't have CLL. So, those are the ways I kind of tackle that question. But I agree. It's a difficult question. It's a difficult thing that our patients experience. And unfortunately, we don't have many interventions to help them. So, it's definitely an area that we should be looking more into.

Lizette Figueroa-Rivera
Thank you. And another side effect that participants are asking about is peripheral neuropathy. Anything to help with neuropathy?

Dr. Adam Kittai
So luckily, with our new therapies, peripheral neuropathy is not as common. We do see it, but it's not as common. So, in general, unfortunately the only things that we can do about peripheral neuropathy are make sure that patients are taking B12 and folate and we also make sure that patients report the neuropathy as soon as they're experiencing it, because unfortunately, neuropathy is sometimes irreversible, and if it's irreversible, we need to make a treatment change or a dose adjustment or a treatment holiday to try to figure out what's going on. Additionally, you can try a treatment holiday if your disease is under control to see if it's actually the treatment that's causing the peripheral neuropathy versus something else. And if I think that it might be something else, I often refer to neurology as well.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Marilyn. Marilyn asks, "Why does the new BiTE require long-term continual use?"

Dr. Adam Kittai
Good question. So, what she means by BiTE therapy-- that's the same thing as the bispecific antibodies. Once again, the bispecific antibodies are not currently approved for CLL. But in general, the way that they were originally studied was for long-term use. So, the current one that is approved for long term for diffuse large B cell lymphoma is epcoritamab. But I know that the other bispecific antibodies, glofitamab (Columvi™) and mosunetuzumab (Lunsumio™), are actually time-limited. So, I know that the people who developed

epcoritamab are now looking at it from a time-limited perspective as well. So, whether they will be approved for CLL in a time-limited way or in a prolonged way is still to be determined. But in general, it might be the prolonged way as you are stating because these patients typically are refractory to both the therapies that we currently have. And so, right now they're just not approved. So, I'm not sure how they're going to be approved, but I know that they are trying to move all bispecifics to be time-limited, if possible, but sometimes it's just the way the drug is designed and how we expect it to work.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Janet. Janet's asking, "I was diagnosed with CLL at 73 and I was told I don't need treatment, just ongoing blood tests. They said there's a 15 percent chance I may never need treatment. If I do get symptoms, what usually comes first?"

Dr. Adam Kittai
It really depends on the patient. So, I think that for the most part, if I were to guess, just anecdotally of what I observed, most patients have a rising white blood cell count and then most patients have associated fatigue. But honestly, it's different for every single patient. They present all in different ways. I would say anecdotally, when I experience in the clinic, it's the fatigue and the high white count.

Lizette Figueroa-Rivera
Thank you. And Deborah's asking about the side effects of obinutuzumab.

Dr. Adam Kittai
Obinutuzumab is associated with both an infusion reaction, tumor lysis syndrome, and increased infection risk for about a year after receiving it. So, we start off with a test dose of obinutuzumab of 100 milligrams for the first day that you get it. And the reason why we start off with a test dose is, A, there are patients who can have allergic reactions to it and, B, it can cause that infusion reaction, which is basically your heart might start racing. You might feel nauseous. You might get flushed. So, we start with a small dose because some patients can have inappropriately big responses to just a small dose. So, you come in cycle one day, one cycle, on day two, you get the bigger dose at 900 milligrams and once you get through cycle one day one and day two typically there's a very low risk of infusion reaction or allergy moving forward. So, the big things moving forward are going to be infection risk. Specifically, it targets all of your B cells and so you have trouble, patients might have trouble with viral infections, and that may last up to a year after receiving the therapy. So, those are the biggest things I think about with obinutuzumab. I forgot to mention also it can cause cytopenia. So, we typically watch their blood counts also very closely.

Lizette Figueroa-Rivera
Thank you. And we'll take our next question from the telephone audience please.

Operator
Thank you. This question comes from Donna calling from Florida. Please state your question.

Donna
Hi. Did you mention that in the watch and wait phase after 16,000 lymphocyte number, that's when you would start a treatment or is that still considered the watch and wait phase?

Dr. Adam Kittai
Yeah, that's generally still considered the watch and wait phase. So, the data I showed was the -- it was a prediction model that helps us determine how long someone might be in watch and wait. So, we look at three

things: IGHV unmutated status, absolute lymphocyte count over 15,000, and palpable lymphadenopathy. If you have zero those things from diagnosis, the time to first treatment on average, it's going to be greater than 16 years. So, as one of our prior callers, if you noted, if you have none of those things, the chance of you needing treatment is actually pretty low in that 20 percent of those patients may never need treatment. Now, if you have one of those things, the time to first treatment is probably around six to eight years from diagnosis, and if you have two to three of those things, the time to first treatment is about two to four years. Now in terms of a cutoff for ALC that would make someone need treatment or high lymphocyte count that would make someone need treatment, there's no actual cut off. A lot of my patients will slide to 200,000-300,000 white blood cells. Once they get past 300,000, I typically get a little bit nervous, and I'd want to start treatment then. But usually by that time they're symptomatic and so they require treatment anyways. So, in general there is no ALC top cut off that means we should start treatment now. It's kind of provider-dependent. But in general, I found that once you get to greater than 200,000 white blood cell counts, there's usually some other indication to treat that's met. But it kind of depends on each patient.

Lizette Figueroa-Rivera
Thank you. And our next question comes from Kara. Kara is asking, "Are there any treatments or therapies on the horizon that would allow an immunecompromised patient to be able to participate in large gatherings rather than constantly have to shelter or isolate?"

Dr. Adam Kittai
So, unfortunately, there's no randomized controlled trials that look at isolation versus social -- not isolation. I think that this has become a really difficult conversation to have with patients as well, because I understand their fear, especially after going through the COVID pandemic. And in general, I've mostly switched back to what I've been telling patients before the COVID pandemic, that for the most part, good hand hygiene, not touching your face, staying away from sick people is probably the -- really what you need to do. In terms of wearing masks, wearing N95s, it ultimately comes down to what you're comfortable with.

Unfortunately, even though I think that wearing a mask likely reduces risk of transmission, it hasn't really been proven in trials or studies. And so, if you are going to wear a mask, N95s do prevent transmission to you. And so, it depends on how comfortable you are. But for the most part in the modern era of COVID, we see much, much, much, much less hospitalizations in patients with CLL. And we still see some hospitalizations, but it's much less.

So, I think in general, my opinion is that patients with CLL should go back into the world and experience life. And in general, if you want to be careful and wear an N95 when you're in crowded spaces, that's probably something that you can do that might reduce your risk. But as long as you're staying away from people who are actively symptomatic, I think it's okay to go out and enjoy your life because ultimately this is the world we're living in currently, and we're seeing generally not as bad outcomes with COVID and CLL anymore. And so, I think patients should feel reassured that they can go back and enter society.

Lizette Figueroa-Rivera
Thank you. And Mike is asking, "Are there some new advances for high-risk TP53 mutation relapsed patients?"

Dr. Adam Kittai
Yeah. So, the continuous BTK inhibitor therapies generally are not associated with worse outcomes with patients with high-risk disease. So, I think that just knowing that is a really good thing. We don't have anything specifically for T53 deletion, 17P patients. There was going to be a study of a novel inhibitor of TP53,

but it didn't seem to work so well. But in general, our drugs are becoming much better and better for those patients with high-risk disease.

One thing I forgot to mention for the last question about risk of COVID -- if you're worried about COVID too, there are new versions of the Evusheld (tixagevimab/cilgavimab) drug that was available back in the day, where basically, it's a long-term antibody that prevents COVID for patients with CLL. So, I know that one recently got approved by the FDA. So, feel free to ask your doctor about that as well, because it may also provide you some comfort when interacting with other people as well.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our phone audience please.

Operator
This question comes from Elizabeth calling from Pennsylvania. Please state your question.

Elizabeth
Yes, hello. My husband was diagnosed with CLL on September of 2010. So, he's had it for 14 years now. He's lost a ton of weight. He went from 200. He's 149 now. 2019 he would get his IVIG treatments every 28 days. Then he would get chemotherapy three days out of the month every 28 days for approximately two years. Then, the doctor retired, and the new doctor put him on Imbruvica, the pills, 420 milligrams per day. And my question to you, in your opinion would it be better for him to go back on the chemotherapy IV drip for three days in every 28 days as opposed to the pill every night cause it's $15,000 a month. That's what this pill costs. And it's very expensive.

Dr. Adam Kittai
Yeah. So, unfortunately dealing with the cost of medication is something that's also very difficult. So, I'll say a couple of things. In general, I no longer use chemotherapy to treat my patients with CLL. I haven't used it in-since I've been in practice. I didn't use it while I was in fellowship, and my colleagues who are specialized in CLL -- we just don't use chemoimmunotherapy anymore. And the reason why we don't is that the trials that led to the approval of the pills led to improvement in survival.

Now the question of cost commonly comes into play, and I would encourage you to reach out to the LLS folks here as well as the Lymphoma Research Foundation and the CLL Society, as there are grant programs that you might be eligible for that might cover the cost of drug. Additionally, your hematologist-oncologist can also reach out to the drug companies, as they also typically have programs that might help cover the cost of the drug as well. And so, those are opportunities that you could use to get some of that cost covered.

And in general, when I was practicing at Ohio State University, there were only two, maybe three patients who I could not find a way to cover the cost of their drug. And so, there usually are outlets to do so and I encourage you to use those outlets that we just described.

Lizette Figueroa-Rivera
Thank you. And our last question today, Doctor Kittai, what are you most excited about with the advancements in treatment for CLL?

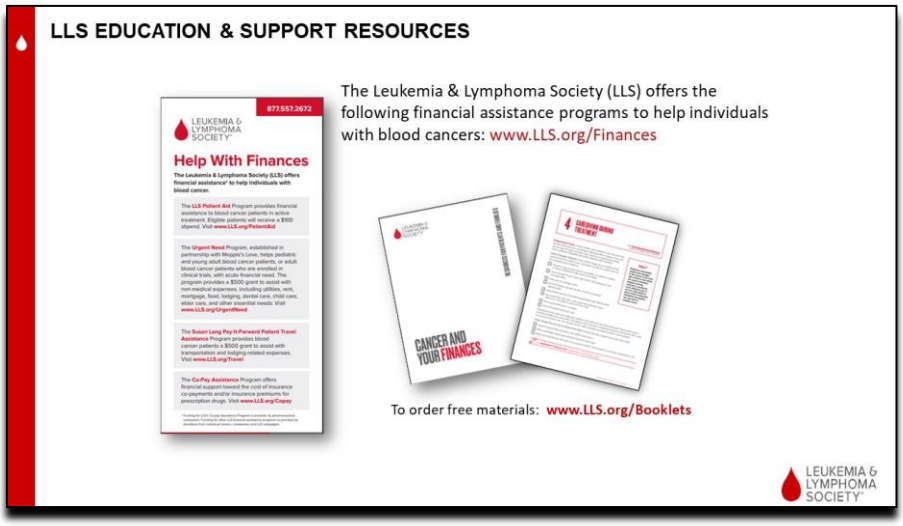
Dr. Adam Kittai
Yeah. So, I was really excited to see that ibrutinib versus age-matched control data that I showed you all, which shows that our patients are living close to age-matched control or as good as age-matched controls with

our modern day therapies. And I'm also excited about the development of these new drugs that are safer. So, we now have these drugs that are leading to equal life expectancies. Now, we got to get them safer. And we also have to focus on how do we give them in a time-limited matter so that patients aren't affected by that financial cost that we just talked about and the finance, the physical cost of our time. So, I'm really excited about some of these novel combinations combining acalabrutinib and venetoclax or pirtobrutinib and venetoclax that are currently being reported. Because this might be time-limited therapy that is both safer and financially efficacious for our patients.

LLS Education & Support Resources

Lizette Figueroa-Rivera
Right. Well, thank you so much. And again, special thanks to Dr. Kittai for sharing your expertise with us and for your continued dedication to our blood cancer patients. So, thank you so much for your participation. But if you we weren't able to get to your question today, you can contact an LLS Information Specialist at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time or go to lls.org/informationspecialists to chat online or you can e-mail them at lls.org/contactus.

LLS Education & Support Resources



LLS Education & Support Resources

If you have not already done so, please, as Dr. Kittai mentioned, please visit our financial assistance webpage at lls.org/finances as we currently have a copay assistance program that is open for CLL patients. You may also call toll free 877-557-2672 for more information. Again, our copay assistance program for CLL is currently open.

We also are a proud partner with Dollar For, a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free, and you can visit them at lls.org/dollarfor. That is lls.org/dollarfor for more information.

We also have a Clinical Trial Support Center where Clinical Trial Nurse Navigators will personally assist you throughout the entire clinical trial process. And you may reach them at lls.org/navigation. Thank You!

Thank You!

Again, we'd like to acknowledge and thank AbbVie, BeiGene, Genentech and Biogen, and Lilly for their support.

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Take good care and continue to provide us with your feedback and concerns. Thank you.