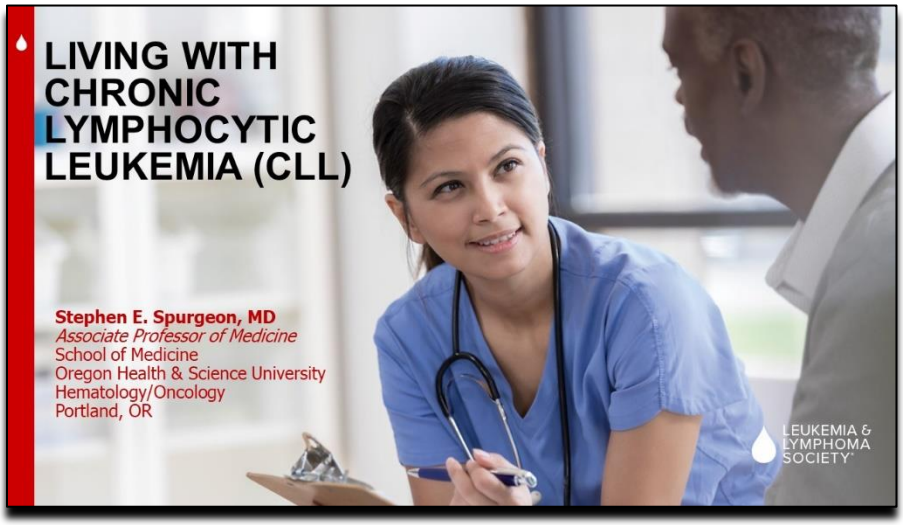
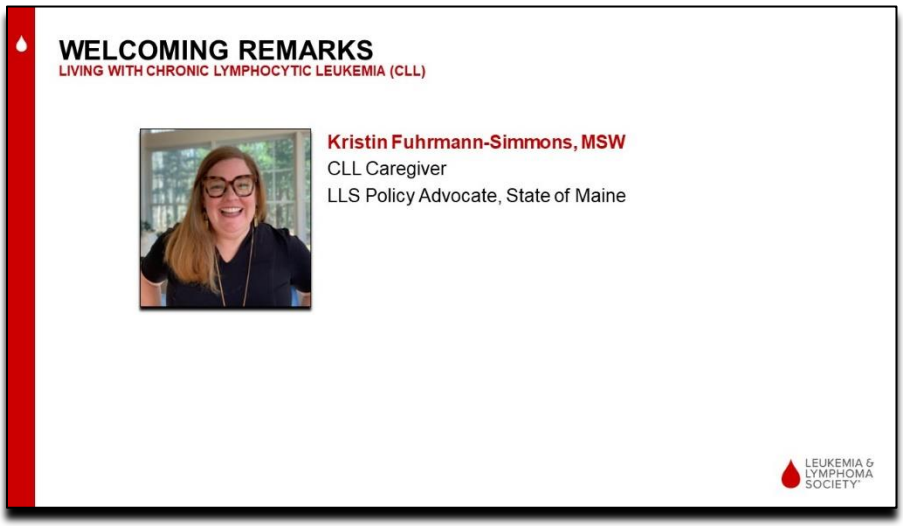


Living with Chronic Lymphocytic Leukemia

Operator
Greetings, and welcome to Living with CLL, a live telephone and web education program. It is my pleasure to introduce your moderator, Lizette Figueroa-Rivera.

Welcoming Remarks

Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 1,300 people participating from across the United States as well as other countries, including Canada, India, Iraq, and Portugal. Special thanks to Dr. Stephen Spurgeon for sharing his time and expertise with us today. Before we begin, I'd like to introduce Kristin Fuhrmann-Simmons, an LLS volunteer policy advocate, and a caregiver for her father, who is living with CLL.



Welcoming Remarks

Kristin Fuhrmann- Simmons
My name is Kristin Fuhrmann-Simmons, and I am from the great state of Maine. I have been part of the LLS community since 2012 when my dad was first diagnosed with CLL. I've been a team captain with Team in Training for eight years and I overlapped that time with LLS as a volunteer policy advocate.

In my most important role, I've been a caregiver to my father who has CLL. I've learned a great deal about this disease and its treatment. I've watched as my father has battled CLL and. I know how this diagnosis can impact a patient, their family, and the entire community that surrounds them. Having a loved one diagnosed with blood cancer can be extremely difficult. And I know the information my family and I have gathered throughout the years has assisted us in being better advocates for my father.

I'm also an advocate for LLS. And it's the stories that help bring data and research to life for our state and federal policymakers. This has been hugely meaningful work to me and, of course, patients around the country. We've really have been able to make an impact.

I want to welcome you to this program where a key opinion leader, Dr. Spurgeon, will provide us with the most current information about CLL and its treatments. We're fortunate to have Dr. Spurgeon speak to us today about the latest advancements for CLL. So much has happened just in the past 10 years since my dad has been diagnosed. It's very exciting news.

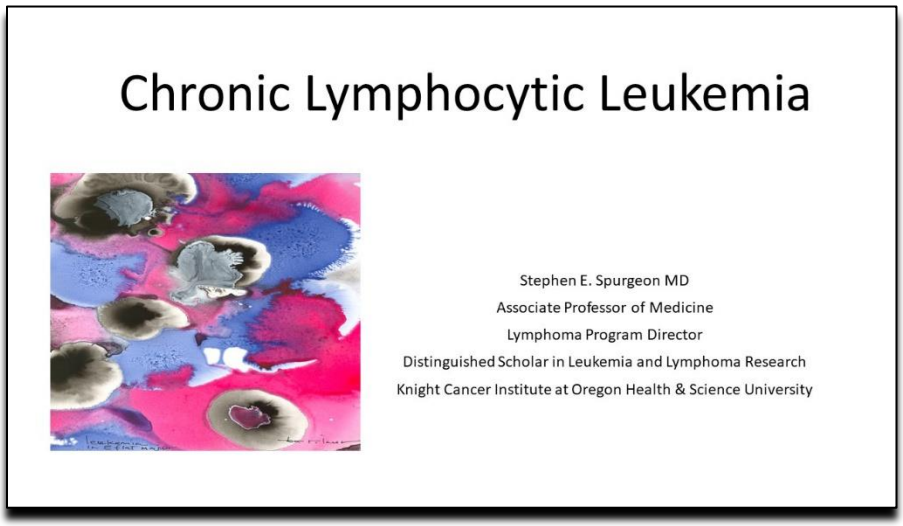
Also, as a caregiver, I wanted to let you know that LLS will also be providing us with education and support. On June 9th, alongside a health care professional, I'll be featured in a webinar especially for CLL caregivers where we'll focus on self-care. And then on June 16th, LLS will have a caregiver question-and-answer session called Caregiving over Coffee. I know you know this but LLS sees the value in providing education and support to both patients and caregivers.

Thanks again to LLS, the leading source of free blood cancer information and a leader in advocating for patients and their families, helping us navigate cancer treatments and ensuring that we have access to quality, affordable, and coordinated care. Back to you, Lizette.

Lizette Figueroa-Rivera
Thank you, Kristin, for your welcoming remarks and we look forward to hearing more of your story next month at our Caregiving for CLL webinar. For this program, we would like to acknowledge and thank Genentech and Biogen; Eli Lilly and Company; and Pharmacyclics, an AbbVie Company; and Janssen Biotech for their support.

Disclosures

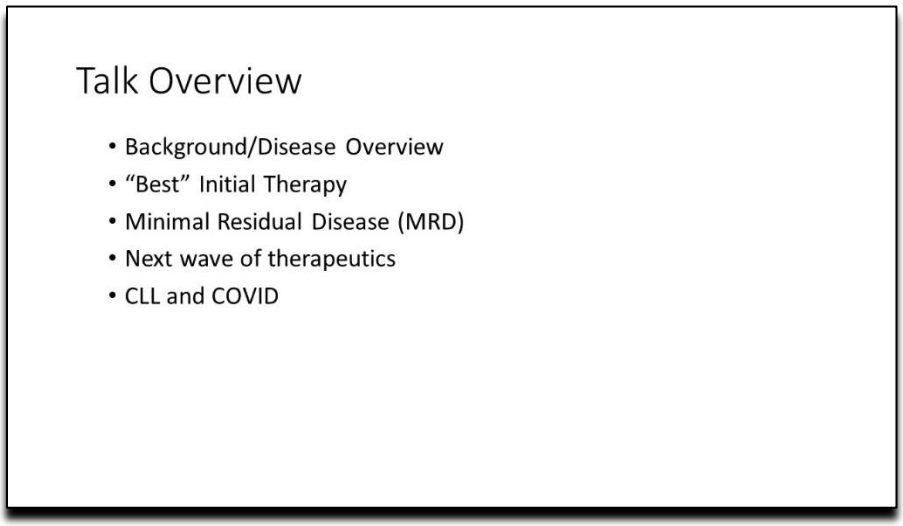
I am now pleased to introduce Dr. Stephen E. Spurgeon, Associate Professor of Medicine, School of Medicine at Oregon Health & Science University, Hematology Oncology in Portland, Oregon. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us, Dr. Spurgeon and I am now privileged to turn the program over to you.



Chronic Lymphocytic Leukemia

Stephen Spurgeon, MD
Thanks to all of you for joining. I was just saying it's so wonderful to be part of the LLS community and such a strong network of CLL patients. Thanks to Lizette, and to Kristin for that patient-support overview.

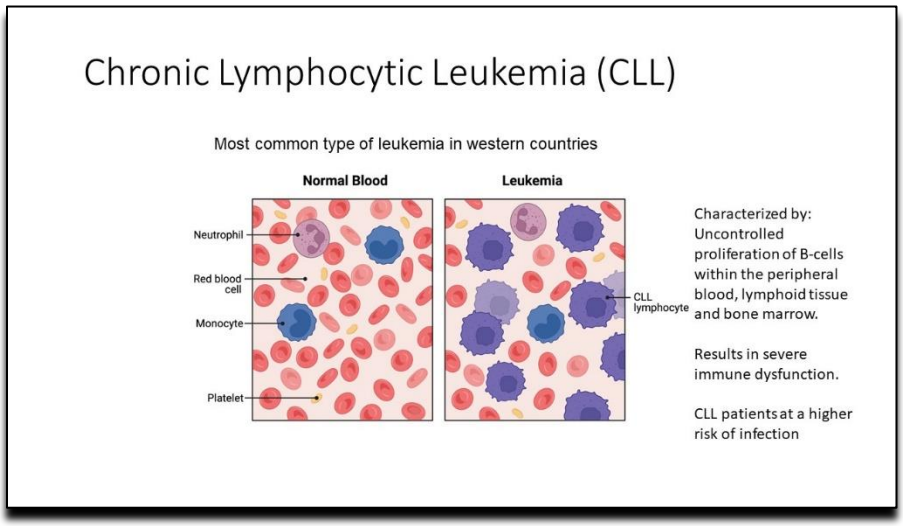
I always like starting with this. This is a patient of mine from about 12 years ago when I was working at the VA who was a musician. And this is what he called his leukemia E flat major. And this is what he thought his blood looked like. And as you'll see from next slide, it's actually not that far off. This is always a reminder of many people are living with this and doing it in different ways.



Talk Overview

Today, we have a number of things to cover, some of which will be more basic for some of you. Some of it will be over other people's heads. And that's okay. This is a chance to get to know some of the issues that I get asked about every day in clinic. I encourage all of you to ask questions afterwards. We will be talking about a brief background and disease overview. Then, we'll focus on the "best initial therapy."

There are different approaches to the disease with pros and cons. We'll also talk about minimal residual disease (MRD), which has become front and center in the treatment of CLL as a treatment outcome. Briefly, on the next wave of therapeutics, there are many. Then, no talk would be complete right now, without a mention of CLL and the COVID-19 pandemic.



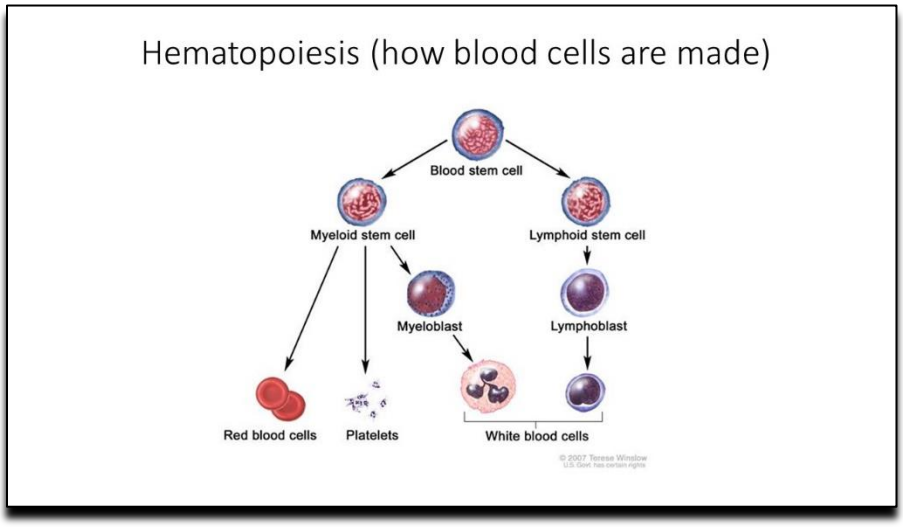
Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia, as a way of background, is the most common type of leukemia in Western countries and it's actually rare in Asia, for unclear reasons. It's characterized by an uncontrolled proliferation of our B lymphocytes, or B cells, which is a type of white blood cell within the peripheral blood, lymphoid tissue and bone marrow. This results in severe immune dysfunction. One way I look at this disease is as an immune disease.

Remember, B cells are a type of white blood cell. And they're critical to the immune system. We know CLL patients are at a higher risk of infection. Over the course of the disease, that's it's continuing to be

one of the main challenges. On the left here, you can see what our normal blood looks like. A neutrophil is a type of white blood cell that fights bacterial infections. There, you can see red blood cells and monocytes.

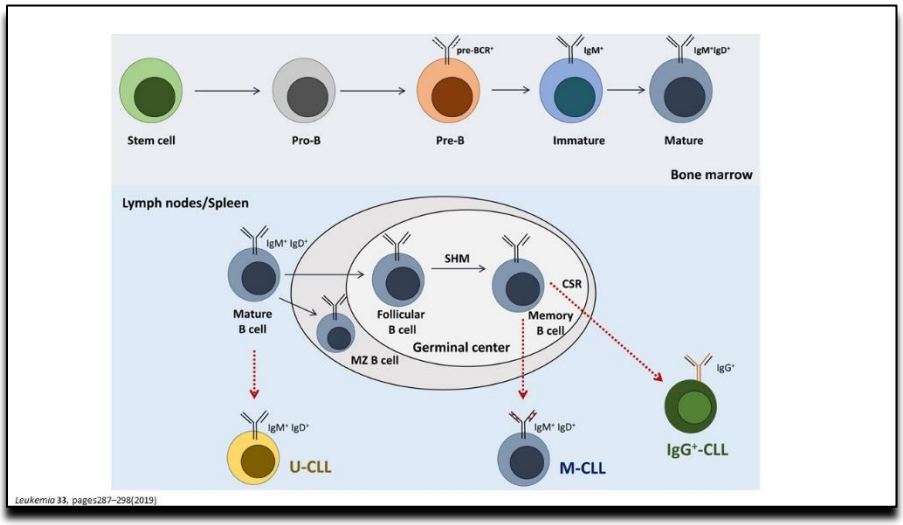
Monocytes, actually in the context of CLL, support the CLL cell. They are not a CLL cell, but they actually provide protection for the CLL cell. In that context, they are called nurse-like cells. On the right panel, you can see leukemia cells that are a little bigger than a red blood cell. And that's what we would see if we looked on a blood smear.



Hematopoiesis (How Blood Cells Are Made)

I always like to think about this when talking to patients about what's happening in the bone marrow to produce these cells. Remember, the bone marrow is the organ that makes all of our blood cells. You start with a blood stem cell, and you get a myeloid stem cell and a lymphoid stem cell. The myeloid stem cells give rise to red blood cells, which carry oxygen throughout the body. They give rise to platelets, which help the blood clot. They give rise to myeloblasts, which form certain white blood cells, in particular, neutrophils, which are of interest.

On the other side, we have lymphoid stem cells where we get a lymphoblast, and we get B lymphocytes and T lymphocytes. When we talk about an issue of B CLL, or CLL, it's in this pathway something goes awry and we to develop CLL.



Image

This is a little bit more involved slide here. It highlights how our normal B lymphocytes work. We all have B lymphocytes. When we get a vaccine or we see a viral infection, that activates the B cell. That B cell then becomes a memory B cell that recognizes that specific insult. For example, my flu shot from two years ago was a specific flu shot. When I got that flu shot, the B cells expand and adjust their receptors to recognize that specific insult. If we query my body today, we would be able to find a cohort of memory B cells that recognize that specific insult. That is essential for immune function.

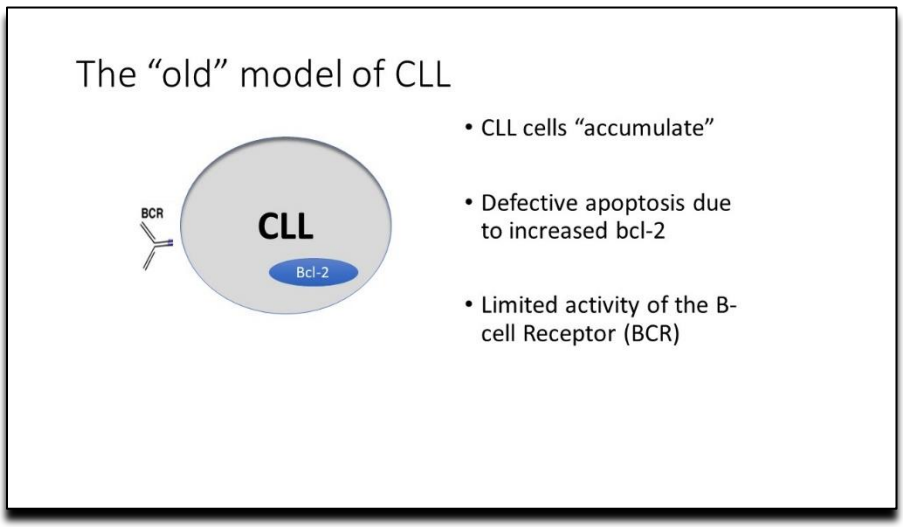
Now what happens is after you get expansion of those cells, they die back. And you have many, many populations, as you can imagine, every sort of insult we've ever seen from a viral standpoint or infectious standpoint. We've developed some degree of memory B cells. And this assumes that your immune system is intact. CLL has sort of co-opted this mechanism. If you look here, you have the stem cell I just mentioned on the last slide. It becomes a Pro-B cell, a Pre-B cell, immature, and then a mature.

As you can see, you start developing a B cell receptor along the way. This is the part that actually recognizes the specific insult, virus, vaccine, or what we call antigen. That will then come out of the bone marrow. New cells will go into the lymph nodes where they will adjust or mutate this B cell receptor.

And what will happen when they mutate the B cell receptor its mutated so it's specific to that antigen again. Therefore, whatever that flu shot was, you have a specific population from the B cell mutation. What you're left with is some mutated cells and unmutated cells.

In CLL, this process happens where some go on and become mutated CLL at this B cell receptor what is called the IGHV Others go on to develop unmutated CLL. Why am I mentioning this? Well, they're very different biologically. We'll talk about that when it comes to therapy. But this speaks to the idea of how normal B cells work and how CLL cells work.

For example, if I take an unmutated CLL cell to my laboratory, and I stimulate the B cell receptor, it will activate and make more cells. Conversely, if I take the mutated CLL cell, it's as though it's already mutated in seeing that insult. It will sit dormant and not really recognize that antigen or that triggering activator. And the reason that it is relevant because you can imagine an unmutated CLL is much more active—and more promiscuous, if you will—and is more likely to become active and make new CLL cells. Where a mutated CLL cell in the body typically is more slow growing, and makes fewer progeny cells.

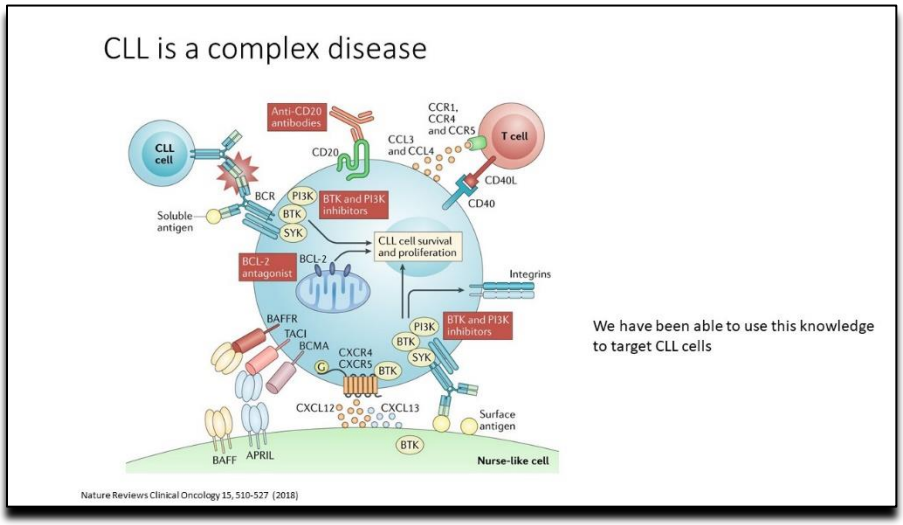


The "Old" Model of CLL

How can we use that in our understanding to come up with therapies and move the field? Well, this is the old model of CLL. When I was coming up as a Fellow, this is what we learned. We had a CLL cell.

We had a B cell receptor that I displayed in that last slide. And, we had way too much protein called BCL2. BCL2 is a protein that keeps the cells from dying or undergoing apoptosis. If you have too much BCL2, these cells are inappropriately resistant to cell death. Because as we know from sloughing skin cells and things like that, cell death is very important. It is equally as important as cell birth.

The old model was the CLL cells would just accumulate because there was too much BCL2. And they had limited activity of the B cell receptor, meaning not much was going on to activate that B cell receptor to make new cells.

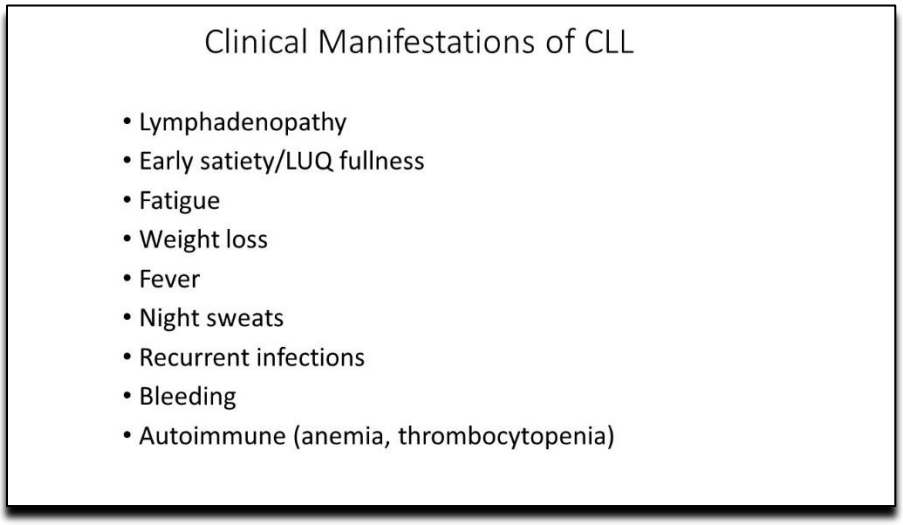


CLL Is a Complex Disease

This is the current model. This is much more reality as we've gotten better molecular techniques to understand. I won't belabor the points, but you can see it's a complex interplay between nurse-like cells, which are monocytes; bone marrow cells; and activation of the B cell receptor; interaction with T cells; and very active enzymes that promote cell growth and activation. It turns out, this is not a static old model. But instead, it's a model that is very dynamic. In fact, it really has co-opted this piece of machinery inappropriately.

Unlike a normal B cell, which will just be sitting there, inert waiting for that insult to come along, these cells may have a very active B cell receptor at rest, at baseline, gets activation of these various enzymes. That allows us to target the cell. If you have an active enzyme on which the CLL relies for cell survival, you can knock it out with certain drugs.

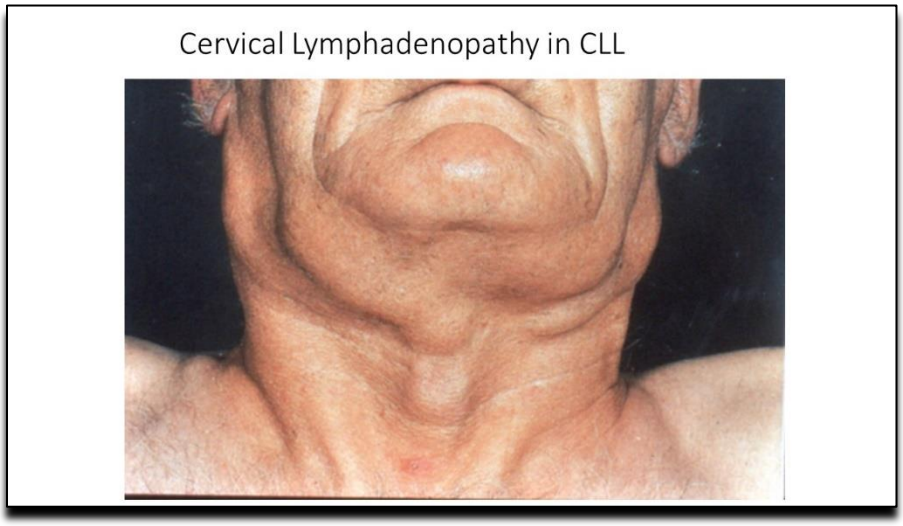
At the same time, we now have drugs that block BCL2 that increase the ability for the cells to die. We also have many things that can target cell surface markers, including CD20 antibodies, such as in obinutuzumab (Gazyva®) and rituximab (Rituxan®). I'll be throwing around a lot of names here. Hopefully, they will become familiar by the end of the talk.



Clinical Manifestations of CLL

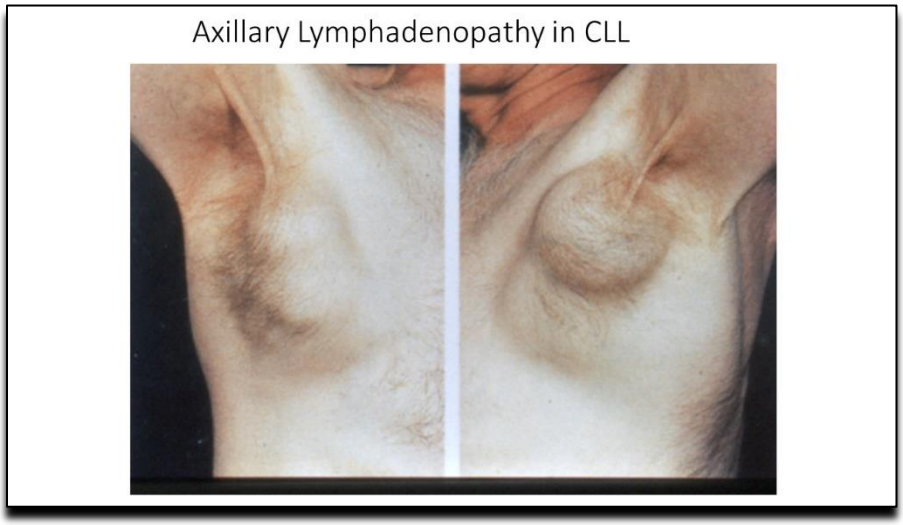
What are the clinical manifestations of CLL? Many of you on the call have experienced these things, which can be swollen lymph nodes, early satiety, or left-upper quadrant fullness. Of course, patients don't come in saying they have early satiety. They say, “Well, when I eat, I have to eat smaller meals.” That's because the spleen gets enlarged, and CLL cells like to go into the spleen.

If that happens, it's next to the stomach so people have to eat smaller meals. They may describe fatigue from the disease expanding or also from anemia; weight loss; fever; night sweats; recurrent infections; more rarely, bleeding if platelets are low; and, then, autoimmune phenomenon where the new cells inappropriately produce antibodies that target the red cells and the platelets for destruction.



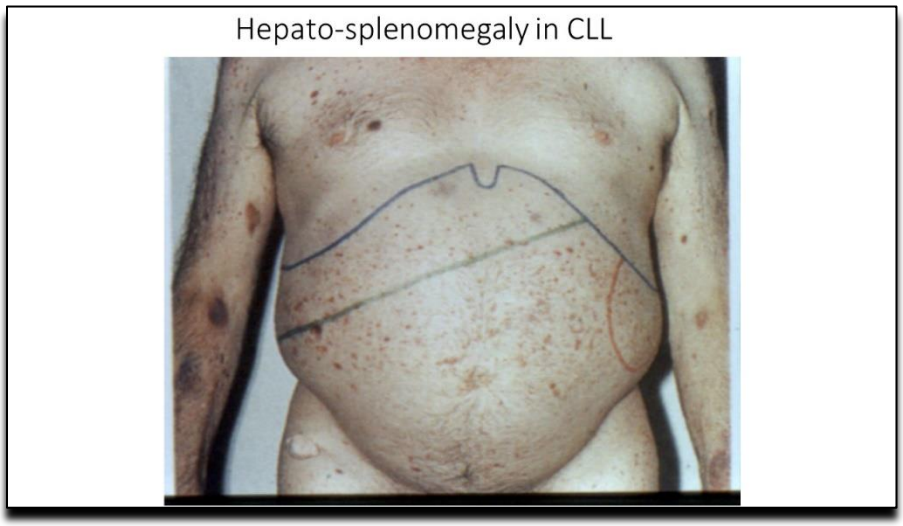
Cervical Lymphadenopathy in CLL

Here's an example of some enlarged lymph nodes in the neck. Many patients nowadays will present just with an abnormal blood count. They will not have lymph nodes that come to the attention of their physician. However, many patients will go on to say, “Well, I noticed a lump over here the other day.” And lo and behold, the biopsy shows that it's consistent with CLL.



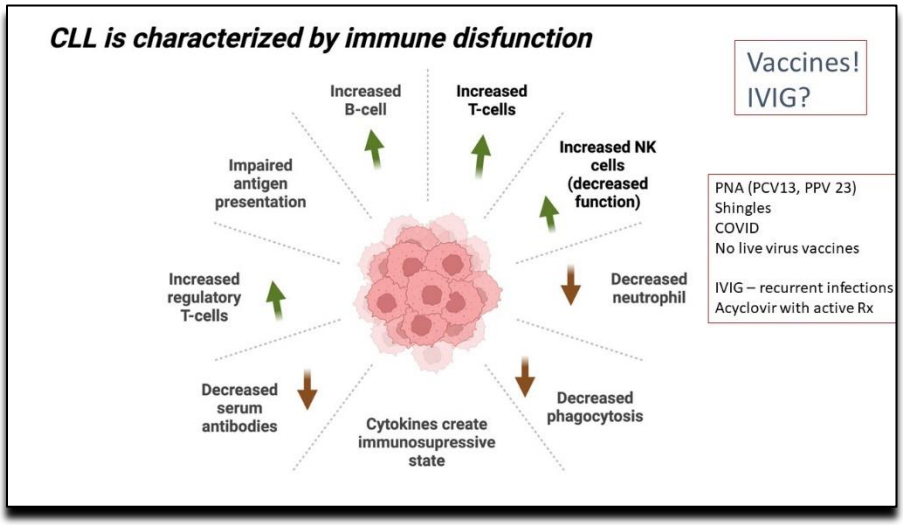
Axillary Lymphadenopathy in CLL

Here's another example of an enlarged lymph node in the armpit. How symptomatic these lymph nodes become really depends on where they are. You can imagine there's a lot more room for growth in the armpit than there would be back here behind the head because there's not a lot of room to grow.



Hepatosplenomegaly in CLL

Patients may have what we call hepatosplenomegaly. The CLL cells, in addition to going to lymph nodes, like to go to the liver and the spleen. The liver is on the right side. This is a gentleman from many, many years ago, actually that I took from a textbook, that had very advanced CLL. The enlarged spleen is on the left side. That's something we always look for when we are examining patients.

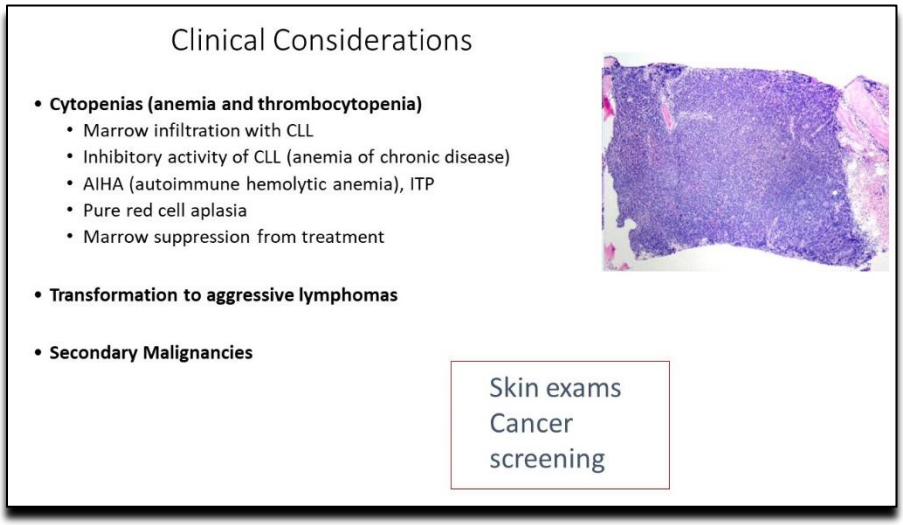


CLL Is Characterized by Immune Disfunction

The thing to remember is that CLL is characterized by immune dysfunction. The simple way I like to think of this is as you get more CLL cells around, you have a bigger population of nonfunctioning B lymphocytes. And really that crowds out the norm of the activity of your other immune cells. It is not only that you have these increased B cells, you have increased T cells, but they don't work properly. When it says impaired antigen presentation, that means when you see that virus or that viral protein, it's blind to it. Nothing happens. You also have decreased antibodies. You have a chronic inflammation, which creates an immunosuppressive state, and a number of other defects that impair the immune system.

The key thing here – and we'll talk more about COVID. And some of this is beyond the scope of this talk. At diagnosis, I always like to make sure people are up to date on their vaccines. This is true, whether they're 25 or 85 years old. We always vaccinate for pneumonia with the) vaccine and then PPV 23, or the Pneumovax® 23. We vaccinate for shingles, with the Shingrix (Varicella-zoster Recombinant, Adjuvanted) vaccine. Of course, we vaccinate for COVID with four vaccines. And no live virus vaccines are permitted.

We also give immunoglobulin, or intravenous immunoglobulin, for those patients that have low immunoglobulin levels in recurrent infections. We also give antivirals to anyone getting active therapy. So, if you start therapy, these are the things you want to think about. You want to make sure you get your vaccines before you start therapy because that's usually when your immune system is the most robust.

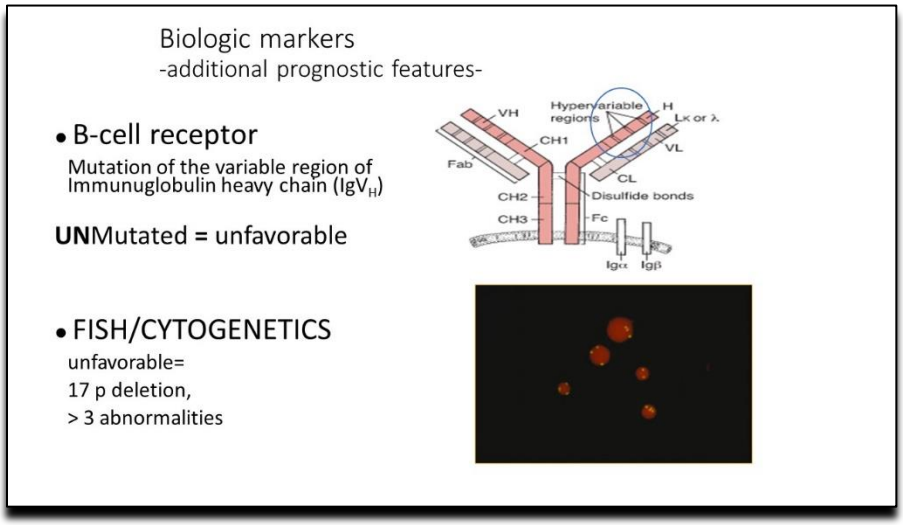


Clinical Considerations

A couple of things to consider when we're seeing patients is cytopenia, which means low blood counts, anemia, thrombocytopenia, or low hemoglobin and low platelets. And that is from a number of things. It can be marrow infiltration from CLL. It can be anemia of chronic disease from inflammation. It can be destruction. It can be immune destruction in the bone marrow of red blood cells or it can be marrow suppression from treatment. We also want to think about if someone who has an indolent course or slow-growing disease, and then comes in with very aggressive growth of lymph nodes or just feeling horrible, we sometimes need to think the CLL has transformed to something more aggressive.

We also need to think about secondary malignancies. The immune system is imperative for immune surveillance against malignancies. It's as though the immune system has blinders on. You may have an abnormal skin cell that someone who is immune-competent may recognize, the cell may recognize. But in this case of the immune system being blind, you're at a slightly increased risk for other cancers. We definitely recommend increased skin exams and cancer screening.

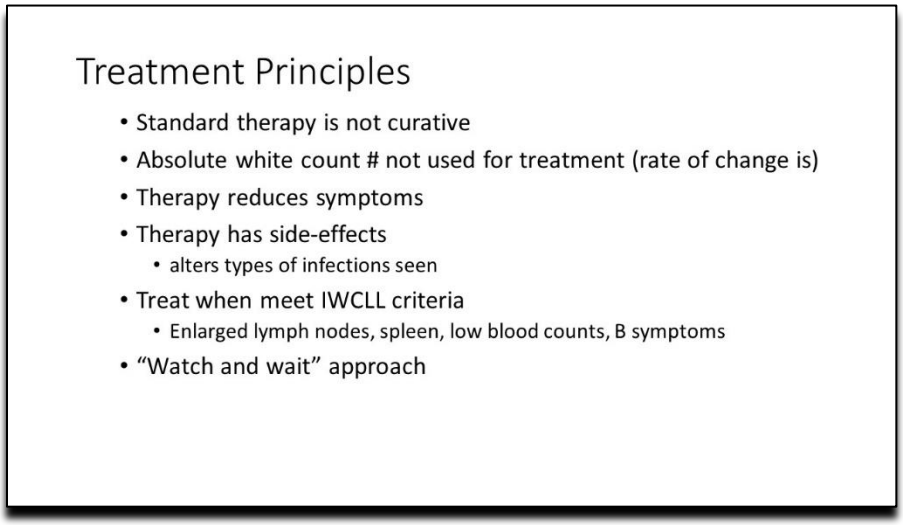
This panel on the right shows a normal bone marrow. As we age, it gets replaced by fat, like many other things. One can see why someone might have low blood counts because this is a marrow full of CLL. All those blue cells represent CLL cells. And so, when you have that, you can't grow your normal red cells or normal platelets. The simple analogy is your marrow is like a healthy garden. And it gets overrun with weeds. Obviously, you can't grow your healthy garden back until you take care of those weeds.



Biologic Markers

What are some things we look at when we're working with patients to understand their risk factors? We have the B cell receptor, I mentioned, mutated and unmutated. The unmutated is unfavorable. Mutated is favorable. That's because, again, unmutated are more likely to be immature, and recognize a broad range of signals to become stimulated. We also look at FISH (fluorescence in situ hybridization) and cytogenetics the study of chromosomes in a cell) . When we think about FISH (the B cell receptor with the hypervariable region gets mutated on the surface of the B cell), we also look at FISH and cytogenetics, which has been long-standing. In fact, the seminal paper was now around 2000. You can see that, basically what we do, by we I mean the pathologists, who are experts pathologists, who are experts in this field, mark the cells and have probes for the chromosomes.

Here is a cell. Normally, we have two copies of each chromosome. However, in this case, this person has an extra copy of chromosome 12, which can be one of the recurring themes in CLL. That is called Trisomy 12. There is a whole CLL FISH panel we get. Importantly, in this day and age with our new therapies, the key thing is 17p deletion. You're missing part of chromosome 17. If someone has more than three abnormalities within their panel of chromosomes, those are considered high-risk.



Treatment Principles

Some key treatment principles we know going in is that standard therapy is not curative. Our goal is to knock back the treatment and give people long remissions and normal life, and a normal life expectancy. We also know the absolute white count number is not used for treatment. Instead, the rate

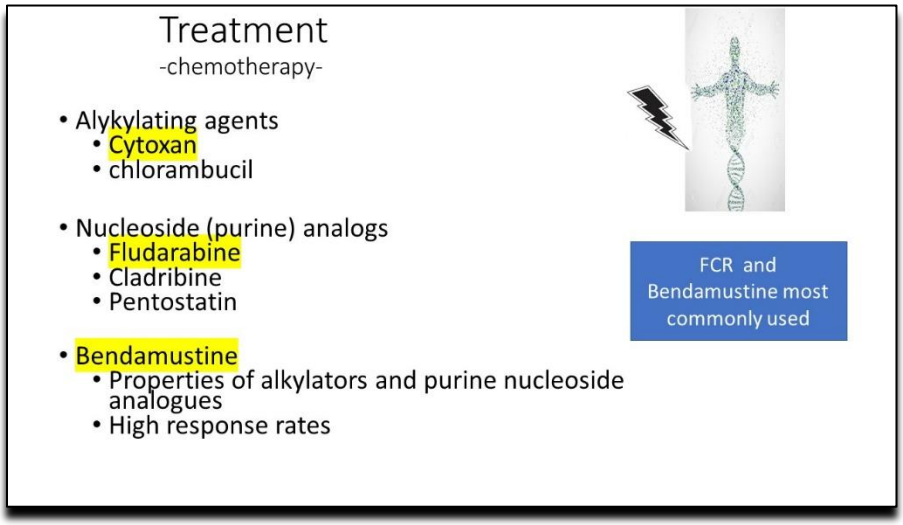
of change is used. I often have patients that come in and say, “What is the absolute white count at which I must be treated?” That varies for each patient.

So you can imagine if someone comes in with a white count of 150 ([150,000] (a normal white count is about 11,000) and someone comes in with a white count of 150. And these are all cancerous lymphocytes or CLL cells. If they've taken 10 years to get to that point, often they don't need treatment. It's as though the body has been able to adapt. It hasn't harmed the other systems. The disease is not really active.

However, if they come in with a white count of 150 that’s gone became that way in a span of two years, they often will need treatment. The rate of change is very important. We know therapy reduces symptoms. We know therapy has side effects. It all can alter the types of infection seen. We also know the current models we treat when people meet either of the CLL treatment criteria. That is with enlarged lymph nodes, symptomatic large spleen, low blood counts, or what we call B symptoms, which might be fevers or weight loss. Typically, most people when they're diagnosed are approached with a watch-and-wait.

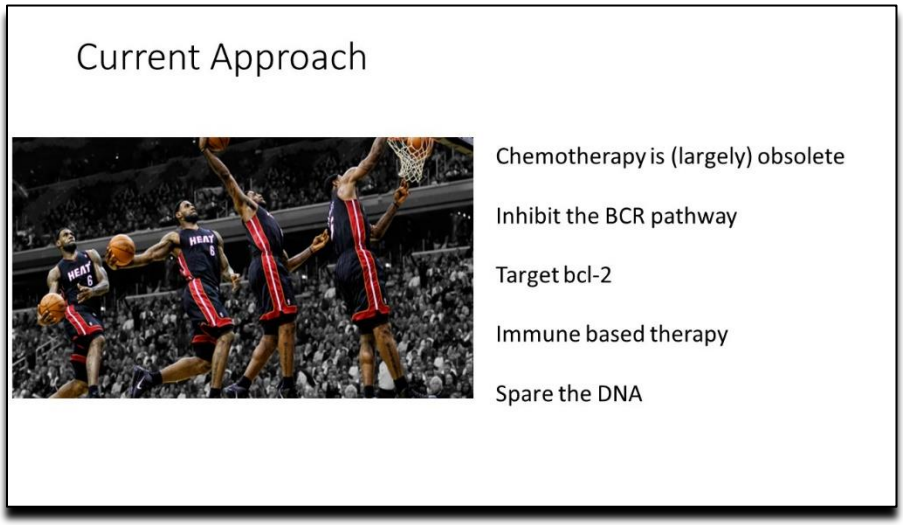
Rapidly Evolving Treatment Landscape

We know that it’s a rapidly evolving treatment landscape. The old approach was DNA -damaging chemotherapy was the king. So chemotherapy hit [every divided] DNA of every dividing cell and was not targeted. The biggest problem is that it eventually stops working. It's one mechanism of action, essentially. Over time, the cells outsmart the chemotherapy. And, there is increased risk of long-term toxicity.



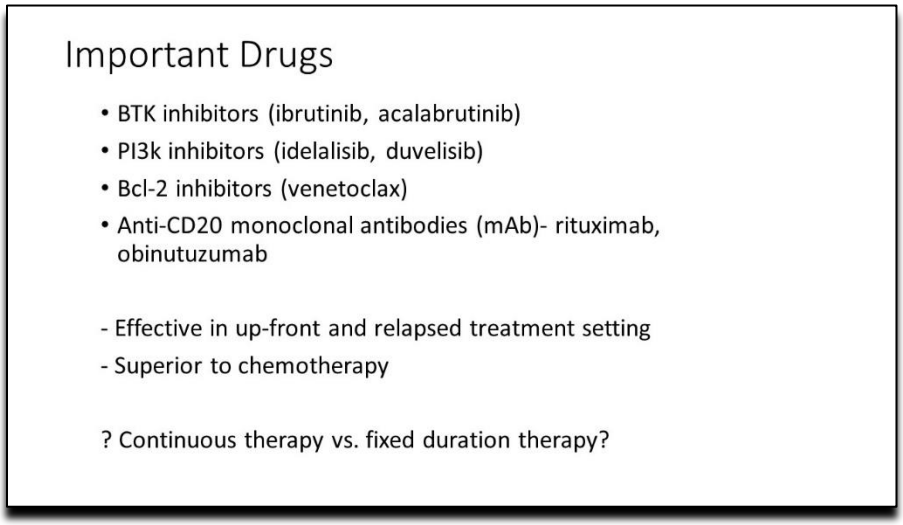
Treatment

I mention these agents here because these are agents that have traditionally been used for the treatment of CLL. Classically, Cytoxan® (cyclophosphamide), and chlorambucil (Leukeran®) have been around for many, many years, many decades, and have been the mainstay of CLL treatment for a long time. Then, we developed (and I use 'we' very loosely) nucleoside analogs, including fludarabine (Fludara® or Oforta™) and, more recently, bendamustine (Treanda® Bendeka®, Belrapzo®). And FCR, which is fludarabine, Cytoxan®, and Rituxan® (rituximab), as well as bendamustine have been the most commonly used agents over the course of CLL chemotherapy treatment.



Current Approach

However, we've been able to leverage our understanding of the disease pathophysiology to develop new targeted agents. So, chemotherapy is largely obsolete. We'd like to inhibit the B cell receptor pathway. We'd like to target the BCL2 protein. We'd like to use immune-based therapy. Our motto now is spare the DNA, if you can, of normal cells.



Important Drugs

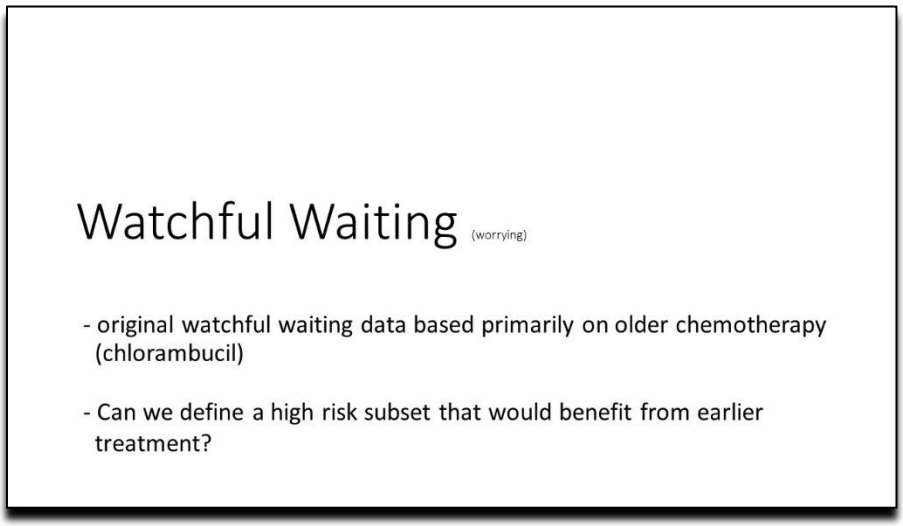
Bruton's tyrosine kinase (BTK) inhibitors are important drugs. BTK is an important enzyme and CLL signaling. It gets activated when the B cell receptor is activated. Remember, CLL cells get inappropriately activated most of the time. We have drugs, ibrutinib (Imbruvica®) and acalabrutinib (Calquence®), and more recent, zanubrutinib (Brukinsa®), which inhibit that. We also have PI3 kinase inhibitors. The PI3 kinase pathway also is activated in CLL. We have idelalisib (Zydelig®) and duvelisib (Copiktra®). For BCL2 inhibitors, we have venetoclax (Venclexta®). And anti-CD20 monoclonal antibodies, rituximab and Obinutuzumab (GAZYVA®).

These are drugs that target the outside of the cell. They activate the immune system to kill the cell. This is really a form of immunotherapy. We know that these are effective in and upfront and relapse treatment settings. We know they are superior to chemotherapy.

The question becomes: Do we want to do continuous therapy or fixed-duration therapy? When we first started developing these new drugs, we thought, "Here are some oral drugs that are pretty well-tolerated and work differently. Maybe we can manage this like hypertension."
The challenge has been the cost of these drugs. And any drug has potential side effects. As we've learned more about them, the pendulum has shifted back. Do we really need to continue these drugs indefinitely?

CLL "Best" Initial Therapy

What is the best initial therapy? This is my opinion. You may get other opinions if you talk to other CLL specialists. The real question: Is watchful waiting still the best option at diagnosis? Is there any role for chemotherapy? What is MRD negativity, minimal residual disease? 'And is that a treatment goal we need to think about? If we're doing ongoing continuous therapy with a BTK inhibitor, like acalabrutinib or ibrutinib, which one do we use? Do we use in combination? Does this really need to continue forever? What about fixed-duration therapy? Is our goal MRD negativity?

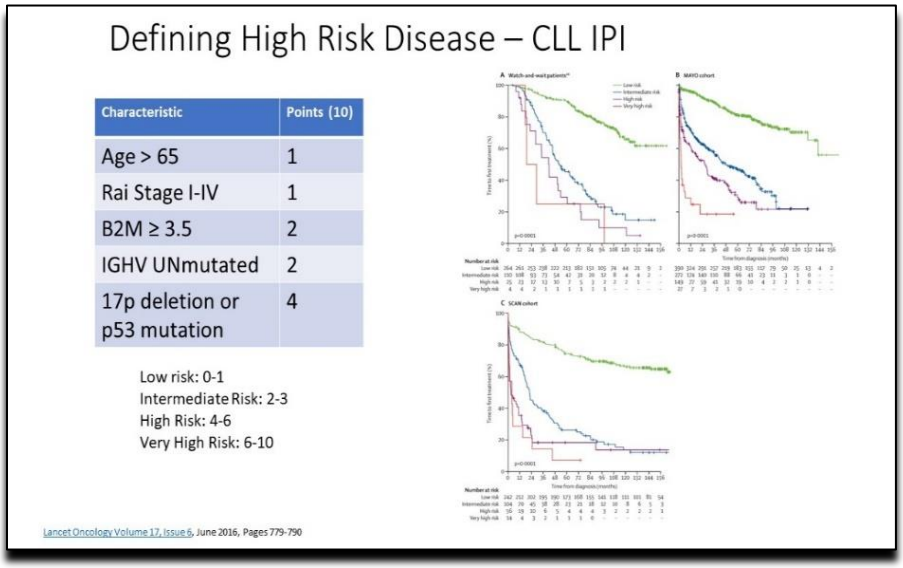


Watchful Waiting

One of the hardest things when someone is diagnosed is watchful waiting, more aptly put 'watchful worrying.

It's really hard to come in to see your oncologist and hear them say you've got a blood cancer and we'll see you later. That was based on original, older data with older chemotherapy. There was a trend towards doing worse in people that got treated out of the gates. Because of that, the IW (International Workshop on Chronic Lymphocytic Leukemia) CLL treatment criteria are based on symptoms and active disease. That is also based on the fact that about a quarter of people with CLL, their disease will be so slow growing or indolent that they actually never need treatment.

Of course, if we could identify a high-risk subset that would benefit from earlier treatment, that would be great. Is there anything we can do with our new therapies that might impact the disease? When we first started, there was a trial accruing in the early 2000s that went to patients with what we thought were higher-risk disease who were asymptomatic. We went to them and said, "You can either get this chemotherapy with this huge list of side effects or you can just continue on the golf course every day without coming in for treatment." Not surprisingly, that trial had to close down because patients weren't interested in that trial. As we've gotten better therapies though, we can challenge that paradigm again.

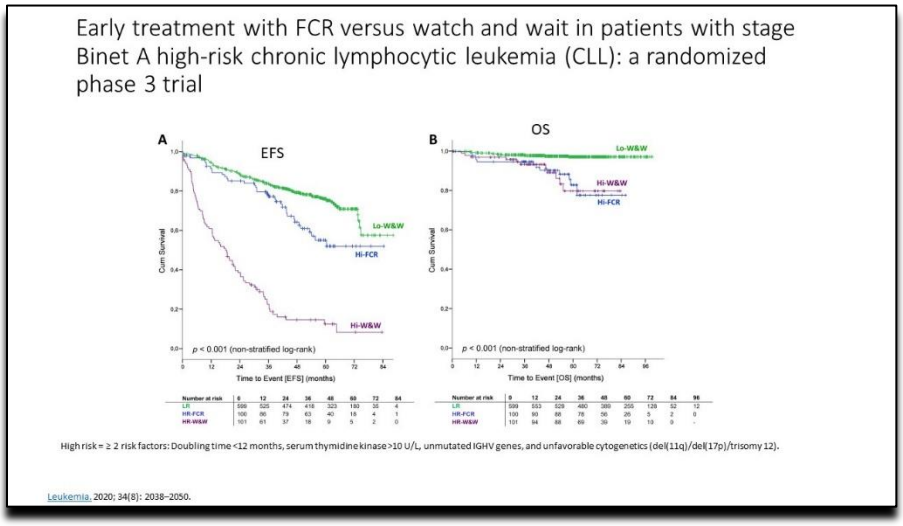


Defining High-Risk Disease – CLL IPI

Obviously you want to pick the high-risk patients to decide, do these patients need watchful waiting or should they be treated early? There is a high-risk disease score called the CLL International Prognostic Index (IPI), which is made up of age greater than 65, with advanced stage, something called beta 2 macroglobulin, a lab test, blood test, mutated and unmutated IGHV, or a 17p deletion or p53 mutation.

Here you can see the breakout of why this is. This is basically a couple different cohorts. One is a cohort that is developed; the other is a test cohort where the actual model is applied. On these axes, the y-axis you see time the first treatment. The x-axis is time in months. As you can see, patients that who are low-risk, watch-and-wait patients don't need treatment for a long time. In fact, some very low-risk patients in this cohort of 120 months didn't get new treatment. You didn't even get a median to treatment.

Conversely, intermediate-risk patients, those who had two to three risk factors, needed treatment on average of about 48 months. High-risk and very-high-risk patients needed treatment quickly. This held true on any data set that was examined. The question is can we use this to really define which patients might benefit from early treatment?

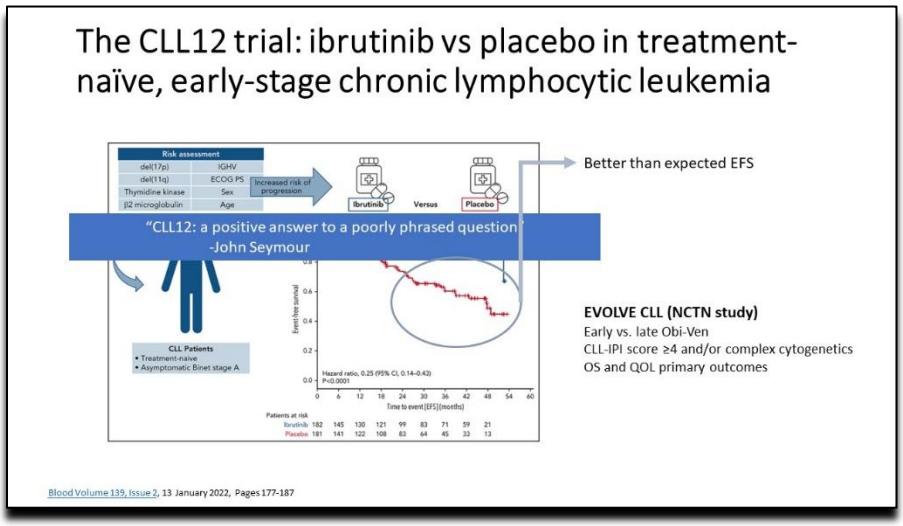


Early Treatment with FCR Versus Watch-and-Wait in Patients with Stage Binet A High-risk CLL: A Randomized Phase 3 Trial

And there have been some studies, this is a study from Germany. The Germans are very active in CLL. They took low-risk patients and high-risk patients. EFS is event-free survival, which means is their disease progressing, do they need treatment, or are there some sort of medical events? Overall, survival is just that. Are these patients still alive over time? Again, we have that on the y-axis. We have the number of patients that are still event-free, or the number of patients or the proportion of patients that are still alive.

On the left panel, you can see the patients that who are low-risk in watch-and-wait. Again, they do quite well. These are patients that were not intervened upon with chemotherapy. Conversely, these other patients got FCR chemotherapy, which we don't do as much anymore because of the reasons I mentioned earlier. Here you can see they haven't progressed. And if they're observed, they progress. But we know that anyway. The question is, is this really changing the natural history of the disease or is it better to treat these people when they needed treatment?

So yes, these patients needed treatment. And, they needed treatment if they were high-risk, between years one and two on average. But then, if we look at overall survival, we don't see a difference. We do not have lots of long-term follow-up. It seems with FCR chemotherapy early on with the high-risk group, (understand FCR is inferior treatment now), these patients had the same survival whether they were observed and then treated or they got chemotherapy right out of the gates.



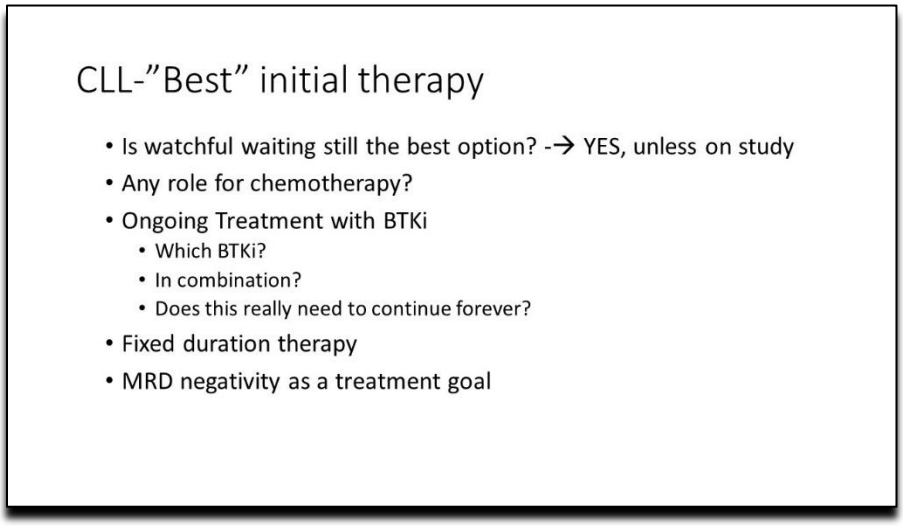
The CLL12 Trial: Ibrutinib Versus Placebo in Treatment-naïve, Early-stage CLL

The question was asked, what if we used ibrutinib? That is a much better-tolerated treatment. And we take patients with high-risk disease and increased risk of progression, and randomize them to treatment with ibrutinib versus placebo. And you can see event-free survival.

Again, people that got the treatment, they did well. They did not progress. That makes sense. They were on active treatment. But people not in active treatment progressed. We also know their high-risk groups seemed to do better than the historical high-risk groups. So as one of my colleagues pointed out, this is a positive answer to a poorly phrased question. This does not answer the question of deferred treatment, waiting until patients need treatment after a period of observation. Instead, it says our treatment works. Of course, if you use it earlier, it is going to help. This didn't really answer much of the question

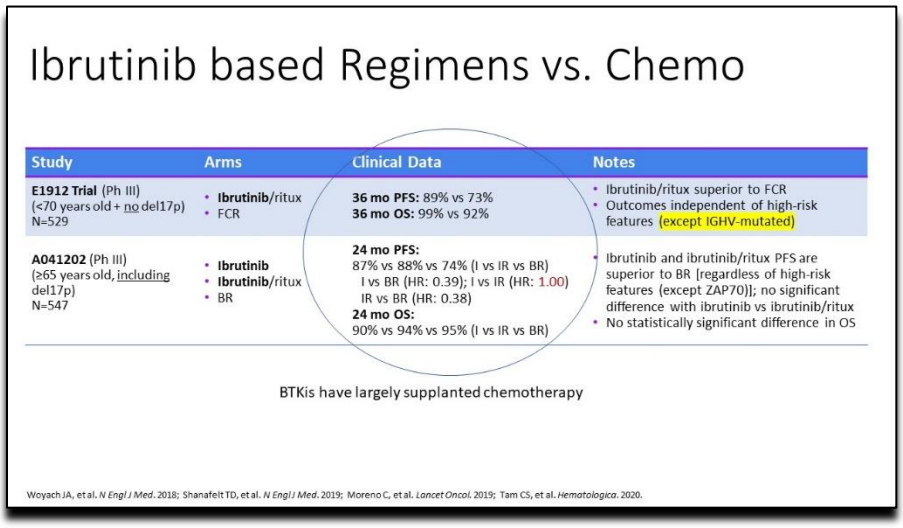
Importantly, there's a study going on in the United States. It's an NCI- [National Cancer Institute] sponsored study. There are places open throughout the country. This is the idea of trying to answer the question the other study did not: early treatment versus later treatment. High-risk patients get treated early at diagnosis, or they get treated (per standard) later when they meet treatment criteria. It looks at overall survival and quality-of-life outcomes. Patients who are diagnosed out of the gates, if

they are interested in clinical trials (and I hope everyone gets more knowledge about clinical trials) they can have the disease characterized early on and see if they're eligible for this study.



CLL—"Best" Initial Therapy

Is watchful waiting still the best option? Yes, unless on study. Is there any role for chemotherapy? Well, let's see.

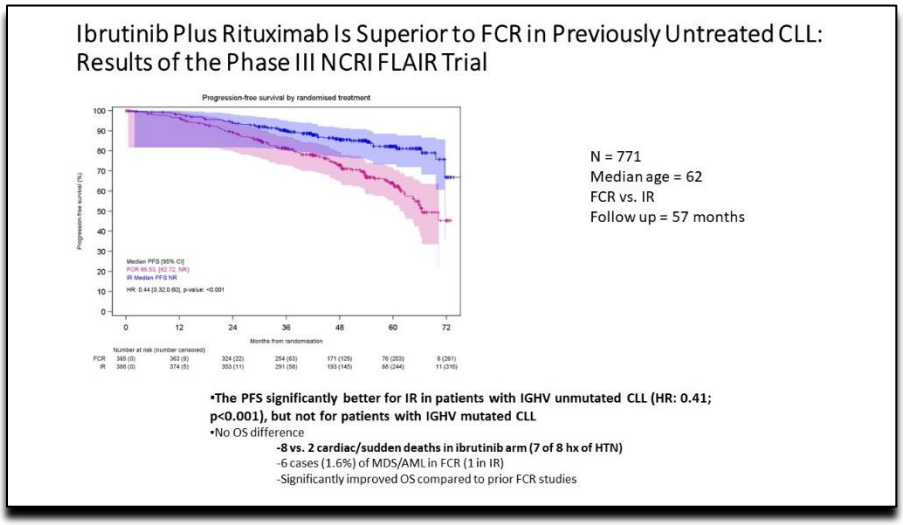


Ibrutinib-based Regimens Versus Chemo

Current data would suggest there is a very limited role of chemotherapy. So these are two very important studies that compared ibrutinib-based treatment, our oral targeted therapy, plus rituximab, the CD20 antibody with FCR. The benefit was that ibrutinib outperformed FCR. It was superior in terms of the progression-free time.

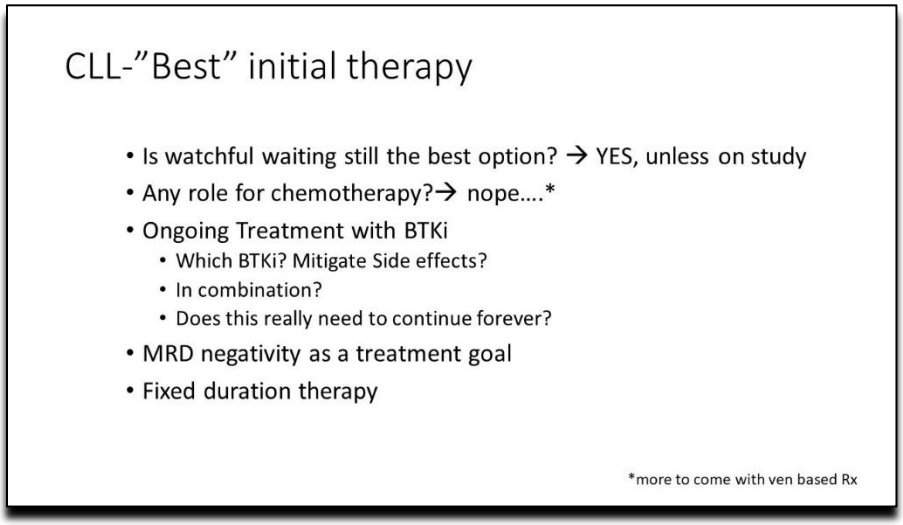
That was largely the trial used to adapt ibrutinib over chemotherapy up front. That is also true with the Alliance trial in older patients, which also used ibrutinib, or ibrutinib-Rituxan® versus bendamustine-Rituxan®. PFS is progression-free survival. Here you can see PFS, a time when someone was in remission, was significantly better than patients that got ibrutinib versus standard chemotherapy.

The exception is: patients with really good risk disease didn't seem to do any better with the ibrutinib chemotherapy as compared to FCR.



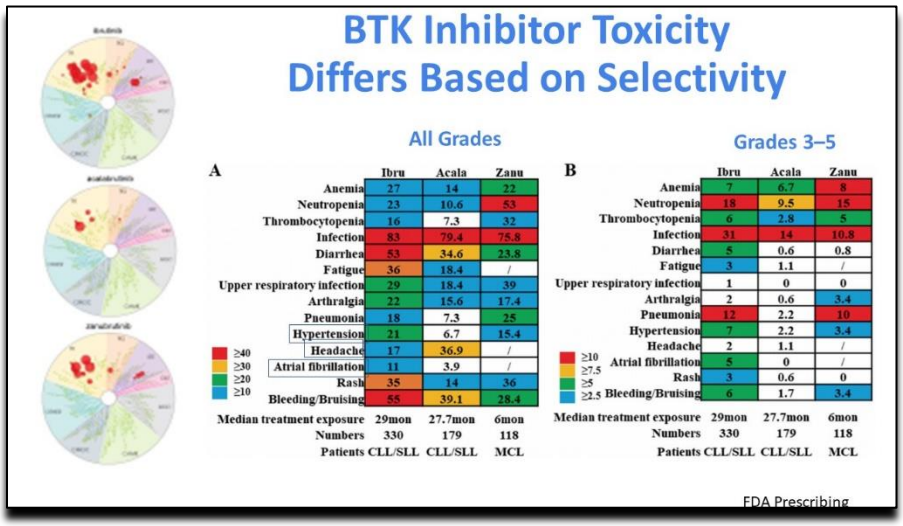
Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial

This is another trial looking at FCR. This trial is from the UK (United Kingdom) . It looked at FCR compared to ibrutinib and found the same thing, that Progression-free survival. It is shown here. This is the FCR group. And this is the ibrutinib-Rituxan® group. And the ibrutinib-Rituxan® group had a longer time of remission.
Remember, this is ongoing treatment where the FCR people just get six months of treatment. You can see ongoing that they had significantly longer remission. Not just in the United States, but also internationally, has this been seen.



CLL —"Best" Initial Therapy

So I would say generally any role for chemotherapy and we'll come to more of that with venetoclax (Venclexta®)-based treatment.



BTK Inhibitor Toxicity Differs Based on Selectivity

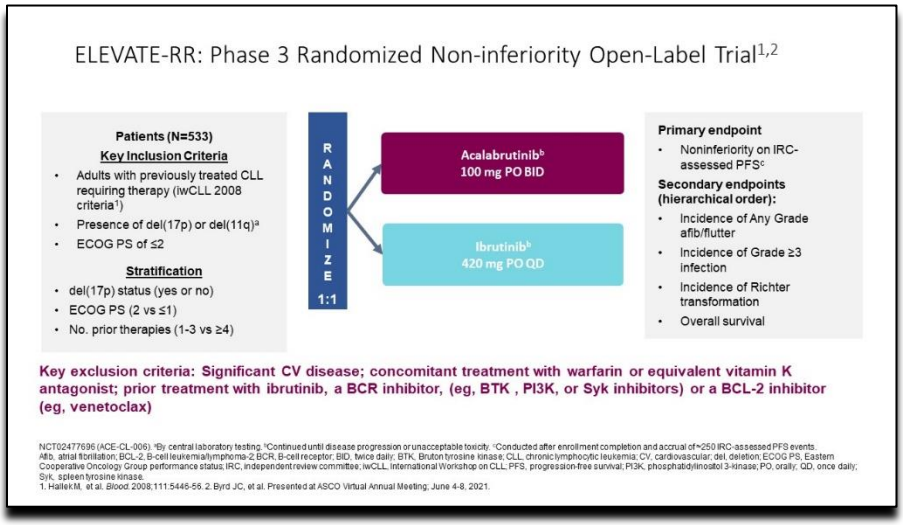
The big thing that has come up, ibrutinib has been a game-changer for CLL. This is drug that really changed our ability to salvage patients' disease, even though they had progressed on chemotherapy. It really has been a game-changer. But' the question is, can we improve on ibrutinib? And for the first time we've always thought this would be the answer, but really we have definitive evidence I think the answer is "yes."

On the left side, when we think about these targeted drugs, the targeted drugs are exactly that. They have a specific target we try to knock out. But like anything else, when you're trying to target something, there can be collateral damage. In this case, collateral damage is that it is hitting other enzymes off target. This is what's called a KINOMEscan® where you can actually measure the affinity of the drug in terms of concentration for given kinases. Now ibrutinib, what you can see, yes it targets BTK (Bruton's tyrosine kinase). But, it is a relatively dirty drug, meaning it hits some other kinases. Now of course when we first saw the efficacy of this, we thought is if that was one reason it worked so well—because it does not just targets BTK and maybe there are some off-target effects that can be beneficial. Then, a couple other drugs came along, acalabrutinib and zanabrutinib (Brukinsa®), and hey have the same mechanisms of action essentially with a little different properties. But they too target BTK, but they have fewer off-target effects.

So the question is were these better drugs? Or were they just going to be "me-too" drugs like another antihypertensive medicine? We can see across studies the side effects we care about most were lower in the patients that got the second-generation BTK inhibitors acalabrutinib and zanabrutinib. The things we care most about when we're seeing these patients, obviously, are quality-of-life side effects, that are critical like arthralgias (joint aches). Those seem to be lower in patients getting the second generation.

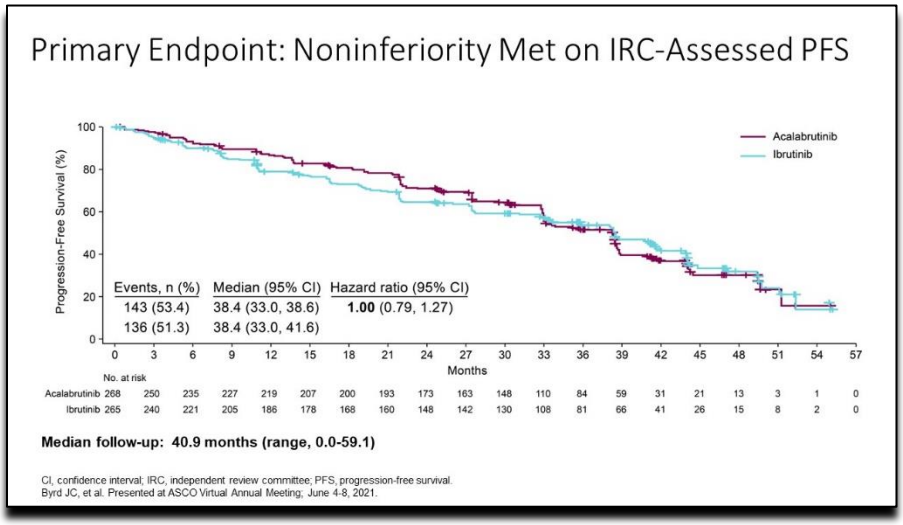
Diarrhea seems to be lower. A lot of these things may happen out of the gates but we can control over time. But the big things that can be very difficult over time is hypertension and atrial fibrillation. We know hypertension can be increased in patients on BTK inhibitors, as can the risk of atrial fibrillation, which is a non-life-threatening heart arrhythmia. More recently, other arrhythmias have shown to be important.

Here you can see hypertension is definitely lower in acalabrutinib and zanabrutinib, as is atrial fibrillation. One thing unique to acalabrutinib is headaches. About more than a third of patients will have a significant headache, especially during the first month, that typically can be controlled with Tylenol® (acetaminophen) and caffeine.



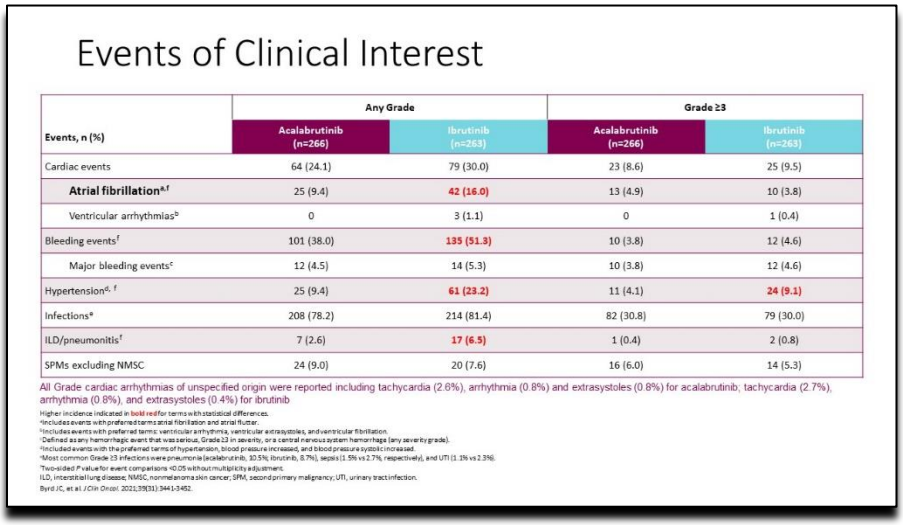
ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-label Trial

It looks like these drugs are not "me-too" drugs. But the only way to settle that is through a randomized clinical trial. And this is a trial that compared ibrutinib to acalabrutinib in the relapse setting called ELEVATE relapsed refractory (ELEVATE RR). This shows the type of patients who came into the study. They were higher-risk patients, whether they had the 17p deletion, yes or no. They were randomized to acalabrutinib or ibrutinib ongoing with a primary endpoint is, are these the same, is one non-inferior to the other. And then, secondary endpoints—what are the side effects?



Primary Endpoint: Non-inferiority Met on IRC-assessed PFS

You can see identical – they performed identical. This is progression-free survival on the y-axis; and on the x-axis, months of progression-free time. They were identical, equally as effective.



Events of Clinical Interest

Events, n (%)	Any Grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a,f]	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events[f]	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d, f]	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis[f]	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

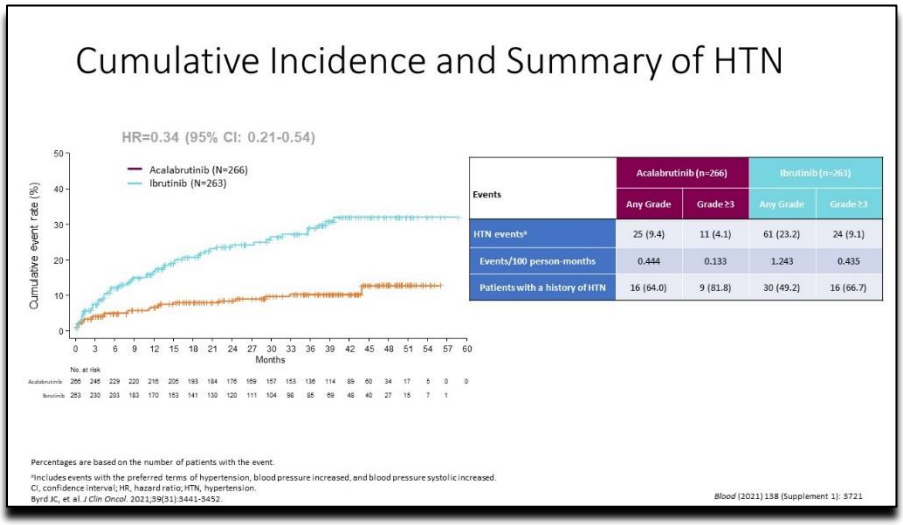
All Grade cardiac arrhythmias of unspecified origin were reported including tachycardia (2.6%), arrhythmia (0.8%) and extrasystoles (0.8%) for acalabrutinib; tachycardia (2.7%), arrhythmia (0.8%), and extrasystoles (0.4%) for ibrutinib

Higher incidence indicated in **bold red** for terms with statistical differences.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation.
[c]Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common Grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
[f]Two-sided *P* value for event comparisons <0.05 without multiplicity adjustment.
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPM, second primary malignancy; UTI, urinary tract infection.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

Events of Clinical Interest

As far as the secondary endpoints, this is what we were most excited about. The rates of atrial fibrillation were significantly lower in the acalabrutinib arm at 90%, versus 16% in the ibrutinib arm. Also, we saw there was more hypertension with ibrutinib. And, there was a little more higher rate of inflammation of the lungs, which can happen rarely with these drugs.

One thing to point out is this was not a blinded study. Both the physicians and patients knew what they were taking. So, there could be a little bias there. However, it does look like the acalabrutinib is better tolerated.



Cumulative Incidence and Summary of HTN

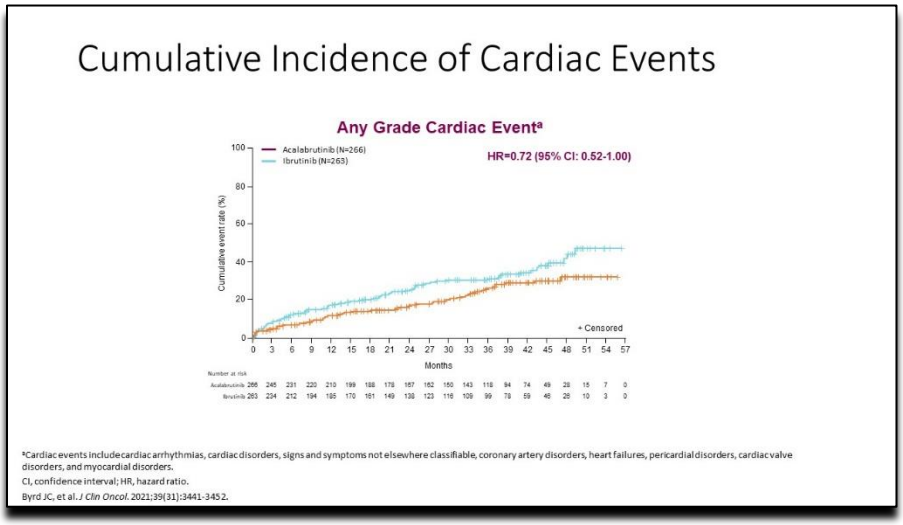
HR=0.34 (95% CI: 0.21-0.54)

Events	Acalabrutinib (n=266)		Ibrutinib (n=263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
HTN events[a]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Events/100 person-months	0.444	0.133	1.243	0.435
Patients with a history of HTN	16 (64.0)	9 (81.8)	30 (49.2)	16 (66.7)

Percentages are based on the number of patients with the event.
[a]Includes events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
CI, confidence interval; HR, hazard ratio; HTN, hypertension.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.
Blood (2021) 138 (Supplement 1): 3721

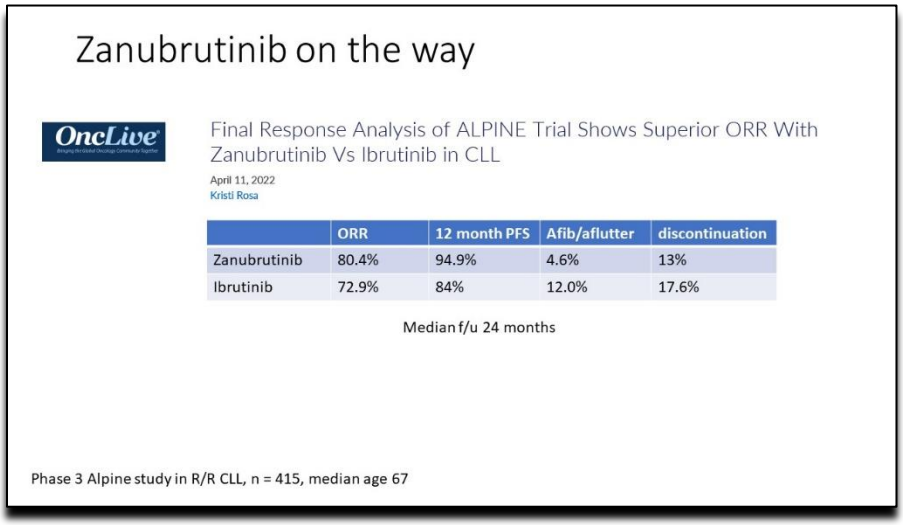
Cumulative Incidence and Summary of HTN

Importantly, if you look over time, this is the percentage of events looking at hypertension or high blood pressure. In ibrutinib, there were significantly more hypertensive events over time. It does seem to plateau after a certain period of time because most of these people we picked it up by then and have started hypertensive treatment.



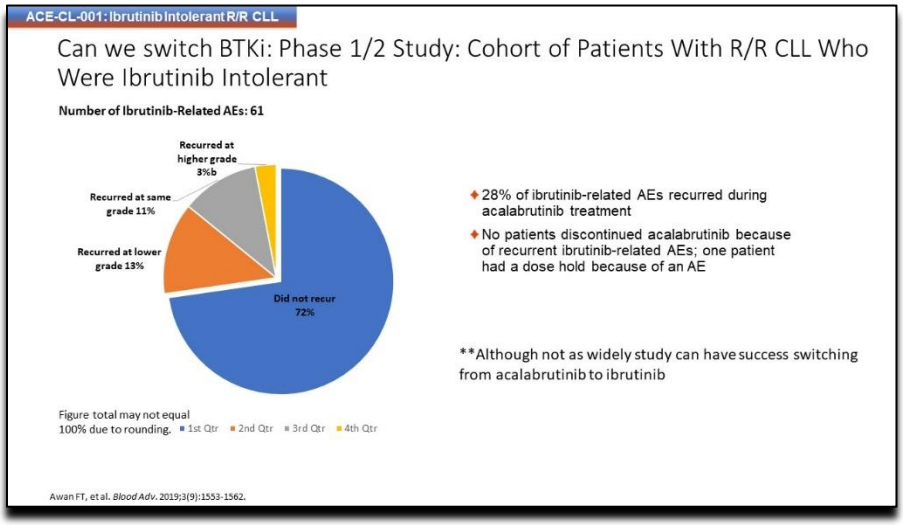
Cumulative Incidence of Cardiac Events

This is any cardiac event. You can see the ibrutinib had a higher rate of any cardiac event.



Zanubrutinib on the Way

Importantly, this is a trial which we've participated in. We don't have an analysis, but there was a press release that showed the responses of zanabrutinib, another second-generation BTK inhibitor, showed a very good overall response. It showed very good progression-free survival; seemed to be superior to ibrutinib; and, importantly, lower rates of discontinuation. Typically, this is due to side effects and a low rate of atrial fibrillation, things that are all important for us and our patients.

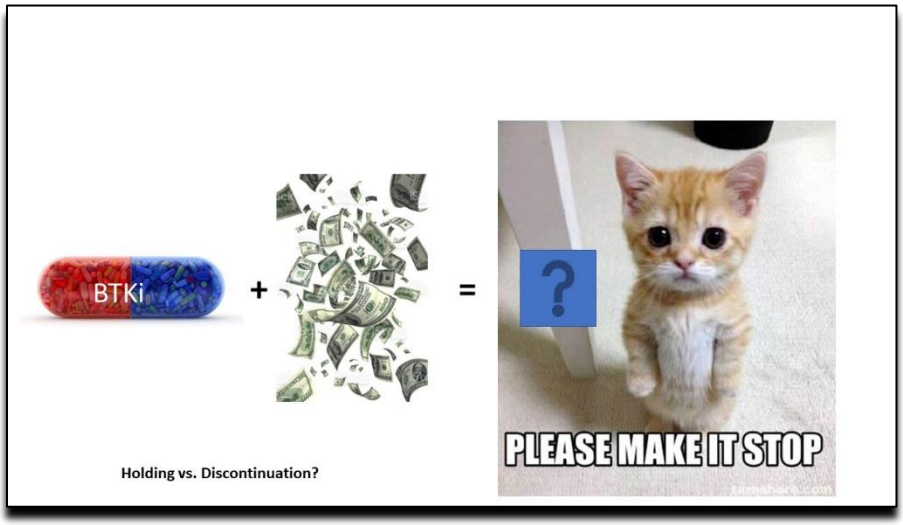


Can We Switch BTKi: Phase 1/2 Study: Cohort of Patients with R/R CLL Who Were Ibrutinib Intolerant

So the question is, what do you do if you're on a drug like ibrutinib, or acalabrutinib, or zanabrutinib (which zanabrutinib is not yet FDA approved for CLL), but if you're on these drugs and you develop a side effect, what do you do? Often, it depends when someone develops the side effect. If it's early in the course of treatment and the disease is not under control yet, we can often switch to another BTK inhibitor and that can be tolerated because, as I mentioned, they're not exactly the same.

If you look at about a third of people who get treated with ibrutinib, and then retreated, do not get recurrence of that, what we call, adverse event (AE)when they get retreated with acalabrutinib. Typically, in that setting, we take people off the ibrutinib, let them recover quickly from any side effects, then restart the next BTK inhibitor, acalabrutinib.

Let's say someone's been on ibrutinib for two years and develops atrial fibrillation and their disease is under good control. Often, in that situation, we just stop and observe for a period of time. The same thing can happen if someone doesn't tolerate acalabrutinib. You can switch them to ibrutinib, and they may tolerate ibrutinib. There is a class effect, but often we need to do some trial-and-error. If someone doesn't tolerate one BTK inhibitor, they need to go on to the next.



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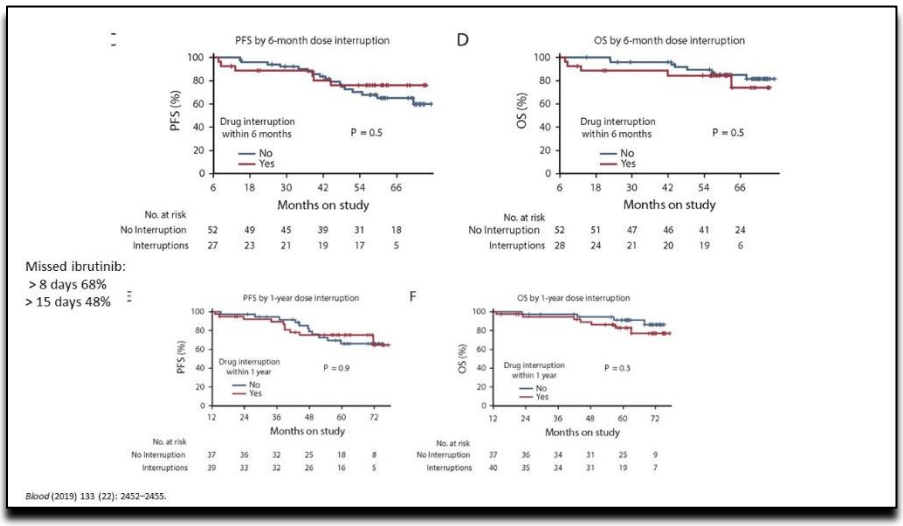
This question comes up all the time in clinic. “Well, I'm on this drug that costs $14,000 a month. You've told me it's a great drug. I've been on it for three years. I'm tolerating it well. Do I really need to do this? Do I really need to continue? I'm on Medicare. It's got a big copay, et cetera, et cetera.” Unfortunately, there aren't as much data as we hoped, and it's more anecdotal data from our experiences, but I think increasingly this is an area of interest in something that has been studied.



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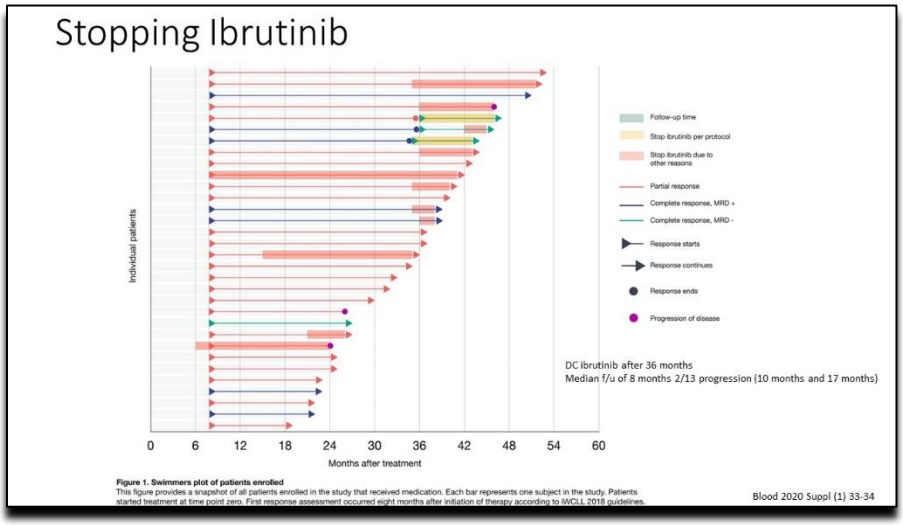
There was an initial study that came out said, if you held your ibrutinib for more than eight days, you were more likely to progress over time. This was a group from the National Cancer Institute (NCI), which basically looked at patients who missed their ibrutinib within six months of treatment, and then missed ibrutinib within a year of treatment. Now, they use that eight-day threshold because that is what had been described. But, they also said about half the patients had held it more than 15 days.

This doesn't necessarily answer the question, “Can I stop indefinitely?” I think the point is, if you look at the progression, people progressing over time that who hold their drug within the first six months for some reason, or if they hold their drug within that first year, for some reason, there is no difference in outcomes. We run into this all the time. Not only do people want to stop the drug, in some cases, many times and more likely, people are afraid to stop the drug because they're worried the disease is going to take off while they're holding the drug. With rare exception, this is nothing to be worried about. If you need to hold the drug, we can hold the drug and restart it. It often needs to be held for surgeries. It may need to be held for side effects. It may need to be dose-reduced. This data would suggest we're not doing any harm if we do that.

I would point out that some patients, especially with relapsed disease, control of their disease becomes very dependent on that BTK enzyme and the B cell receptor pathway. So, sometimes when we discontinue the drug, people can get a rapid flare that manifests as fever. It manifests as rising lab parameters and just feeling lousy. Sometimes, we learned that the hard way, but there are ways to mitigate that.



Stopping Ibrutinib

What about stopping ibrutinib more indefinitely? This is a trial that begins to address this question. This is called a swimmer's plot. These are each individual patients treated over time. The way this study was designed was, say you made it to 36 months and you had a response, you can go off of the ibrutinib.

As you see, these bars here, these are all patients that went off ibrutinib, many of whom went off for other reasons. They didn't get to the planned point. There are other people that stopped per protocol. All these shaded areas are people that came off of ibrutinib. You can see that they haven't been off ibrutinib that long. And the follow-up is only eight months.

But of those people, there are only a few purple dots. The purple dots are progressions. So, this person progressed on the drug. These two progressed off the drug. You can see that only 2 of the 13 patients had progressed while off the drug after having had a good response. We see this in the clinic as well. So, some people that have had really good responses over time, you can give them a treatment holiday. It's just not well-described in the literature.

"Best" Initial Therapy

Any role for chemotherapy, I would say, not really–ongoing treatment was single-agent BTK inhibitor. Which BTK? At this point, I favor acalabrutinib, understanding that sometimes I need to switch to ibrutinib. Also, understand that if patients are tolerating ibrutinib currently, I do not stop and switch to

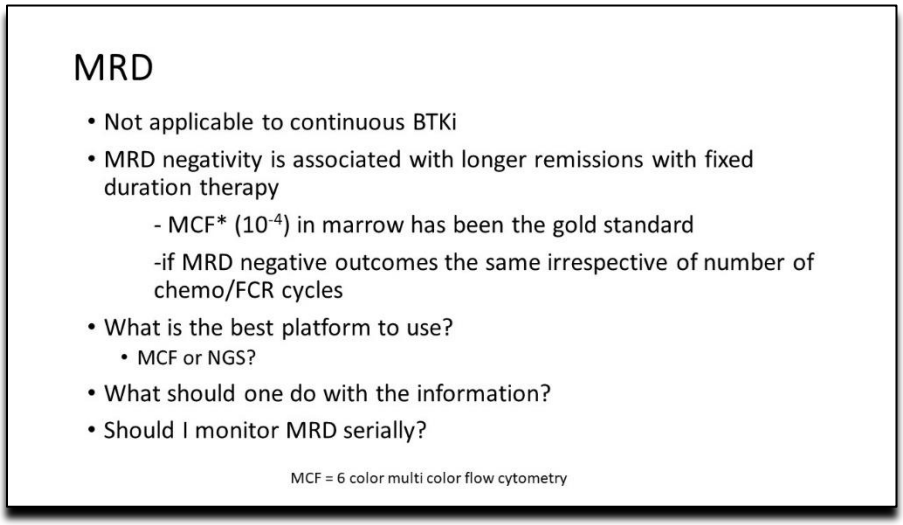
acalabrutinib. So, if you're already on ibrutinib, it's effective, and you're tolerating it well, I would continue. If you're not tolerating it, I would talk to your doctor about the possibility of switching to acalabrutinib as long as it's still working.

I'm not really going to touch on the combination aspects today. But what about treatment interruption? Perhaps, I think, overall, again, if you are needing to stop treatment for a period of time in the first six months to a year, that is okay, and even later in the course of the disease. I would say, generally, the standard of care remains continuous therapy. But, if you have to stop the drug, or really say I'm tired of this cost, the quality-of-life is not what I want it to be, I think it's reasonable to have that discussion with your doctor to go off the drug.

Minimal Residual Disease- Is This the Goal of CLL-directed Therapy?

What about MRD negativity as a treatment goal? MRD (Minimal Residual Disease), this is the idea–and here are some links, if you want to watch that. One link I came across is a guy that was in Paris at a museum, that hit the art exhibit was him literally trying to find a needle in the haystack. That is one of the links. The second link is a link from a company called Adaptive, which does a lot of this work, really outlines–a two-minute video. I'm sorry I couldn't import it here. But it really outlines the idea of what MRD is.

Essentially, it really is like a needle in a haystack. If each one of those pieces of hay represents a cell, we're trying to find one cancer cell within that stack. Because you can imagine, the deeper the remission, the fewer cancer cells, the longer the remission. And as our platforms have gotten better and technologies have gotten better, we can really search for this in real time.

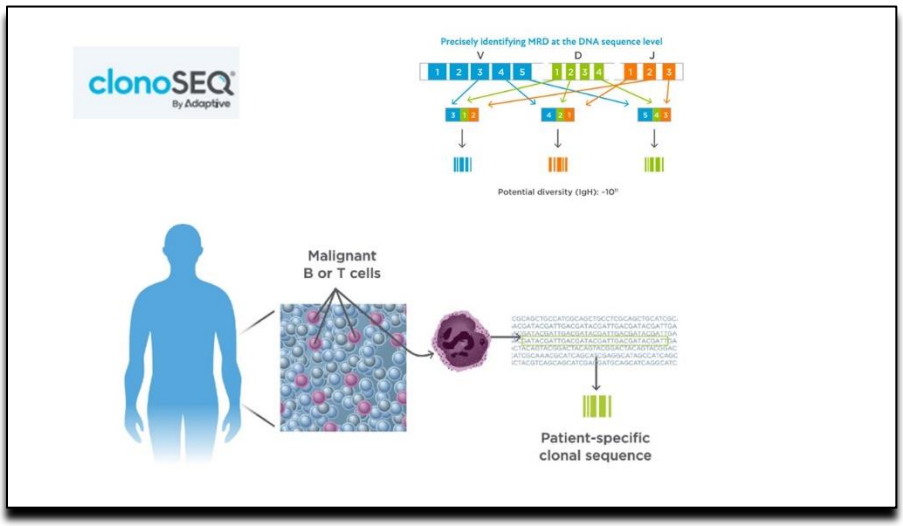


MRD

First of all minimal residual disease this approach really isn't applicable in patients getting BTK inhibitors. We do know, though, stating back to FCR chemotherapy that MRD negativity is associated with longer remissions when we give fixed-duration therapy. If we give therapy for three months, and people are MRD negative and you can't find a single CLL cell using our most sensitive techniques, whether it's six months, eight months, if you're MRD negative, you tend to have a longer remission. The question is that our goal?

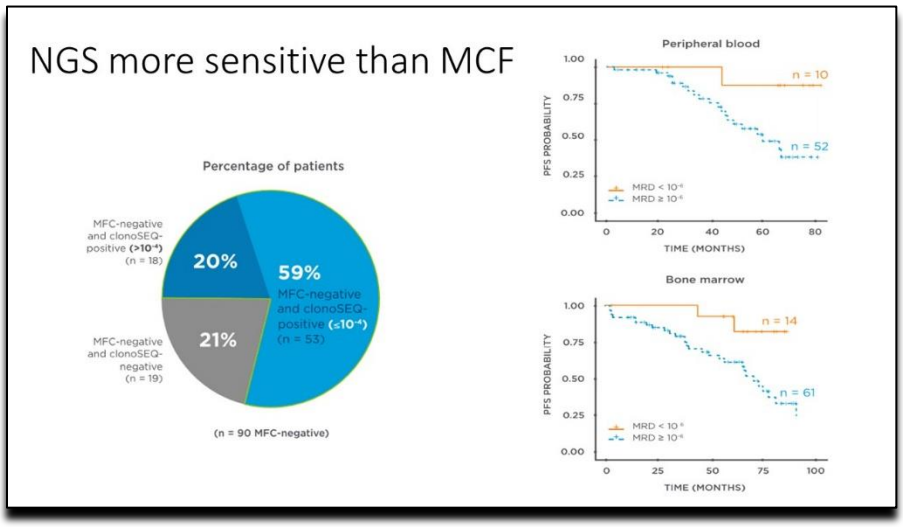
Initially, there was something called multi-color flow cytometry where you run the cells through a special device with radio (or, excuse me) fluorescently identified markers that can bind to cells and light up in certain gates so we can recognize are these are CLL cells or not, or are they just normal, other white blood cells, or B lymphocytes.

Classically, we've had a sensitivity of 1 in 10,000 cells in the bone marrow, which has been the gold standard. Again, we know that MRD negative outcome is the same no matter how you get there. The question is: What is the best platform to use? Flow cytometry or next-gen sequencing? And then, what do I do with this information? It's all over the place about MRD. But what does it really mean? Should I be talking to my doctor about it? And should I monitor this serially? So, I'm MRD negative now. We can't find any cancer cells. Does that mean I should get this test every three months?



Image

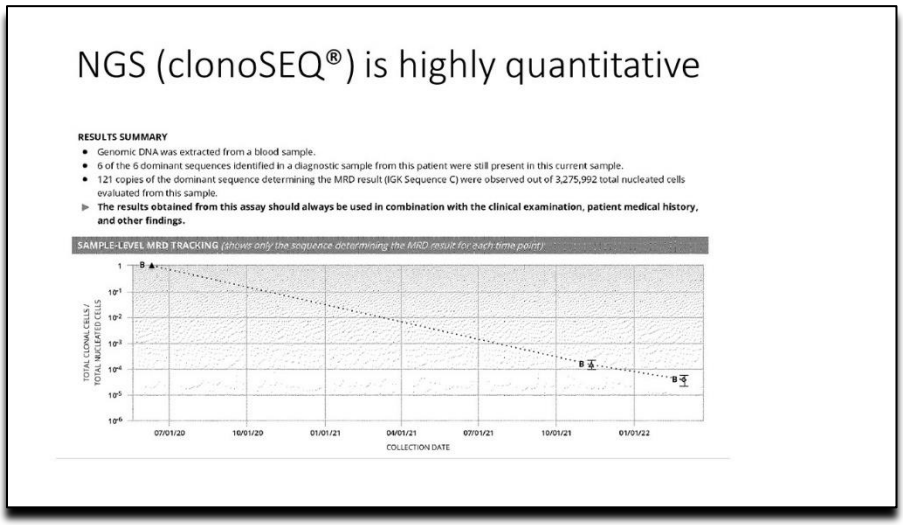
The key thing to understand here is we're able to identify it. And you need to get a sample pretreatment because everyone's CLL has unique markers on it based on, essentially, the B cell receptor and how different parts are exchanged in that specific sequences. What we can do is identify specific genetic sequences in the cancer cells that we can track over time. And this is highly sensitive.



NGS More Sensitive than MCF

This is what we call next-gen sequencing and not multicolor flow cytometry. But the reason this is nice – it is more sensitive than the multicolor flow cytometry. That means we don't have to do bone marrows on people to understand this, where the gold standard before was in the marrow. As an example, 60% of people may have negative multicolor flow, but a positive clonoSEQ® test or next-gen sequencing test.

And you can see, here also they may have detected–so this is the depth of detection as well. I think the key thing here is whether it is bone marrow or blood, you can see they operate the same way. You can see that MRD is detectable in the bone marrow for all these patients in a very predictable way and in the peripheral blood.



NGS (clonoSEQ®) Is Highly Quantitative

So, how do I use this? Again, I mentioned it's really not applicable to patients getting ibrutinib, acalabrutinib, or zanabrutinib because those drugs are designed to control the disease, not fully eradicate the disease. That's why it requires continuous therapy. MRD is really used best when you're

doing a fixed duration, aggressive (I shouldn't say aggressive but more a) treatment that is more likely to kill all the disease.

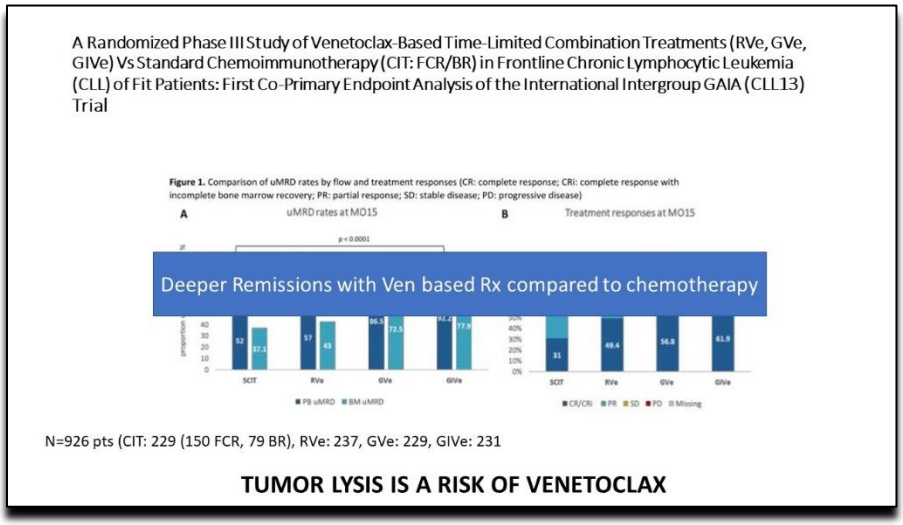
And so the way we use this – this is a patient of mine who's on ventoclax which is highly potent and given for a finite or fixed-duration period. Here, you can see at the start, this is the tracking: high-level of MRD, which is what we expect because of a high level of disease. As we treat over time, we can see that clone, or that CLL population, come down.

What do I do with this? I actually use it to see if I can stop treatment early because some patients will achieve MRD negativity early. Why predispose them to the longer treatment course if they don't need it? And then, I also use it to see are things dynamic? Are they changing? So, here's an example. Well, I had a pretty good response. But, look, it's still coming down. And it's now less than 10 to the minus four, which is outstanding. Only less than 1 in 10,000 CLL cells can be identified. And perhaps with ongoing treatment, it'll go even deeper. So, the idea is that it's deeper, someone can get a longer remission.

Conversely, let's say this person's response had plateaued than what's here. That's a situation that I don't think pushing more treatment to try to get MRD is really going to be effective. So that's when we have the discussion. Well, you know what, you're not MRD negative. But you're not going to become MRD negative with this treatment. Perhaps we should just stop treatment.

Fixed-duration Therapy

So that's really where this idea of fixed-duration therapy and MRD are meaningful endpoints. The question always is, chemotherapy, we did a pretty, pretty good job of getting MRD.



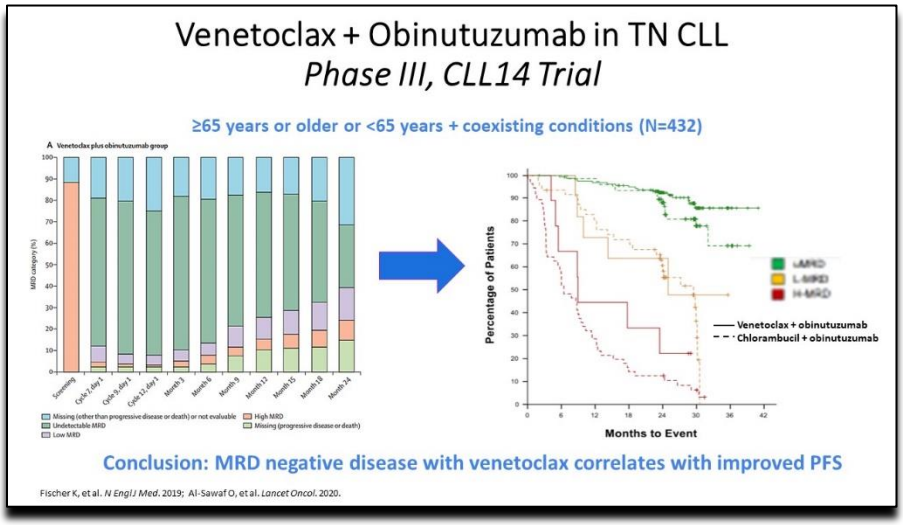
A Randomized Phase III Study of Venetoclax-based Time-limited Combination Treatments (RVe, GVe, GIVe) Versus Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

But this is a trial that really compares the idea of venetoclax-based fixed-duration therapy or time-limited combination treatments, versus standard chemoimmunotherapy. So that could be fludarabine Cytoxan®, and Rituxan®, or bendamustine/rituximab in the frontline treatment.

And, basically, the important message here, these are MRD, undetectable minimal residual disease rates at month 15—after these patients have completed their course of therapy, compared to standard chemoimmunotherapy versus venetoclax-based therapy. And these are just different combinations of venetoclax with rituximab,with obinutuzumab with obinutuzumab plus ibrutinib, so different combinations. And, importantly, you can see the MRD rates negativity rates, are much higher in the patients that got venetoclax-based therapy than those who got chemotherapy.

I think this gives us more evidence that not only are the BTK inhibitors very effective as compared to chemotherapy, but venetoclax-based therapies, even though it's fixed duration, are also very beneficial, especially when we're using deep remissions as an endpoint. And so, in my mind, this just gives us more fodder to say, you know what, we're kind of phasing out chemotherapy in the fixed-duration approach.

So, if I have patients that were going to do ongoing therapy with the BTK inhibitor, we do that. Conversely, if I have patients role want to do fixed duration, there's really not a roll of chemo anymore because we know that venetoclax-based treatment is superior.



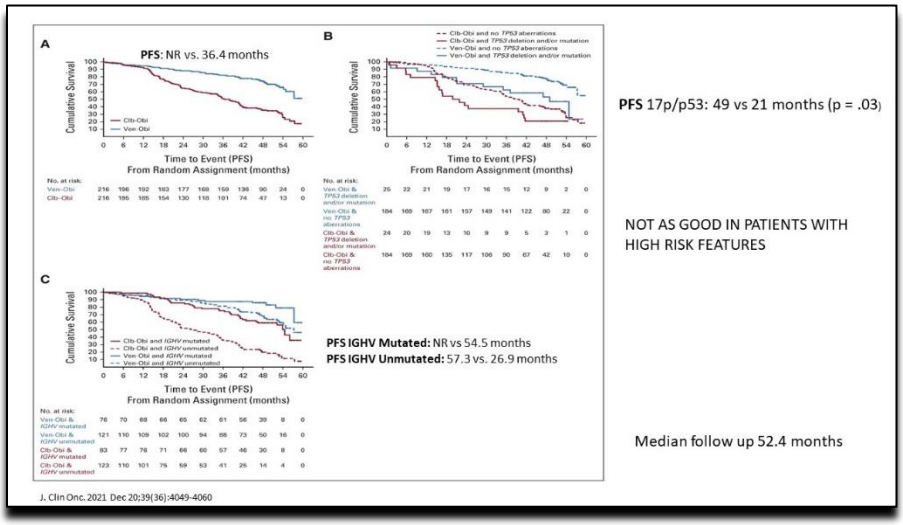
Venetoclax + Obinutuzumab in TN CLL Phase III, CLL14 Trial

We see that in the trials of patients we treat with venetoclax and obinutuzumab. Remember, this is an antibody that binds to a molecule on the surface of the CLL cell called CD20. In doing so, it activates the immune system to kill the cell.

This is over time. These patients all have disease. They're all MRD positive, which is what we expect, not only that minimal residual disease positive, they've got that whole hay bale of disease. Over time, you can see, basically this green represents patients that have undetectable MRD, or no minimal residual disease. We can't even find that needle in the haystack. And you can see a high percentage, even though this is a 15-month regimen or a year of combined therapy, a high percentage will be MRD negative at cycle seven. So, I often when checking this starting earlier on so I can say, look, you're MRD negative. We can stop treatment.

On the right panel here, you can see this is over time, patients that – how they do based on their status. So these are patients that had – no we can't find that needle in a haystack. They're MRD negative. In this case, they use multicolor flow, but now we're using more of the next-gen sequencing, or clonoSEQ. Over time, you can see undetectable MRD. Now this just is a little different regimen. This is venetoclax. This is another based regimen. But I think the important thing to note is if you're undetectable MRD, you have a superior outcome.

These are patients that had low MRD, so still some MRD, but not large amounts. And they did a little better. And then, this group had detectable MRD. And so, you can see, if you're still MRD positive, you can kind of counsel patients on this is what we expect moving forward.



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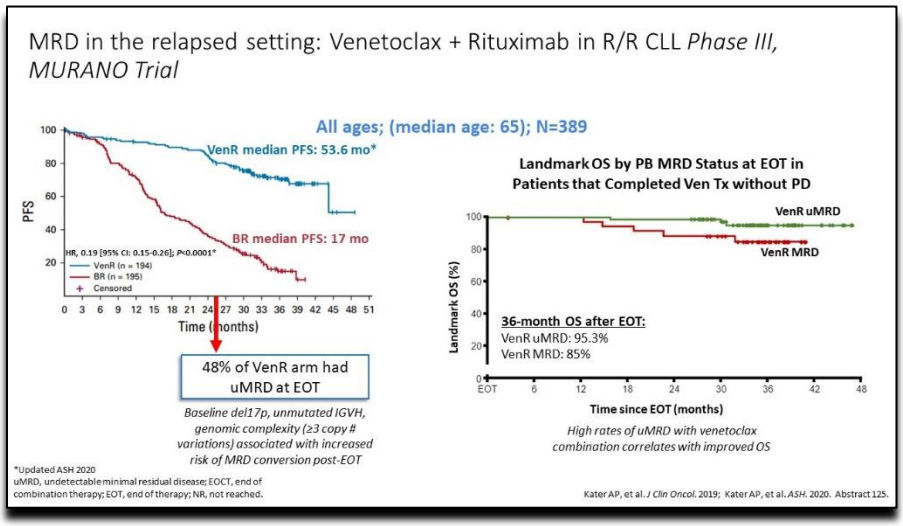
And, this is just an update of what I showed you. And, I think the key thing here is how do high-risk patients do with this? This helps me in understanding, do I want to do a BTK inhibitor or do I want to do this fixed-duration therapy? And so, I want you to focus on this blue line. This is an inferior treatment that we don't actually use anymore. But, this blue line shows all the patients that have high-risk disease. Namely, they have p53 abnormalities or 17p deletion, so some of those high-risk markers. And, you can see that their progression-free time was about three years.

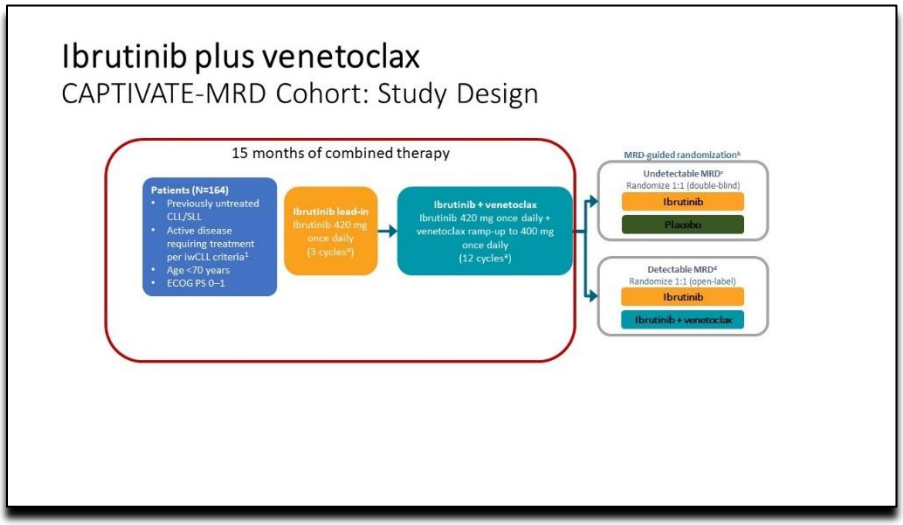
And that was or, in this case, you have 21 months versus 49 months, the different types of chemotherapy. But in patients who had venetoclax-based therapy, their progression-free survival is 36 months in patients with higher-risk disease. Importantly, also, if you look at mutated or unmutated, so remember mutated is good risk, unmutated is poor risk. You can see that patients who had a mutated IGHV had a follow-up of over four years, not enough people have progressed to calculate a progression time. So, fewer than 50% of the population has progressed at four years.

Conversely, if you look at patients who have an unmutated IGHV, they have progressed already. I think the bottom line of all of this talk is that venetoclax fixed-duration therapy is not as good in patients with high-risk features as those with low-risk features. And that is not a surprise, but that does influence what I'm recommending as far as my initial therapy as far as fixed duration or not.



MRD in the Relapsed Setting: Venetoclax + Rituximab in R/R CLL Phase III, MURANO Trial

And this also holds, I won't belabor this, but this also holds true in the relapsed setting using venetoclax and rituximab. Patients treated with chemotherapy had a much shorter remission time than those treated with venetoclax and rituximab. So, what can we expect if you're MRD negative? If you're MRD negative and you're followed three years, your overall survival is 95%. This is in the relapse setting, people who have had many treatments. So, the bottom line is, venetoclax-based treatment, if you're MRD negative, you have a longer remission.

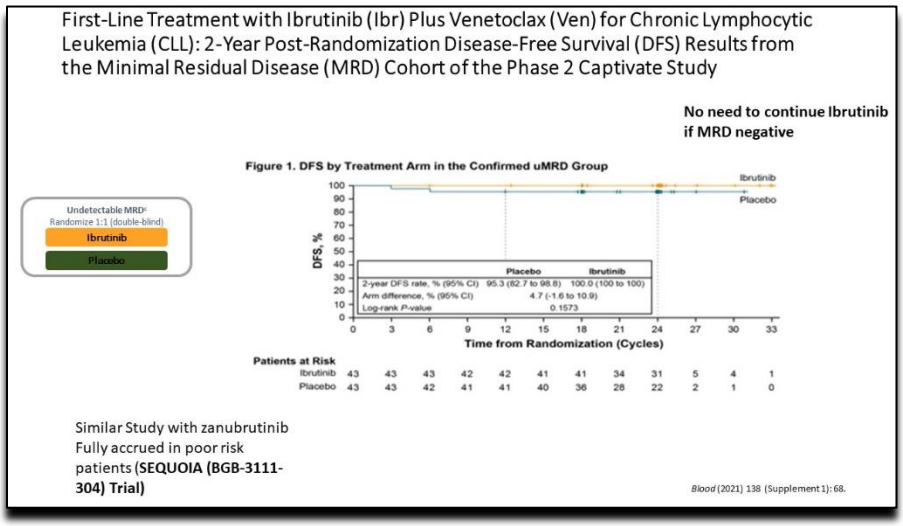


Ibrutinib Plus Venetoclax

What about patients who are MRD negative and have been treated with ibrutinib plus venetoclax? So, there is a combination treatment that does this. How do they do? Do they have to stay on ibrutinib? Should they come off ibrutinib? This study was a study that took patients ibrutinib plus venetoclax for combined treatment for a total of 15 months, which has really become the standard of combination therapy, 15 months.

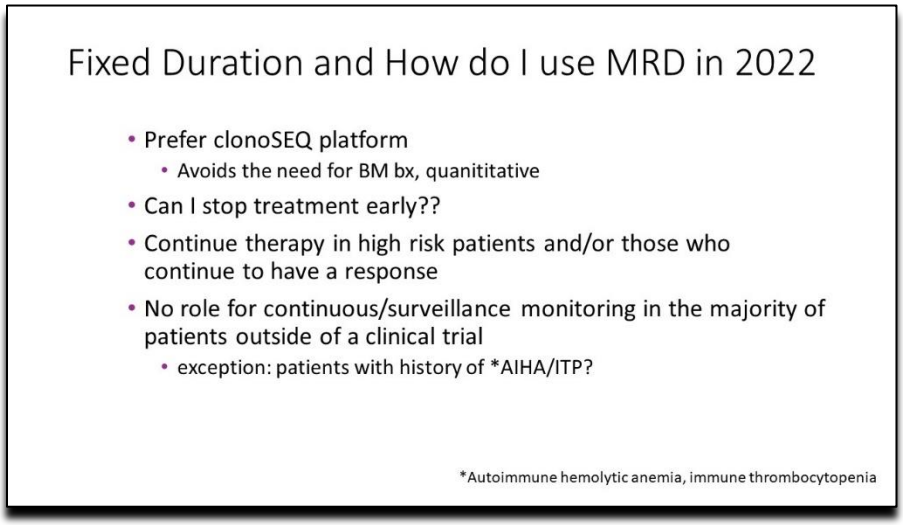
And, importantly what it did, it didn't just look at the initial responses. It looked at patients – it then had another randomization. So, if people had undetectable MRD, it randomized them to ongoing ibrutinib or placebo. If you had detectable MRD, you got ibrutinib and ibrutinib/venetoclax.

But, I really want to focus on these undetectable MRDs because, again, the question is, if I'm on an ibrutinib-based therapy with venetoclax and I have an amazingly deep remission, no needle in a haystack, can I go off my ibrutinib? And how will I do? And this does a nice job of answering that question.



First-Line Treatment with Ibrutinib (Ibr) Plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-randomization Disease-free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study

If you have a really deep MRD negative remission on ibrutinib and venetoclax, and I think we can extrapolate that to any venetoclax or ibrutinib-based regimen, you don't need to continue therapy. You can stop the therapy, even though this did not include a monoclonal antibody. This is the randomization. So, these are the patients that continued on ibrutinib. These are the patients that continued on the placebo, the exact same rate of disease-free period. And, importantly, these patients are disease-free 30 months out, so a very good outcome.



Fixed Duration and How Do I Use MRD in 2022

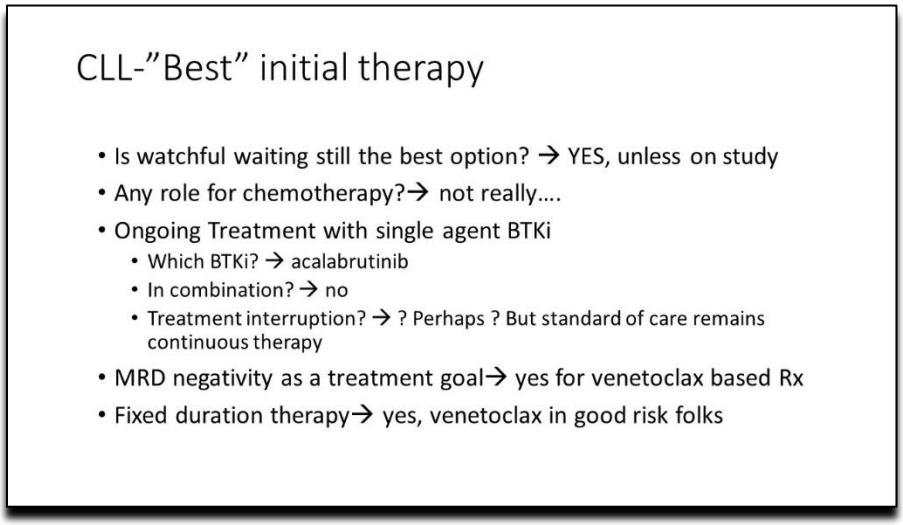
So, how do I make sense of all this gobbledygook I've been talking about? Well, fixed duration and how do I use MRD in 2022? I prefer the clonoSEQ platform, and mainly because it avoids the need for bone marrow biopsies in patients. And it's highly quantitative. It's just a blood test. Now remember, this has to be done prior to treatment and also only for fixed-duration therapy.

I use it to inform, can I stop treatment early? Are there dynamic changes? And, then, in some cases, it informs, leads to the discussion should I continue therapy, and high-risk patients that are those who continue have a response, and the response hasn't plateaued, even though the studies may say, well, you know, you do this for a year, 15 months, you do this for two years and you stop. This allows us to really personalize it for each patient. In my opinion, there's very little, if any, role for continuous

surveillance or monitoring in the majority of patients outside of a clinical trial. So, the clonoSEQ website, I would definitely recommend. Adaptive is a company that performs all this. It's FDA approved for this indication.

And, they do a really nice job of explaining things. That said, they talked about, oh, you can do surveillance every three months. And I really do not see a need for surveillance in the setting, with the rare exception. If patients have a history of autoimmune phenomenon leading to hemolytic anemia, that's where the body in the presence of CLL will inappropriately breakdown red cells, or they'll attack platelets, that can happen at very low levels of recurrent disease.

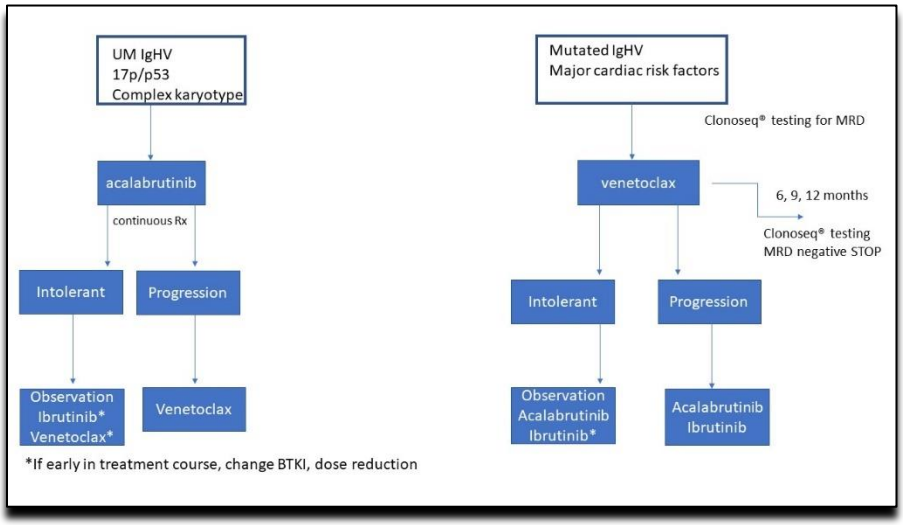
In those patients, we do have the discussion about, let's monitor your MRD status. And, if you turn MRD positive, we may consider reinitiating treatment even though you've been off of it because it may fuel this other disease complication.



CLL- "Best" Initial Therapy

To summarize, I think watchful waiting is still the best option, unless it's on study. And we have that CLL study for high-risk patients with high-risk CLL IPI. Any role for chemotherapy? Not really. And I actually only use chemotherapy in patients that we haven't been able to get some of these more expensive medications. So, I can count on one hand how many times I've used chemotherapy definitely in the last five years, maybe the last 10 years.

Ongoing treatment with single-agent BTK inhibitor, acalabrutinib is as my BTK inhibitor of choice. Typically, in combination is not needed. Perhaps we can do treatment interruptions again. No worries if you have to stop treatment for a period of time, but the general standard of care remains continuous therapy. MRD negativity is a good treatment goal for venetoclax-based treatment. I like to use the clonoSEQ platform. And fixed-duration therapy is a yes with venetoclax-based treatment really in patients with better risk disease based on the superior outcomes.



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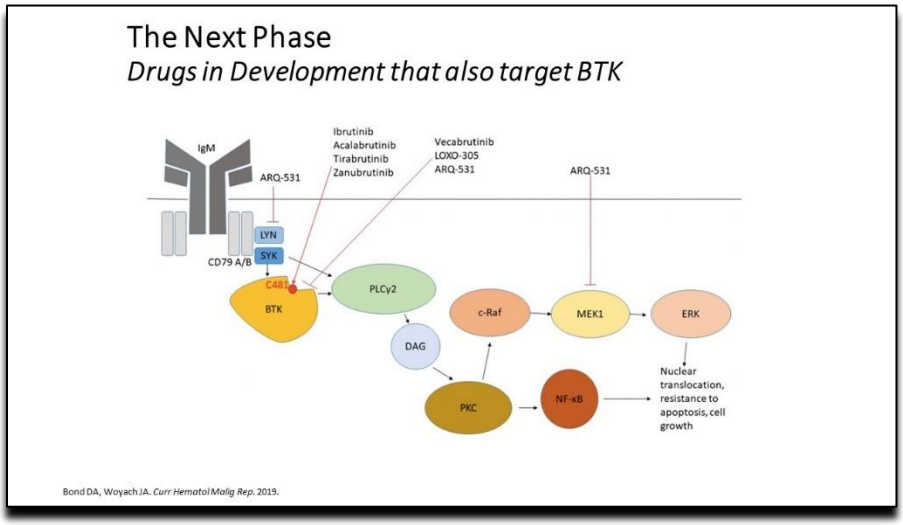
So, this is a very stripped-down, bare-basic, bare-bones approach, in my approach. There are much more detailed approaches. But, I thought, especially at this point in the talk, leave it pretty simple. So, my approach is, if patients have an unmutated IGHV, or they have a 17p deletion or p53 mutation and/or complex karyotype, more than three abnormalities on their cytogenetics or FISH panel, (and remember, these are all patients that meet the IW CLL-treatment criteria), these are patients I recommend acalabrutinib, a frontline study as continuous therapy. If they're intolerant, and they've been on treatment for quite a while, and their disease is under good control, I'm very comfortable observing and retreating when needed.

If their disease is not under good control yet, or the patient really wants to continue to pursue treatment and we've got a way to go, then we go with ibrutinib. Or, if they're intolerant to ibrutinib, then we consider venetoclax. Conversely, if someone progresses, we go to venetoclax.

What is not shown here is option number one, in my opinion, should be clinical trial. Option number two, a progression should be clinical trial, et cetera, et cetera, for patients who have better-risk disease, so they have unmutated IGHV, they don't have a complex karyotype, they don't have 17p deletion or p53 mutation, and they don't have major cardiac risk factors. This has become more front-and-center with high blood pressure, atrial fibrillation, history of heart failure, or history of multiple heart attacks. I'm much more cautious using BTK inhibitors in those patients now, because we do have increased morbidity and in some cases mortality when we use some of these drugs. So that has to be looked at very closely in certain populations.

But in those patients, I'll look, I'll do some clonoSEQ testing at baseline so we can get an MRD signature. Then, we'll start venetoclax-based treatment. And it's typically in combination with obinutuzumab. So venetoclax/Gazyva® – venetoclax or obinutuzumab, that's the same thing. At months 6, 9, and 12, we will do clonoSEQ testing. If we're MRD negative, we will stop.

At the end of treatment, we will do it as well just to kind of understand, are we seeing the changes I mentioned? If someone's intolerant, we do same thing, observation or we switch to a BTK inhibitor. If progression, we switch to a BTK inhibitor. So, that's the general approach I'm taking when I'm talking to a patient about treatment.



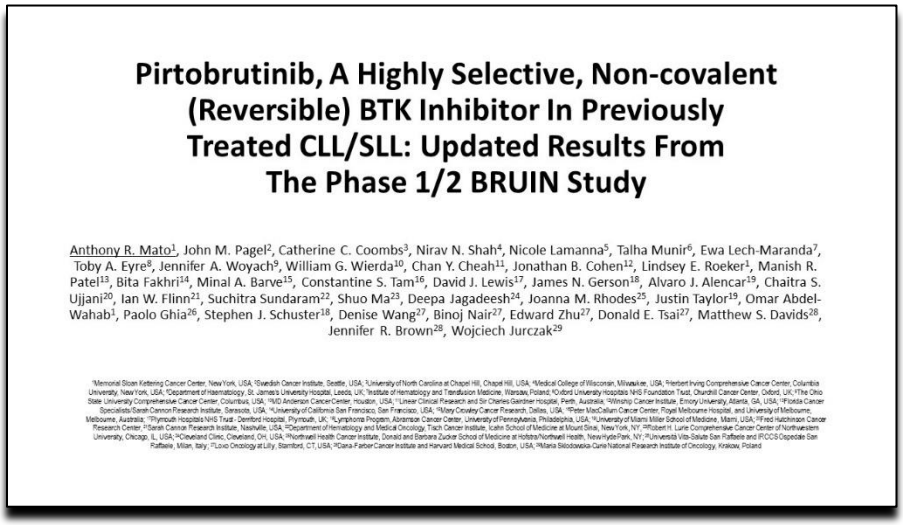
The Next Phase Drugs in Development That Also Target BTK

So, just a couple of things about some very exciting developments. When BTK inhibitors first came out, and we would apply for grants in CLL, we would always – we were saying, oh, we have new therapies. At that time, we would never get the grants because these drugs were so effective. Now, as is often the case, the disease is starting to outsmart some of our drugs, including ibrutinib, acalabrutinib, and venetoclax through pretty well-known resistance mechanisms.

And, in particular, acalabrutinib and ibrutinib, you develop resistance. It's really kind of thinking of it as a lock and key. So, this is the area where these drugs all bind, zanabrutinib, acalabrutinib, and ibrutinib. This is the energy pocket of this enzyme. And there's a certain mutation that develops, the C481S mutations, where you get an amino acid, that one amino acid replaces another amino acid. And what it does is it causes a conformational change.

If it's like this, you get that mutation at the binding pocket and it goes like this. The drug can't fit in there effectively. And that just happens over time with selective pressure, almost like the idea of antibiotic resistance. Well, when that happens, it renders these drugs much less effective. You can also get mutations in a downstream signaling molecule in the B cell called phospholipase C gamma 2 (PLCγ2).

So, the question is, are there BTK inhibitors we can employ that actually can work effectively in these patients? And the answer is “yes.” So, pirtobrutinib, or Loxo-305, and ARQ-531, nemtabrutinib, they target BTK but at a different site. So, they work even in patients that have developed this mutation.



Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

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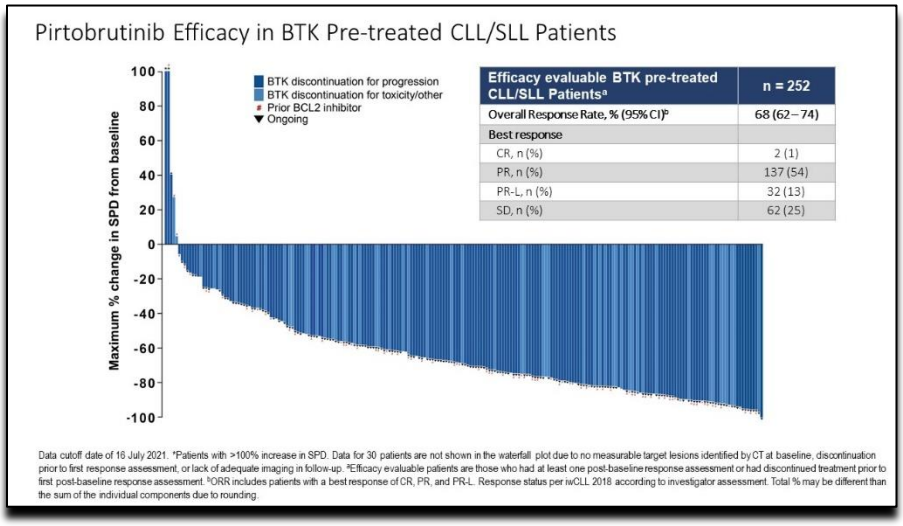
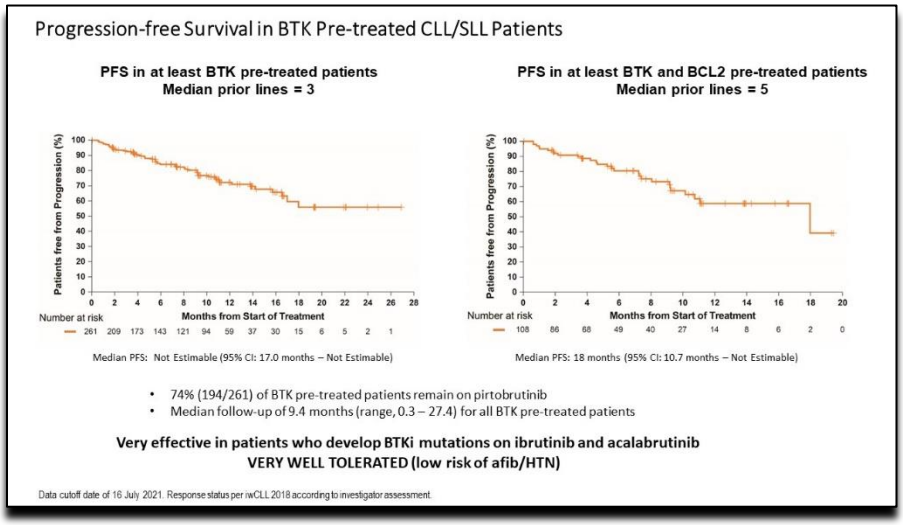
BRUIN Study

This is the BRUIN study that looked at this pirtobrutinib.



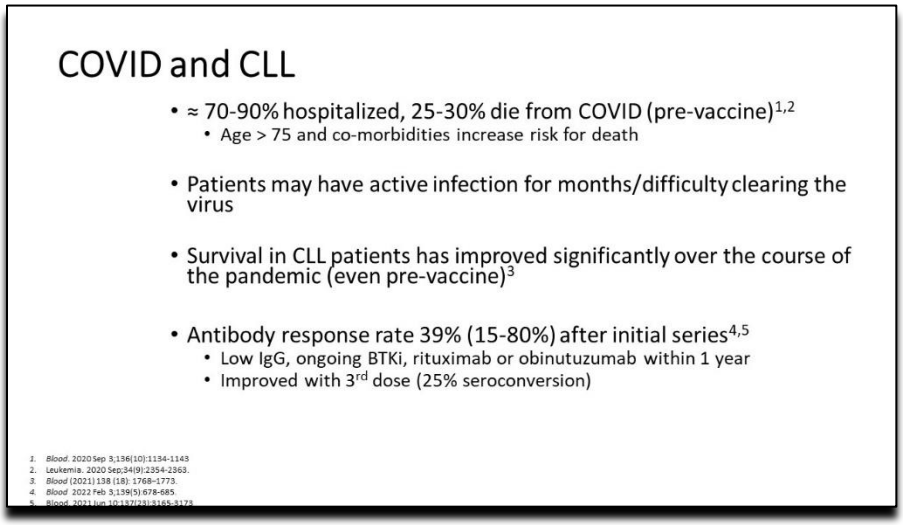
Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

This is called a waterfall plot. Anything below the line is tumor reduction. So, lots of times in early-phase trials, where we're just trying to understand responses. You can see these patients had very good reductions in their CLL-disease burden. Also, these dark bars are these patients that progress on other BTK inhibitors. So, it shows that if you find a different target at that enzyme, a different lock-and-key mechanism, you can still be effective.



Progression-free Survival in BTK Pre-treated CLL/SLL Patients

Here's an example. These are patients that had progressed on previous, or had been treated before with BTK and venetoclax, BTK inhibitors and venetoclax. And, although follow-up is short, it's very encouraging because, again, it's working in patients that have failed prior BTK inhibitors. So, it's very effective in patients who develop BTK-inhibitor mutations on ibrutinib and acalabrutinib. And, it's very well-tolerated. Unlike some of the others, it has a very low risk of atrial fibrillation and hypertension. So, we're very excited about this.



COVID and CLL

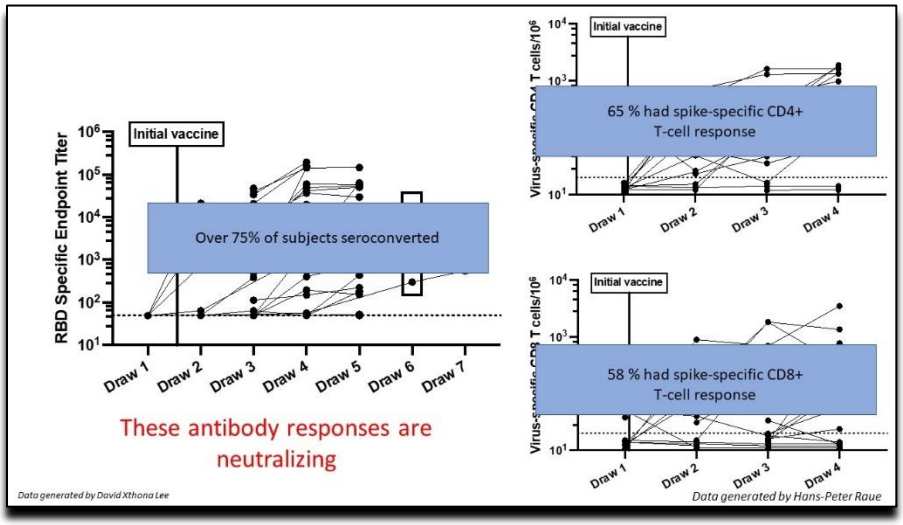
Switching gears. We're almost at the finish line here. So, as most of you know on the call–and we've all been very frightened together during the COVID pandemic. Early on, there were two studies, one in the United States and one internationally, that really looked at COVID outcomes in CLL patients based on them being immunocompromised. And, in those studies, 70%-90% of people were hospitalized with COVID, and about a third of them died from COVID. This is all pre-vaccine. And we know that advanced age and comorbidities increased the risk for death.

The other thing we know is that, because of impaired immunity, patients may have active infection for months or difficulty clearing the virus. My record thus far is a patient followed outpatient for five months with active infection and intermittent fevers, cough, and just never developed antibodies and couldn't clear the infection. That can be problematic for a number of reasons, obviously, for the patient. But it kind of becomes a little incubator for new variants.

We do know that survival in CLL patients has improved significantly over the course of the pandemic. And this is even pre-vaccine. So, there's a study that was published that looked at the first six months of the pandemic and then the next six months of the pandemic, and outcomes definitely improved over the course. And that's due to treatments. That's due to early recognition and testing.

So, what about the vaccines? We were all so excited to see these vaccines come through. But, like many vaccines in CLL, the antibody response rate is lower and, on average, about 39%-40% with the initial series, and a real broad range, heterogeneous response, 15% to 80%. And that really was the ability to develop antibodies. It was associated with if you've had a poor antibody response, that is if you've had a low immunoglobulin level, if you had ongoing acalabrutinib or ibrutinib, or if you had rituximab or obinutuzumab within one year.

That really makes sense because it decreases your B cells and impairs their function, not just the cancerous B cells. And then, also, there was a publication that showed this was improved with the third dose, so we could boost that up by 25%.



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We've done a lot of work in this area. I want to just credit–I've been working with a graduate student on this, who has done outstanding work, and then with the lab technician named here who generated these data.

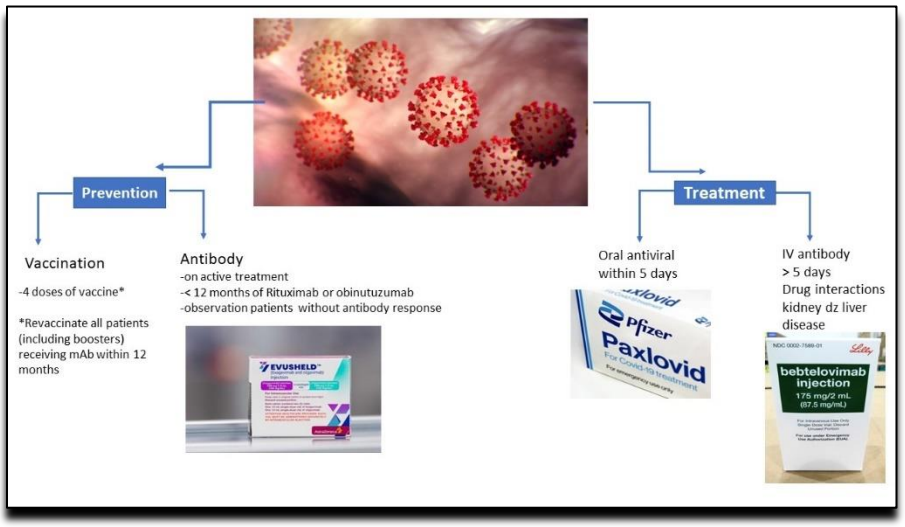
And, so, this just shows over time what we're looking at. The RBD is a part of the spike protein. And what we see–this is pre-vaccine. These are the initial group of patients that got the vaccine. You can see some didn't respond very well. But these are patients who had some response.

Then, we added more patients to the cohort, and we gave them additional vaccines. And you can see between vaccine – this is draw three before their third vaccine. This is after the third vaccine. You can see a significant boost for the majority of these patients. So that just shows that, yes, the boost is necessary. The question is–and persistent over time. So, this is a draw five, usually three months after draw four. So, persistence over time.

What about the fourth dose? So, these are patients who got fourth doses. And, here you can see a patient that actually salvaged a response after the fourth dose. And this patient had an increase after the fourth dose. So, I think the message here is that we want to make sure everyone has had their full booster. There is not yet a role or data for a fifth dose. We don't know that yet, with some caveats. And I'll explain those in a second.

We were able to see that, even in patients, many of whom didn't seroconvert at the beginning and had no antibodies, with additional vaccines, they – additional 75% seroconverted.

These are T cell responses. T cells are also part of the immune system. And they went out more robustly after the initial two, but did have some increases after subsequent vaccines. There are different types of T cells, and had good responses. And these are neutralizing. So, if you incubate these antibodies with different strains of the virus, they do neutralize the virus.



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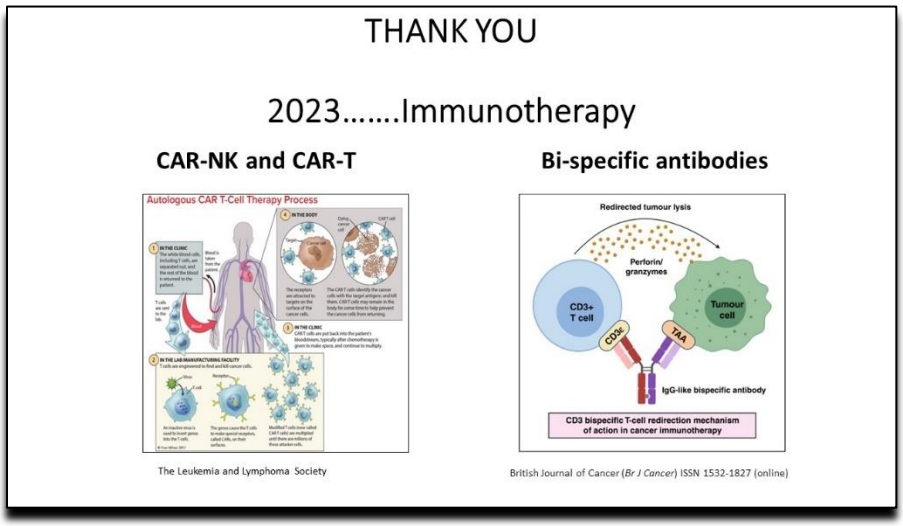
How does this translate into my everyday? My approach on this day–and we have a lot more levers to pull now, so as far as prevention, vaccine early and often. So, four doses of vaccine. Now this is the caveat. Many of the patients got vaccinated early on, on active treatment. We were just trying to get everyone vaccinated. We didn't know exactly what we were dealing with.

I revaccinated all patients, including boosters, and anyone who had gotten Rituxan® or Gazyva™ within 12 months. So, if you got three or four vaccines, and that was all within a year of obinutuzumab or rituximab, or even BTK inhibitors, well, it's time to start over with your vaccines, the full, four-dose series.

Now, we also have Evusheld™ (tixagevimab co-packaged with cilgavimab), which you have to be fairly aggressive to find it. But I give this antibody treatment. It's given in each buttock as an injection, within 14 days people achieve high-antibody levels. And it lasts for five-and-a-half additional months for added protection and a decreased hospitalization in serious and poor outcomes. So, I give it to people that are on active treatment. That includes ibrutinib, acalabrutinib, or people within 12 months of Rituxan® or obinutuzumab. And I do give it in observation patients, but I check their antibodies first to see if they really need it or benefit from it because this is a fixed resource.

What about treatment for COVID? Well, now we have Paxlovid™ (nirmatrelvir and ritonavir). I think the key thing here is starting within five days. Remember that the rapid antigen tests at home may not be as sensitive. Typically, I tell my patients the first day check a rapid test. If it's positive, then you can go get Paxlovid™, if the second day it is still not positive, make sure you get a low-threshold PCR test.

And then, we also have bebtelovimab, which is an injection of monoclonal antibody. This is actually much harder to come by. So, typically, Paxlovid™ is our first line of defense. But some patients may not be eligible due to drug interactions, or kidney disease, or liver disease for Paxlovid™, or they are outside the five-day window. It [bebtelovimab] has to be administered within seven days.



Thank You

All right, I know we've covered a lot of information. I hope we have some questions. Moving forward, I know some patients may have questions about CAR-NK or CAR-T cell therapy or immunotherapy. But, that's really the way of the future. Thank you for your attention.

Q&A

Lizette Figueroa-Rivera
Thank you so much, Doctor. It's now time for our question-and-answer session. For everyone's benefit, please keep your questions general in nature without many personal details and doctor, you had mentioned about CAR-T. Well, Roy is asking, what is the applicability of CAR-T or CAR-NK therapies to CLL? Do the lymphocytes have a characteristic protein that can be targeted?

Stephen Spurgeon, MD
Yes, thanks for that question. Basically, CAR-T is highly applicable to CLL or any lymphoid malignancy. The nice part about CAR-T is you can target any target on a cell. So, there are new targets developing all the time. But, classically, it's against a protein called CD19 or CD20. They're not FDA approved in this population yet, but there are a number of clinical trials.

The CAR-NK is not as far along as far as its development. But the nice part about CAR-NK is that actually it can just be off the shelf, meaning you're not as worried about rejecting the NK cell because it doesn't have some of the immune features that would cause the body to reject it. So, it's definitely a

very promising treatment. Right now, this technology and treatment is really reserved for people with multiply relapsed disease who have failed the treatments I already mentioned. And it's available on clinical trials.

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

Operator
This question comes from Kathy, calling from California. Please go ahead.

Kathy
After taking acalabrutinib and Gazyva, how long does the drug work to keep the blood count, the white cells, low?

Stephen Spurgeon, MD
Yeah, I think it depends. So, typically, with acalabrutinib and Gazyva™ people stay on acalabrutinib. And if you look at five years down the line, about 60% to 70% of people are still on treatment. It's a little less clear if people take acalabrutinib and Gazyva™ and then stop it, because it depends how in depth their response is. But, generally, we think about long-lasting remissions beyond five years.

Lizette Figueroa-Rivera
Thank you. And Lawrence is asking, are antibodies for shingles, pneumonia, COVID, et cetera lost during CLL-drug treatments if vaccinations were given before treatment began?

Stephen Spurgeon, MD
That's a really good question and we don't have a great answer. It depends on the situation. Some antibodies are incredibly long-lived. The classic example is measles. We've checked measles, measles' antibodies in patients, about 80% still had measles antibodies late into their life. But what we found is with the treatment, that really diminished the cells that can make new antibodies. So, what that means is that some patients will lose the antibodies, like COVID antibodies, and lose the ability to make new antibodies. But most of the childhood things, they will persist for a long time. The exception is shingles. And that's why we ask people to get the SHINGRIX® vaccine. Those are given, assuming someone has a good response. They really will be fairly persistent.

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

Operator
Our next question comes from Patricia, calling from Pennsylvania. Please go ahead.

Patricia
Hi. I was just wondering, has anyone experienced hair loss while on acalabrutinib?

Stephen Spurgeon, MD
To be honest, the answer is yes. I think it's always the question is—is it acalabrutinib-related. And that is not well understood. Although the classic thing is–yes, you can experience a little hair loss—the classic thing is a lot of nail changes as well. I don't know if anyone has run into that.

Lizette Figueroa-Rivera
Thank you for the question. And our next question, Bruce is asking what's the best way to manage fatigue. I know that Patricia is also asking about fatigue, as well as others.

Stephen Spurgeon, MD
There are a lot of different approaches there. And it really depends on the situation. So, if fatigue is from the disease, progressive disease, it's really treating the disease. I think a lot of times we get in this no-man's land of going to the doctor and saying, your disease is stable. You don't need treatment. But

people having fatigue. I think the best data for cancer-related fatigue is exercise. And that has held true across a number of different types of cancer.

Otherwise, though, it's making sure primary care physicians don't say that people's symptoms are related to their CLL, and just making sure you have a comprehensive workup for things like depression, sleep apnea, cardiac abnormalities. Sometimes, in patients undergoing treatment who have treatment-related fatigue as well, we will go to stimulants, like Provigil® (modafinil)- or Ritalin® (methylphenidate hydrochloride)-based treatments. But that's probably the exception, not the rule. And it's just ruling out some of these other things as well.

Lizette Figueroa-Rivera
Thank you. The next question is from Wilma. She's asking, I've been on ibrutinib for five years. How will I know if I'm in remission?

Stephen Spurgeon, MD
That's a really good question, as well. I think there are different degrees of remission. So, if you're still on ibrutinib, and your blood counts are normal, and you don't have enlarged lymph nodes on exam, and you're feeling well, you're in remission. This is not something we typically do a lot of CT scans for or additional testing.

That said, if you did get to the point and said, gosh, I want to maybe come off the drug or understand how deep my remission is, then you can talk to your doctor about doing things like bone marrow biopsies and looking for MRD status. But, at this point, I would not recommend that. I would say if you're tolerating it and doing well, again, not knowing your case fully, but the general standard would be staying on the drug and as long as you have normal counts and are doing well.

Lizette Figueroa-Rivera
Thank you. And, Doctor, we want to know what you're most excited about with all of the new therapies that are coming out recently for CLL.

Stephen Spurgeon, MD
I think the pirtobrutinib approach, new BTK inhibitors, I'm very excited about because it also shows we can work to outsmart the disease, employing well-known targets already, but just drugging them differently. And there are also other signaling inhibitors that I didn't discuss today, other oral drugs that are highly effective. But I'm very excited about these bispecific antibodies.

Bispecific antibodies are basically drugs that come in and they form as a link between your good immune cells, your T cells, and the cancer cells. And, basically, what will happen is it'll sit there, the drug, and it'll have your cancer cell here. And it'll come in here and bring the T cell in here. And it tells the T cell to kill the cancer cell.

We've had a flood of activity related to that. And that's proving to be highly effective. So, it's kind of like the idea of using the targets that we know are effective with, rituximab and obinutuzumab, but in a different way to harness the body's own immune system. And we've seen just outstanding responses.

And, then, I don't know if excited is the right word, but I'm pleased, or cautiously optimistic, to see that we have a better understanding of COVID and more options for our patients, that have been so careful over the couple years being able to see grandkids and celebrate with family members. I think, hopefully, we can move ahead with that as well.

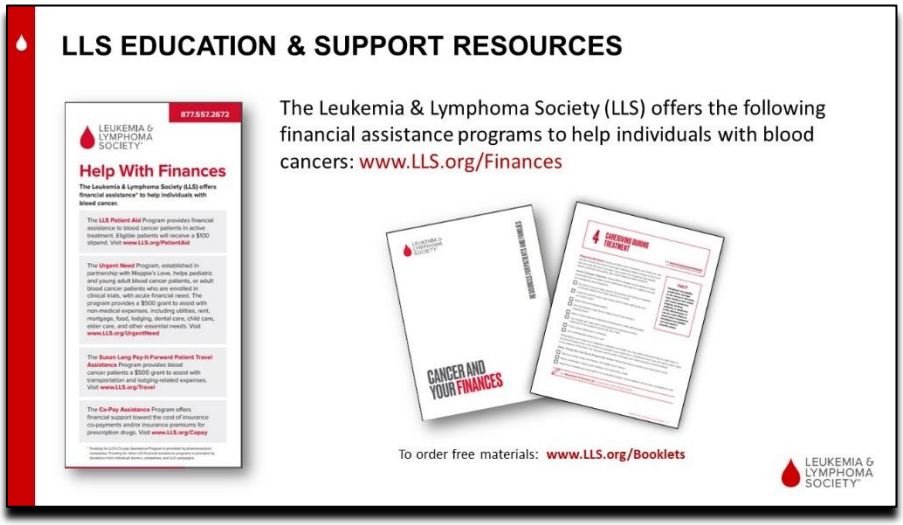
Lizette Figueroa-Rivera
Thank you. Yes, we totally agree. And we did have a lot of questions today in regards to COVID. And, thank you for the discussion and your slides in regards to COVID today. Thank you, again, Dr. Spurgeon, for sharing your expertise with us and for your continued dedication to our blood-cancer patients.

LLS Education & Support Resources

We had many questions today. And I know that we weren't able to get to all of your questions. You can definitely call an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572. We're open from 9 a.m. to 9 p.m. ET, or you can go on our website at LLS.org/InformationSpecialist to chat online or email them at LLS.org/ContactUs. We also have information about COVID-19 on our website at lls.org/coronavirus.

Our Clinical Trial Support Center has Clinical Trial Nurse Navigators who will personally assist you throughout the entire clinical trial process. I know that Dr. Spurgeon did mention clinical trials, and you may reach out to them at LLS.org/Navigation to see if a clinical trial is something that is in your future or is available to you right now.

LLS Education & Support Resources



LLS Education & Support Resources

Thank You

Again, we'd like to acknowledge and thank Genentech, Inc. and Biogen; Eli Lilly and Company; and Pharmacyclics, an AbbVie company; and Janssen Biotech.

Again, Dr. Spurgeon, thank you for sharing your expertise with us and your time with us today. And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. And, please let us know what you need from us during this time. We hope to have you as well as your caregivers on next month to address caregiver issues. Thank you and take good care.

Stephen Spurgeon, MD
Thank you.