Spotlight on Chronic Lymphocytic Leukemia

Operator
Greetings, and welcome to Spotlight on Chronic Lymphocytic Leukemia, a live telephone and Web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 1,900 people participating from across the United States as well as other countries, including Canada, Georgia, India, and the United Kingdom. Welcome to all. Special thanks to Dr. Lamanna for volunteering her time and sharing her expertise with us today.

Before we begin, I'd like to introduce Ms. Heidi MacAlpine, a CLL patient diagnosed in 2019. Heidi, please go ahead.

Welcoming Remarks

Heidi MacAlpine
Thank you, Lizette. I would like to take this opportunity to welcome and thank the patients, caregivers, and healthcare professionals for attending and listening to this program today. My name is Heidi MacAlpine. I wear many hats. I am a wife, mother of three adult children, an occupational therapist, holistic healthcare practitioner with a focus on trauma-informed care and health promotion. Those are what define me.

But I am also a CLL patient diagnosed since 2019. When I was diagnosed, I was planning the next phase of my life, in the middle of finishing my doctorate in occupational therapy. Little did I know at the time that the different therapeutic tools that I taught my patients had helped maintain my quality of life as well. I remember Dr. Nori saying to me, "Whatever you are doing, continue to do them." I was on watch-and-wait every six months and most recently changed to once a year.

The Bloodline with LLS's podcast titled, "Improving Quality of Life Through Wellness Practices," provides more detail on my story and how I utilized wellness techniques to reduce inflammation and maintain a quality of life while on watch-and-wait. Over the past 10 years, The Leukemia & Lymphoma Society, LLS, has invested more than $52 million to accelerate pioneering research in chronic lymphocytic leukemia. The therapeutic landscape for CLL, the most common adult leukemia in the U.S., has evolved significantly in the past decade. Next generation sequencing has expanded our knowledge of the molecular underpinnings of the disease, ushering in promising precision-medicine approaches.

LLS has been at the forefront of CLL treatment innovation and continues to invest in cutting-edge research to find cures. Thank you for joining today's program. We are fortunate to have an esteemed key opinion leader to provide us all with important updates as to new therapies that will help strengthen our professional and therapeutic alliance and the outcomes to improve our quality of life.

I will now turn the program back to Lizette.

Lizette Figueroa-Rivera
Thank you, Heidi. And, as Heidi mentioned, we hope that you listen to our podcast episode on TheBloodline.org. And for this program, we'd like to acknowledge and thank our supporters: AbbVie, Inc.; BeiGene; Eli Lilly & Company; Pharmacyclics, an AbbVie Company; and Janssen Biotech; and the Thomas D. Oxley Fund for CLL Patient Education and Support.

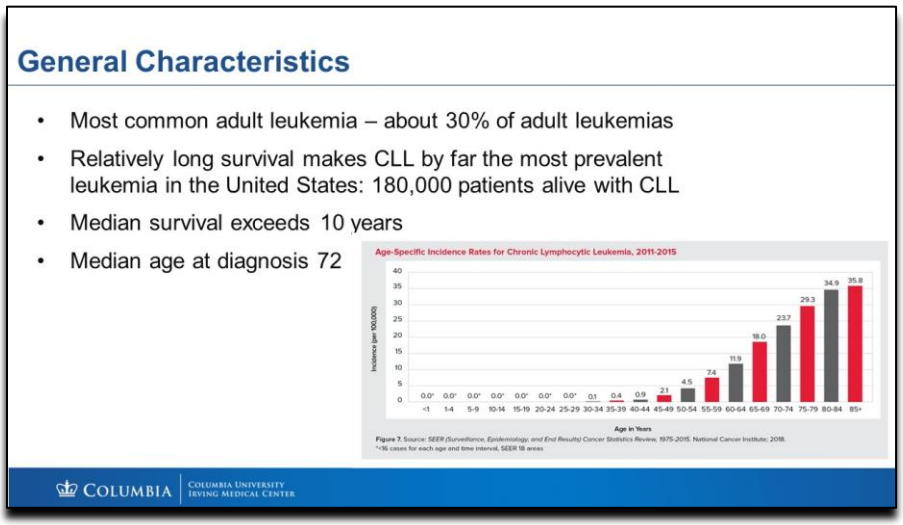
Disclosures

I am now pleased to introduce our speaker, Dr. Nicole Lamanna, Associate Attending, Leukemia Service, Director of the Chronic Lymphocytic Leukemia Program, Hematological Malignancy Section at Herbert Irving Comprehensive Cancer Center, NewYork Presbyterian/Columbia University Medical Center in New York, New York.

Dr. Lamanna, I'm now privileged to turn the program over to you.

Nicole Lamanna, MD
Okay. Thank you so much. It's really, really exciting to be here with everybody today. Knowing that some of you might be recently on your CLL journey—we're really going to try to do a lot today in an hour. I'm going to try to start from the bread and basics of CLL, to testing, to markers. We're going to go through everything, including therapy.

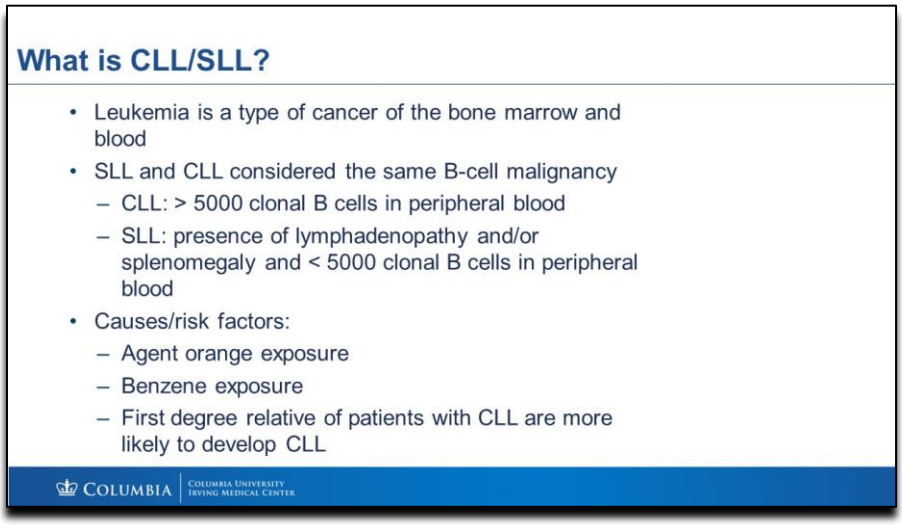
And, for those who are further along your CLL journey or who are on some different types of therapies, we'll be talking about all the therapies and newer therapies that I'm going to highlight as well. So, for some of you, you might have heard some of this before. For others of you, hopefully, this will be a refresher. And for those of you who are just joining us for the first time, hopefully, this will be a wealth of information and education for most of you.



General Characteristics

Okay. So, just to start, because many may not know much about this disease at all, this is a very common leukemia. It's by far the most common in adults. And remember, I think one of the things that I want to stress to you about this particular type of disease in general is that it is chronic by nature. And so, the reason why it's CLL--I mean, first of all, I wish I could say that it's chronic because we have cures that could get rid of it, and it wouldn't be chronic. But, unfortunately, right now, it is still yet un-curative, although I'll talk about some differences amongst that in a little bit. But, people live a very long time with CLL.

And, in fact, the survival keeps getting better and better because the therapies keep getting better and better. So, I want you to know that there's a lot of hope on the horizon because the treatments are getting better, and people are living longer with this disease. Now, it is a disease of older individuals, so keep that in mind, so it does increase by decade. Although I do see, obviously, in my practice, I do have patients in their 40s and 50s. But, generally speaking, the median age of diagnosis is in the early 70s.



What Is CLL/SLL?

Now, what is leukemia? It's really a type of cancer that's in the blood and the bone marrow. So, think of your bone marrow as machinery, a factory that you make all your blood counts, both your good blood elements but also these leukemia cells. So, that's called the leukemia portion. Some people--I want to talk a little bit about those that say, "I have SLL or small lymphocytic lymphoma." I want you to know that CLL and SLL are the same thing.

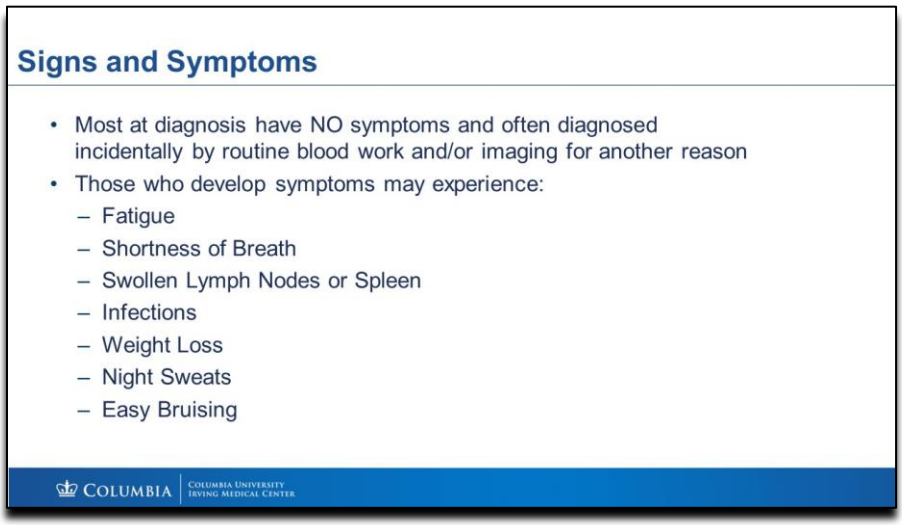
In other words, it really depends on where the disease is burdened in a particular individual. For some individuals, this is really in the blood and the bone marrow, and that's their greatest manifestation of the disease. For others, they really have bulky lymph nodes, but their blood counts are relatively preserved. And so, I just want you to know that when we look at these cells under the microscope, there is no difference between them. They are the same disease. It just might be that the burden of your disease might be in one compartment versus another, or in both compartments. And so, when folks who do need treatment for this disease, the treatment is obviously systemic. In other words, it goes everywhere. And so, it will treat whether it's in the blood or the bone marrow or other organ systems.

And remember this, again, is different than a solid tumor cancer, so different than, let's say, lung or breast cancer or colon cancer where there's a mass, and the doctors try to remove it for curative intent, so that it doesn't spread to other places. This is in your blood, and your blood circulates everywhere. So, if I'm going to do a biopsy for a different purpose on your toe, I'm going to see blood in there, and there will be lymphocytes there.

So, I want you to think about it as it is systemic, it is all over, because your blood vessels are everywhere. And the lymph nodes are part of your hematopoietic or your blood system, so they're part of the disease as well. So, remember, SLL and CLL are the same thing, but some people may have been told by their doctor they are more SLL because they really have big, bulky lymph nodes, and their blood counts are relatively preserved.

What's the cause of the reason why people can develop this condition? There are obviously many risk factors. We think about chemical exposures, such as Agent Orange and benzene or major environmental exposures to toxins, Chernobyl, 9/11, major disasters, which obviously can predispose patients to actually not just CLL but other cancers too, right? So, those sort of major environmental disasters or chemical exposures can affect DNA and then predispose one to CLL or even other cancers. So, those are potential causes and risk factors.

There is a small entity of patients where CLL does run in the families. This isn't very common, but, certainly, this is one of the reasons when we are first meeting a patient, we're asking about their family cancer history to find out if there are potentially other members in the family that have CLL. Or, maybe there are some other predispositions to cancers, not just CLL, that runs in that family, and perhaps they may warrant genetic testing.



Signs and Symptoms

Really, when we talk about signs and symptoms of the disease, at diagnosis, many patients don't have any symptoms, and they're really diagnosed on routine blood work, either with your primary care doctor or your internist. Or, maybe you're having imaging or testing for another reason, going in for surgery for a knee replacement, and they notice that on the blood work, your lymphocyte count is a little elevated. Or for women, they're doing a mammography, and they pick up a lymph node on the mammogram, and that prompts an evaluation.

So, most patients are really diagnosed with no symptoms whatsoever. Those who may have symptoms can experience fatigue. And, obviously, this is one of those symptoms that is really hard to grapple with because sometimes, for sure, it can be related to the disease. Sometimes, there are different reasons somebody should be fatigued. So, I encourage all of you to speak to your healthcare providers because sometimes, there might be a different reason why somebody has fatigue, and it needs to be figured out and looked into.

Shortness of breath can sometimes be a complication or a symptom that patients can develop. When we talk about the red blood cells, in particular, if somebody's red blood count is low, they can feel tired

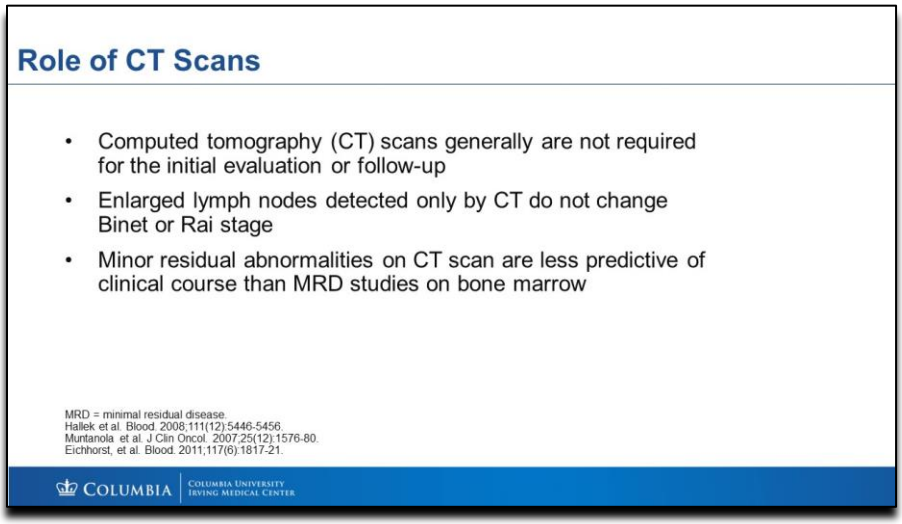
or fatigued due to that reason. Think of the red cells. They carry oxygen to your organs. And if you're anemic, or the red count is low, sometimes people can experience fatigue and shortness of breath when they're doing activities.

Swollen lymph nodes or a big spleen--your spleen is like a big lymph node--and so, again, that might be a symptom or a sign, I should say, that you notice because you might have enlarged lymph nodes, which are part of the disease. Infections are common with CLL patients. So, I kind of liken CLL to a disorder of your immune system. And, for many of these, some patients do get recurrent and frequent infectious complications. They can get bronchitis or pneumonia, sinusitis, skin infections. And so, we always talk to patients to remind them to call their healthcare providers when they have infections going on.

Weight loss is something that patients can sometimes experience as well. Usually, it's in the setting of progressive disease. And so, it's not something that normally we see all the time in CLL, but certainly it does warrant a discussion with your healthcare provider to make sure there's not another reason why someone is losing weight. But, if somebody is losing weight due to the disease, there might be some progression going on.

And similarly, night sweats, that also goes along with progressive disease as well. So, sometimes, when people experience more frequent night sweats, the metabolic activity of these CLL cells sometimes can contribute to that. And so, sometimes that we'll see when patients are progressing. If patients have low platelet counts, so the platelets help one from stopping bleeding, right, so if the platelet count is low, then somebody might experience easy bruising or bleeding.

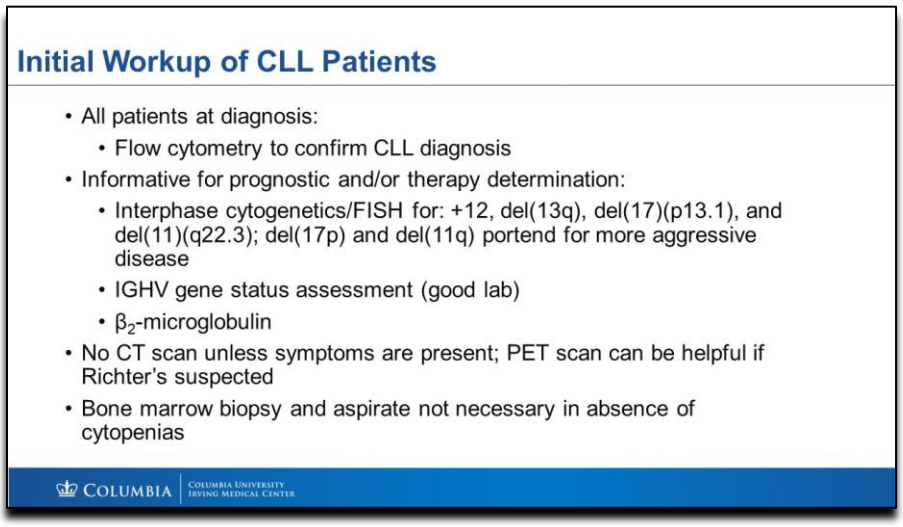
And so, that's something that someone should be on the lookout for as well. And, again, any easy bruising or bleeding, you should bring that to the attention of your care provider as well, so they can check on your blood counts. So, those are some of the symptoms that some people--this is not an exhaustive list by any means, but I just wanted to touch base on a few of those.



Role of CT Scans

Now, patients always ask me about CAT scans. I say to folks that, typically, CAT scans are not something that is done routinely for CLL patients. Certainly, if somebody has got really big, bulky lymph nodes, and I want to also evaluate whether they have big, bulky lymph nodes in areas I can't feel, like the abdomen and pelvis, then a CAT scan is often performed, or if somebody has a complaint of something. So, obviously, if you have abdominal pain or there's an issue, your doctor is likely going to be ordering a CAT scan to find out why.

But, routine imaging on an annual basis just to check the lymph nodes without any symptoms is not routinely done in CLL. So, again, you might do it for a staging prior to starting therapy. You might do it if somebody has got a complaint or if you're concerned that maybe they are hiding a big lymph node that you want to assess to make sure there's not compression on an organ system.



Initial Workup of CLL Patients

In terms of how patients are initially worked up, this is, thankfully, mostly done by routine blood work. So, if your doctor noticed that your white count was a little elevated, they will send some blood work. It's called a flow cytometry test. And what this does is, this will tell us about the proteins or the markers that are on your B cells. You have normal B cells. These cells happen to be abnormal. And, so, it can tell us the markers that are on your B cells. And are they normal or abnormal? And what are these markers?

Because there are other lymphomas and leukemias that also will have different markers on their B cells, and that tells us one disease from another. So, that's called the flow cytometry test. There are some prognostic markers that might be drawn as well. This sort of tells us a little bit about the biology of your CLL compared to someone else with CLL. This is a test called cytogenetics or FISH, fluorescent in situ hybridization. And, essentially, we're looking at chromosomal abnormalities. You are born with these. The chromosomal abnormalities are associated with your CLL cells.

And some have--they give us a little bit of a guidance of prognosis. Just like when you see your internist or your primary care doctor, when they're asking you questions and thinking about your medical problems, they're looking at: Do you have diabetes? Heart disease? How's your kidney function? They can actually make a scoring system of--in--with regards to your medical problems of, what's this person's risk for a heart attack or stroke?

Well, similarly, in CLL, these prognostic markers, these chromosomal abnormalities, tell us a little bit more about your biology compared to somebody else. And so, oftentimes, this might get checked at diagnosis. If not, it should get checked prior to initiating therapy because it does sometimes self-select, although we'll get to therapy shortly. For sure, there are some therapies I might recommend differently depending upon somebody's cytogenetics.

The immunoglobulin heavy chain gene rearrangement, that's that IGHV. That also looks at the maturation of your B cells and whether are they immature or mature? And that gives us some prognostic information—whether somebody is, what they call, mutated or unmutated. It also gives us a little bit of prognosis--tells us, again, somebody who might need treatment sooner versus not. There

are a slew of prognostic markers, and I just listed a few. The beta-2 microglobulin is another prognostic marker as well, but there are many, many more.

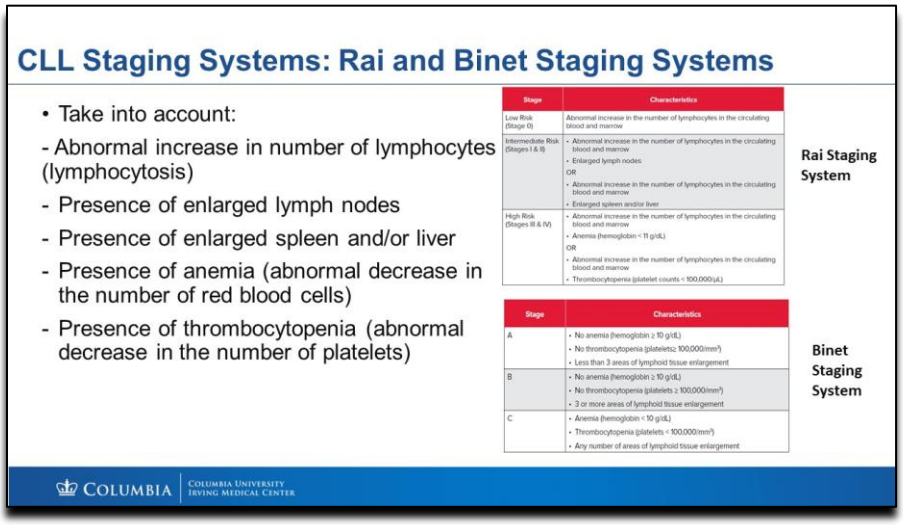
And, we just tend to use this information to figure out where, under the curve, what might be the tempo of your disease based on some of these prognostic markers. And, again, we don't routinely do CAT scans unless there's a reason to do a CAT scan. So, if there are symptoms that one is experiencing, maybe prior to starting therapy, we'll definitely do a baseline CAT scan. But, if there's otherwise no symptoms, we're not just going to routinely scan you every year just to follow the lymph nodes. Okay?

Now, what about a PET scan? People ask me about PET scans. A PET scan is a different variation. It's actually a PET CAT scan. The CAT scan will look at the size of your lymph nodes, all your organ systems. We can look for infection that way. It tells us a variety of information that is 3D and structural. A PET scan actually talks about avidity. It will look at metabolic activity of your lymph nodes. And this can be helpful if I'm concerned that maybe somebody's disease is progressing or behaving more aggressively than I would normally think. And, in some CLL patients, they can transform to a more aggressive lymphoma.

And so, if somebody has a lot of symptoms, a PET scan might be warranted because they're going to look to see, "Is there a lymph node that is behaving a lot more hot or angrily than what we would normally see on a PET scan for patients with CLL or SLL?" And then, that would help guide the physician and team to say, "Hey, that's a lymph node I want to biopsy because it looks a lot more hot than the rest of the lymph nodes," and to utilize that PET scan for a biopsy to see whether or not somebody has changed their disease from CLL or SLL to a diffuse large cell lymphoma or Richter's transformation.

Bone marrow aspirates and biopsies are not done necessarily at diagnosis. Obviously, because of the advent and sophistication of our peripheral blood testing, not everybody needs a bone marrow aspirant and biopsy. I still think they are important. There are some patients who have immunologic complications associated with their disease where a bone marrow might be helpful.

Sometimes, we'll do bone marrows prior to starting therapy or to follow MRD (minimal/measurable residual disease), although, hopefully, our testing will get so much better that we won't need bone marrow evaluations all the time or in the future, if the testing gets really sophisticated off the peripheral blood. We know that these can be unpleasant procedures. But, sometimes, they can be extremely important if somebody has got pure red cell aplasia or, again, another immune complication of CLL, which could be more rare.



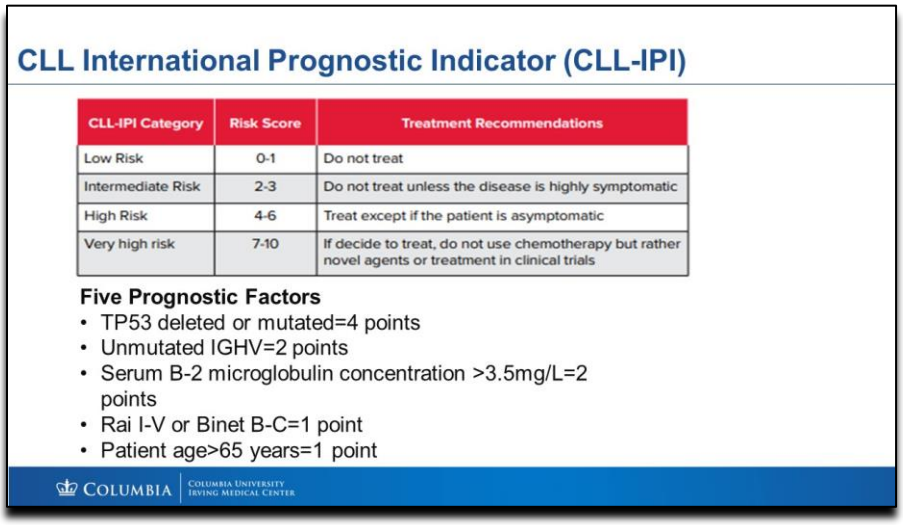
CLL Staging Systems: Rai and Binet Staging Systems

The staging system in CLL takes into account both your lymphocytes and your lymph nodes and whether or not you have organ involvement or liver involvement. And, it takes into account your good blood cell counts like your red cells and your platelets. And so people always ask about staging systems in other cancers, particularly, obviously in solid tumor cancers, where, as I said, if there's a mass, and they want to remove it, they'll often do a CAT scan because they want to make sure it's not in other organ systems. This is everywhere.

But, how the staging system is first used is that when somebody first gets diagnosed, if they just have a lymphocytosis, (an increase in the number of lymphocytes) they don't have any lymph nodes, and their other blood counts look good, we consider that early stage because the likelihood is that person won't need treatment for a very long time because they only have a lymphocytosis present.

So, it helps us a little bit to tell us about somebody's prognosis when somebody first is diagnosed with CLL. If somebody has lymphocytosis or big lymph nodes, and their blood counts are low, that staging system is more advanced. In other words, all that tells the doctor is that that person is more likely to need therapy in the near future versus somebody who just has a lymphocytosis. So, that's where we use just a little bit when somebody is first diagnosed, how to use the staging system?

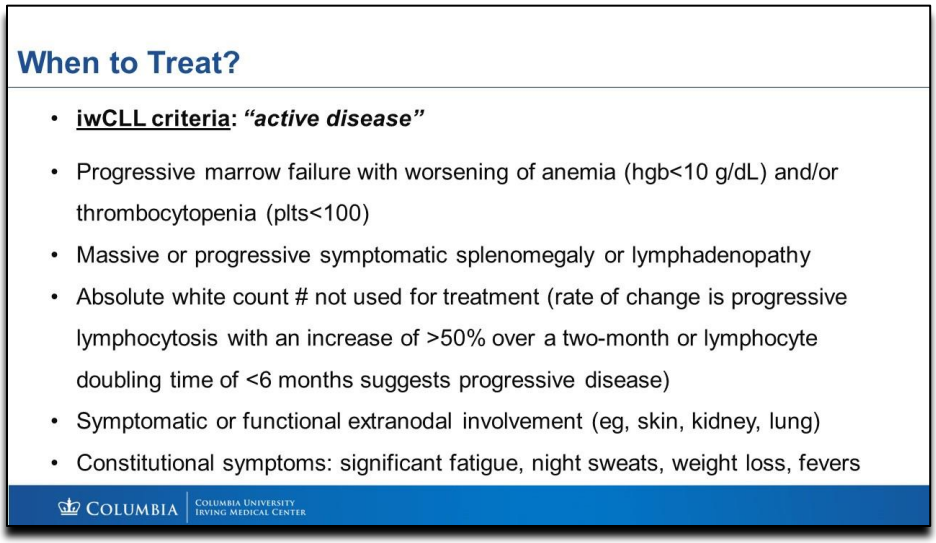
Otherwise, when somebody is treated, obviously, the goal is to improve the lymph nodes and the blood counts and, then, that sort of staging system has limited utility later on. So, it's used at diagnosis just to give a sense of where somebody is in their CLL journey.



CLL International Prognostic Indicator (CLL-IPI)

There are prognostic indicators that the physicians and teams can do just to sort of guide them when somebody, again, is initially diagnosed, to say, “Hey, how soon are they close to needing treatment?”

And they’ll take a bunch of prognostic markers, and they could do a scoring system and say, “Is somebody low risk, where they don’t need any treatment in the near future versus if they have a lot of factors and points that they’re going to be considered high risk?” Those patients are probably going to need treatment very soon.



When to Treat?

Now, the big question always everybody asks is when to treat. And, so, there’s actually some guidelines, although they are guidelines. They are called the International Working Group. There’s actually a small committee. The IWCLL, or International Working Group in CLL, meets every other year. The folks who do research, whether it’s clinical or translational in the laboratory, get together every two years to sort of talk about their research and go through guidelines and new treatments. And so, there’s criteria that’s been generated over the years.

And so, patients who have worsening of their good blood counts, that, again, we talk about the red cell counts. If that is low, someone is likely to be more tired and fatigued. That would be an indication for

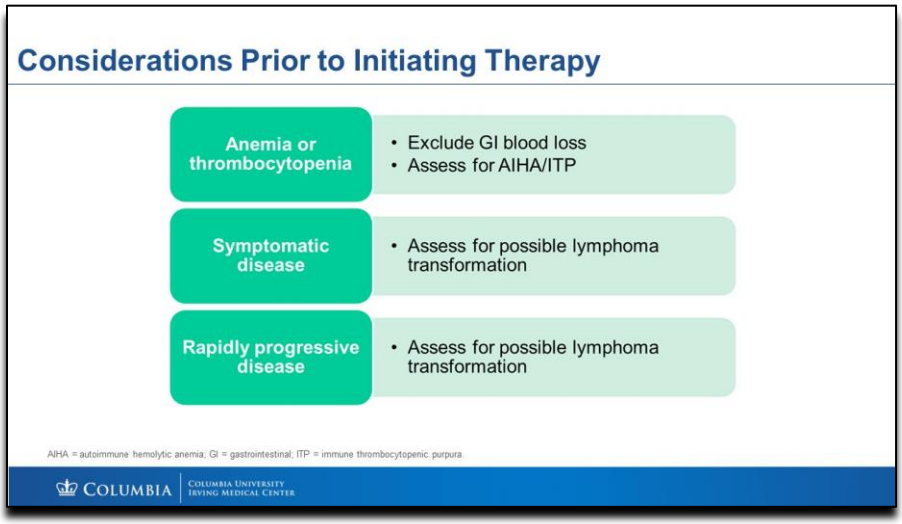
treating somebody. Their platelets, as I said, help with clotting or bleeding. So, if those were low, that would be more likely to have easy bruising or bleeding. That would be a reason to treat somebody.

If somebody has got really big and bulky lymph nodes or a big and bulky spleen that's causing them to lose weight because they are full, because their spleen is so large, or they have a bulky lymph node compressing on something, that would be another reason to treat somebody. The absolute white count, in and of itself, is not the indication for treatment. So, what's most important here is when you see your physician and are monitored, they're looking at your blood counts, and they're examining you.

And they're looking at both of the trajectory of what your body is doing at the time. So, in other words, they're following your white blood cell counts to look at the rise, but it's the rate of change that we're really following. So, if your white count is high, but it's stable, then it's irrelevant. But, if somebody is rapidly rising, and their white count goes from 40 to 80 to 160, and so on, in a very short period of time, that tells us something that the marrow, the lymphocytes and the marrow, are obviously accelerating and likely means that your good counts will start to decline.

So, I use the rate of change to say, "Hey, I might want to see that person sooner in the clinic. I might want them to have a sooner appointment because there's a change on the rate of their white count rising." And so, that's where it's important. There's not a number that we say, "Hey, that is an indication to start treatment in relationship to your good counts." That will probably be seen more in the skin, the kidneys, the lungs. These are less common, but sometimes that might be a reason to treat somebody as well.

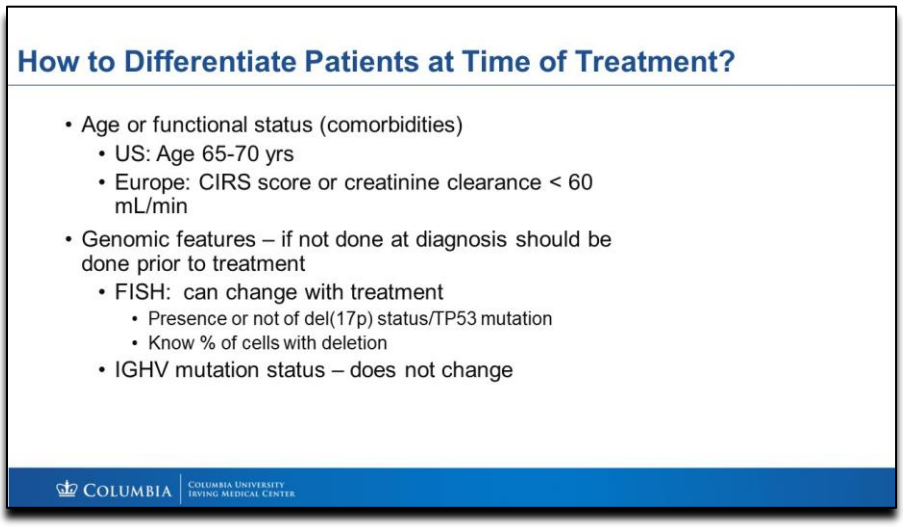
And then symptoms which, again, usually, typically, will go with progressive disease, meaning a change of their blood counts or their lymph nodes, fatigue, night sweats, weight loss, fevers. Those usually go along with progressive disease as well. They're usually not in absence. If they are, usually, I'm doing a workup to try to figure out why.



Considerations Prior to Initiating Therapy

So, what do we think about prior to starting therapy? One is we want to make sure it's due to your CLL. Sometimes, somebody might develop isolated anemia; in other words, their blood count can drop, their hemoglobin can drop, but their other counts are exactly the same. Their white count hasn't changed. And maybe there's another reason that that is happening. Maybe they're having some GI blood loss. Maybe they're having an immune complication. And so, it's always important for the doctor or the care team to try to figure out why. Just, it may not always be just your CLL.

If somebody has got really rapidly progressive disease or a lot of symptoms from their disease, that's when, again, I'll think about a CT PET scan, because has the disease progressed or transformed to a more aggressive lymphoma if they're rapidly progressing? So, there are some other considerations prior to initiating treatment for CLL in and of itself.



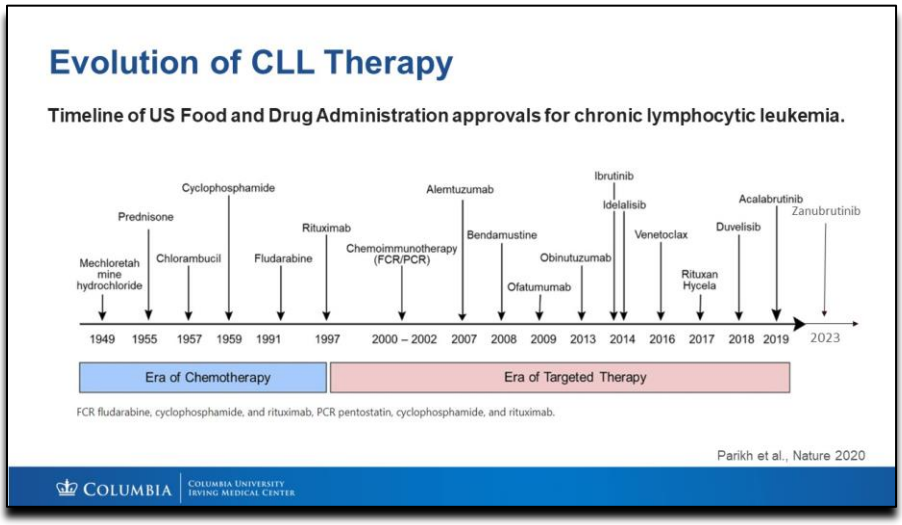
How to Differentiate Patients at Time of Treatment?

When we think about you all, when we're about to start any sort of treatment, we do think about your medical problems. The good news is age, in and of itself, isn't the reason for somebody not to get treatment. Back in the day when we just did chemoimmunotherapy, there were many treatments that older folks would not necessarily be able to tolerate.

Now, in the era of targeted therapies, I think that there's a rare individual where I'll really say they cannot. I don't think I have said that someone couldn't be treated. There's ways around that because of the targeted therapies and the side-effect profiles of some of these newer treatments. But, what we're really talking about age is we're really talking about your other medical problems. We're talking about comorbidities.

So, how is somebody's heart function, their kidney function? Do they have uncontrolled diabetes? What is their blood pressure like? So, we really talk about comorbidities. The Europeans actually have a scoring system that they'll use that takes into account all their comorbidities and, then, rank a scoring system that talks about functional--how somebody is functionally. And that's important to us when we talk about therapy.

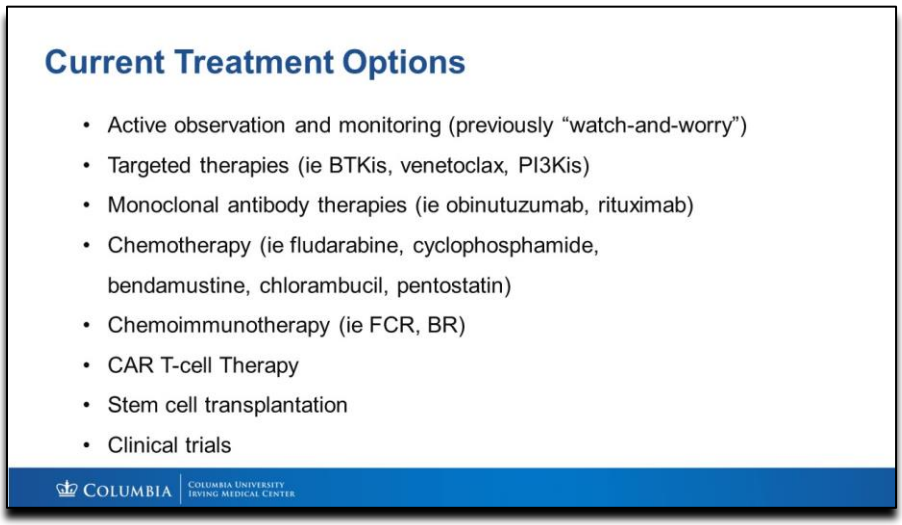
And then, we also do factor in your disease characteristics, some of those prognostic markers that I talked about earlier. We talk about does somebody have a deletion 17p or p53? Those are higher-risk features to have. And so, sometimes I might select certain treatments, depending on somebody's disease characteristics. So, we do take all that into consideration when we talk about treatment.



Evolution of CLL Therapy

Now, the good news is there's been an evolution of treatment that has occurred over time. For somebody like myself who came in on the chemoimmunotherapy era, so back in 2000--early 2000s--and ran some of these early chemoimmunotherapy trials with fludarabine (Fludara®) and cyclophosphamide (Cytoxan®) and rituximab (Rituxan®) and PCR [pentostatin (Nipent®), cyclophosphamide, rituximab], it has come a long way between chemoimmunotherapy and, then, targeted therapies.

Ibrutinib (Imbruvica®) was the first of the targeted therapies. That was approved in 2013. And now, we have all these newer therapies that have improved survival, and we're going to talk about these. But, the good news is survival keeps getting better and better, and we're understanding the biology better of CLL and our newer--and these newer--therapies share with that.

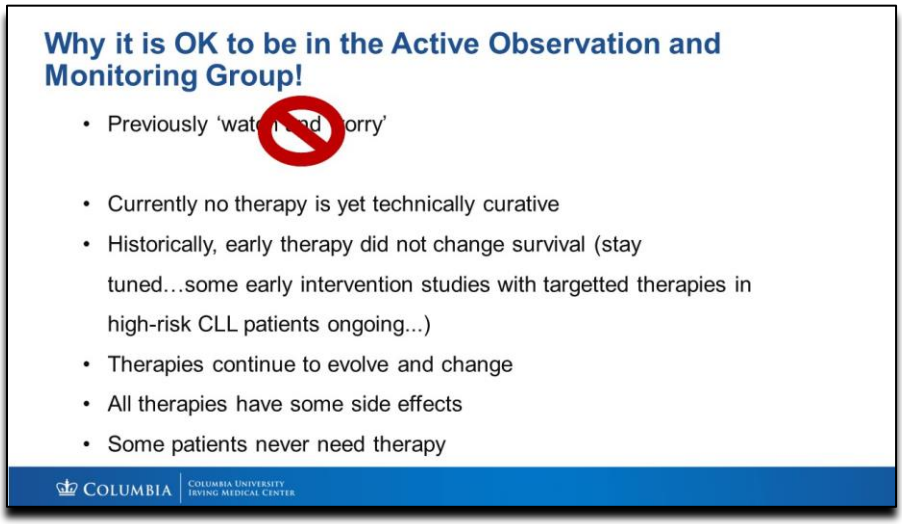


Current Treatment Options

Currently, when we talk about different treatment options, we're going to talk about all these a little bit. So, we're going to talk about the active observation and monitoring group. I like to call that the previously watch-and-worry because I don't like that term. My patients know I don't like that, and we're going to talk about that in a minute. Targeted therapies, BTK inhibitors, venetoclax (Venclexta®), and PI3 kinase inhibitors that are currently FDA-approved, the monoclonal antibody therapies, obinutuzumab (Gazyva®) and rituximab--there are some other monoclonals, ofatumumab (Arzerra®),

alemtuzumab (Campath®), they're not used as much anymore. But, I'm just talking about the more common ones.

Chemoimmunotherapy, or chemotherapy, really stemmed with fludarabine, cyclophosphamide, bendamustine (Belrapzo®, Bendeka®, Treanda®, Vivimusta), chlorambucil (Leukeran®), pentostatin, and there are others. Chemoimmunotherapy is the same as chemotherapy but with the addition of a monoclonal antibody. So, like FCR had the addition of rituximab, or bendamustine plus rituximab. That's chemoimmunotherapy. There's CAR T-cell therapy. We'll talk about other immunotherapy, stem cell transplant, and, of course, clinical trials.



Why It Is OK to Be in the Active Observation and Monitoring Group!

So, let's talk about the active observation and monitoring group because many people are in this group for a period of time. Everybody calls it watch-and-worry. I don't like that terminology. Of course, I understand the concern about, here you've been just diagnosed with something that is a blood cancer. And, unlike other cancers, you're not being treated. And, obviously, this doesn't fit in our paradigm of what we do for most cancers. You get diagnosed with something, you're treated, you either have surgery or chemotherapy. The goal is cure.

As I currently said before, there's no technically yet curative therapy that we have for CLL. There's no doubt I have had patients in my practice for 20 years who got one treatment and have not yet re-occurred And yet--so, they could be cured. But, that is not the majority of patients right now with the therapies that we have. So, that's why we currently say we don't have curative therapy for CLL, albeit, again, there's a couple of patients who have done extremely well with certain therapies.

Historically, when we did treat patients early, so there were some early intervention studies that we did with chemoimmunotherapy, it did not change survival. And, in fact, gave patients side effects from those therapies. And that's why patients are initially monitored and observed because there's a time period that many may not need therapy for many years.

And we haven't proven that starting therapy earlier would change that and, in fact, might give you: A) more side effects, B) might also cause some resistant mutations which will, then, mean that you have less options down the road in terms of therapy, depending upon how old you are or where you are in your CLL journey. So, this is why there is an active observation and monitoring group.

There are--stay tuned, though--with targeted therapies, there are some new trials that are looking at whether or not some of these targeted therapies in patients with high-risk CLL, features that are more aggressive, like 17p or p53, could be randomized to starting treatment on a targeted therapy early

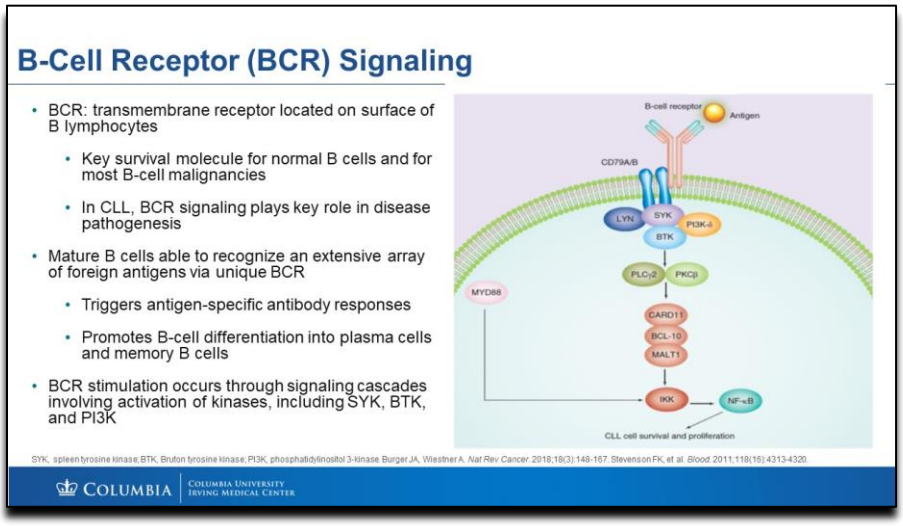
versus waiting until when they need therapy by the criteria that I showed you earlier. So, stay tuned for those trials. Outside of a clinical trial, we would not want to do that because we have not proved it a benefit. And that's why there's this active observation and monitoring.

The other reason to want to be in this group is that the therapies continue to evolve and change, and more so in the past 5 to 10 years than in the prior 10 years when I started in the chemoimmunotherapy days. And, so, what that means is what I might be doing today for a patient may be different in a few years.

And that has--the person who is on the active observation and monitoring group has--the benefit of sitting on the sidelines and monitoring how that might change and how that might be, in a good way, impactful for their future treatment. So, that's why I think I need to switch all your notion about this watch-and-worry, and you really need to think about why it's important to be in right now.

There's also about a quarter of patients who never need treatment for their CLL. And I wish I could do a blood test and knew who you folks were because then we would say you never need treatment. And you can follow your internist or your primary care doctor for your other medical issues and never see me again.

But, until that happens, if you don't need therapy, you don't want it necessarily. All therapies have some sort of side effect. If you do not need therapy, until we have something curative, you should stay on the sidelines. And so, I want you to keep that mind. And, hopefully, I've changed your notion from watch-and-worry to active observation and monitoring.

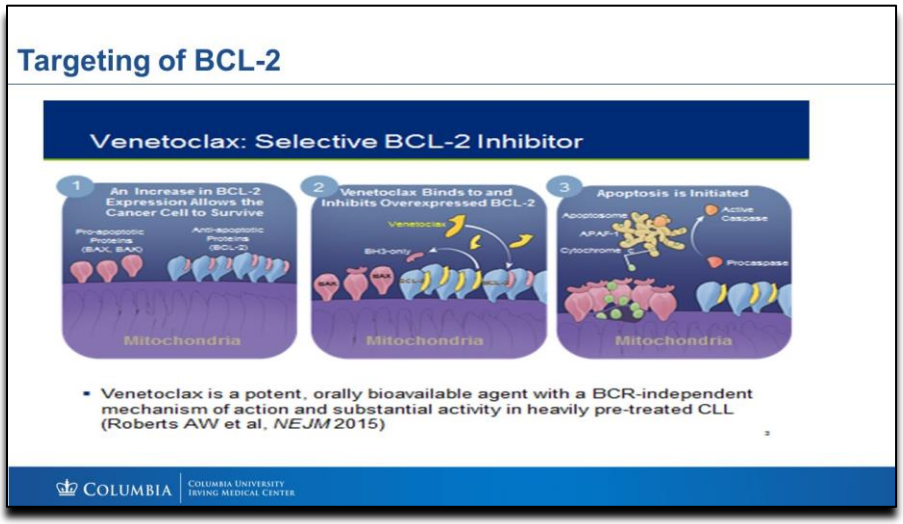


B-Cell Receptor (BCR) Signaling

Now, I'm going to focus on therapies, which I know everybody is more excited about. So, let's talk about how we learned a lot about the biology in the past 10 years from chemoimmunotherapy to now these targeted therapies. We've learned a lot about B-cell receptor signaling. This is--the B-cell receptor signaling--this is a transmembrane receptor on your B lymphocytes. And there are key proteins and survival markers--molecules that are involved in sort of the proliferation and differentiation of your B cells, from normal B cells to abnormal B cells.

And these are key molecules that are really important in the survival of your B cells and, again, both good or these malignant B cells. And so, as we learned about the pathway of your development, proliferation, and survival of your B cells, we've been able to target some of these key proteins, which has led to the improvement of survival in patients with CLL. And we're going to focus on BTK. There were many trials targeting some of these other proteins as well, PI3 kinase, SYK, LYN. We've definitely

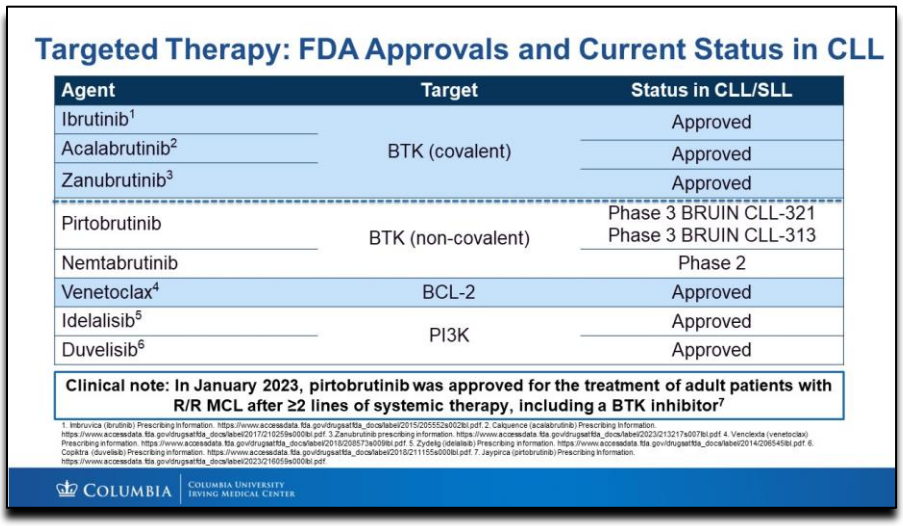
had trials in many of these. And, obviously, some of these are now FDA-approved, such as the BTK inhibitors and the PI3 kinase inhibitors.



Targeting of BCL-2

BCL-2 is something different. So, BCL-2 is over expressed in patients with CLL and other lymphomas. And this, actually, is a regulatory protein that has to do with apoptosis [cell death]. And so, normally, if you over-express BCL-2, you allow your cancer cells to survive. And we've been fortunate enough, many years ago, to have developed a targeted therapy that obviously is able to bind to BCL-2 and inhibit it, so now the cancer cells can die. And that's been a very successful strategy.

And so, these are the two main key players currently in CLL treatment, the BTK inhibitors and the BCL-2 inhibitor, of which there's only one currently approved right now.



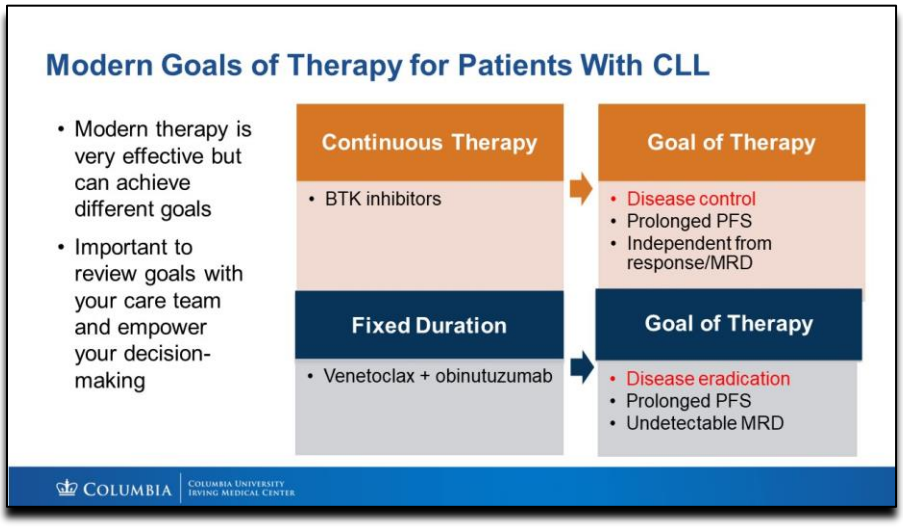
Targeted Therapy: FDA Approvals and Current Status in CLL

And so, when we talk about the approvals in CLL, we have three covalent BTK inhibitors, ibrutinib (Imbruvica®), acalabrutinib (Calquence®), and zanubrutinib (Brukinsa®), which actually just got approved in January of this year.

And then, we're going to talk about some agents that haven't yet been approved for CLL. These are non-covalent BTK inhibitors. The furthest along in development is pirtobrutinib (Jaypirca™) and

nemtabrutinib. Pirtobrutinib actually just got approved for mantle cell lymphoma patients that have been relapsed after two prior lines of therapy. So, it is available for mantle cell lymphoma patients.

And then, the only BCL-2 inhibitor that's currently approved right now for CLL is this drug called venetoclax (Venclexta®). There are others in development, so stay tuned. There are other BCL-2 inhibitors in development. And then, the PI3 kinase inhibitors are--there are two that are approved for CLL, but they are approved in the relapse phase, meaning in patients who have had prior treatment for their disease. And, this is idelalisib (Zydelig®) and duvelisib (Copiktra®).



Modern Goals of Therapy for Patients with CLL

So, when we talk about therapy, what are the goals of therapy? Obviously, I told you we're trying to find curative therapy, so stay tuned. Obviously, the ultimate goal would be to cure everybody with this disease. With these new treatments, I would not say that they are curative yet.

So, when we talk about therapies, we talk about the way these drugs have been approved. And I'm going to show you some of the clinical trial data for those because I know some of you have already been on this journey and want a little bit more meat. So, we are going to talk about the clinical trials that have led to some of these drugs being improved.

But, the BTK inhibitors are currently--and these are pills--are currently taken as a chronic continuous therapy. And they are very, very effective. And so, they provide very good disease control. They shrink lymph nodes; they improve blood counts. But, the reason why you stay on therapy is that we notice that there is always a little bit of disease left over. In other words, in and of themselves, they do not eradicate the disease.

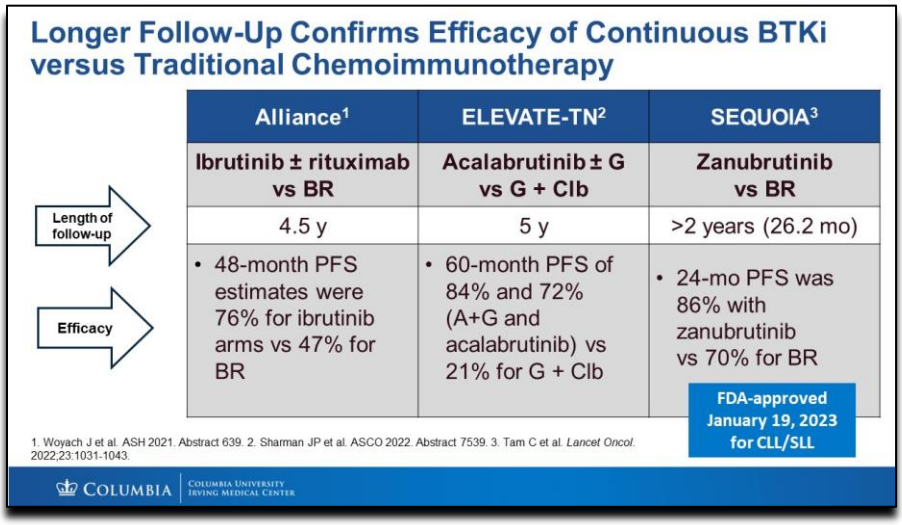
So, if I were to look at somebody's bone marrow, even if their blood counts are normal, there's still going to likely be a little bit of CLL in their bone marrow. So, we sort of, kind of, use them as sort of chronic suppression on the disease. And they're excellent. They have very good disease control.

On the flip side, the BCL-2 inhibitor, venetoclax, does a really, really good job at mopping out the bone marrow. And so, it's been partnered with CD20 monoclonal antibodies, obinutuzumab in the front line and rituximab in relapse, to sort of do a time-limited approach. So, can you give a short course of therapy, give patients a break because the disease can be--people can have what they call low-level or undetectable disease after they finish a course of therapy--and then go back on monitoring again until such time that they might need treatment again for their disease?

So, these are the two main paradigms of how most patients are currently being treated. And here, as I said, the ven-obinutuzumab is a 12-month therapy as opposed to chronic, continuous taking a pill every day with the BTK inhibitors. We do not know that one strategy is better than another. And, in fact, they're both extremely--very, very efficacious therapies.

We do not yet have head-to-head data, although there will be some trials that will look at that, but the point being is that they are both really, really good. And, I'm going to talk a little bit about the nuances of each of those therapies and some of the side effects of those therapies.

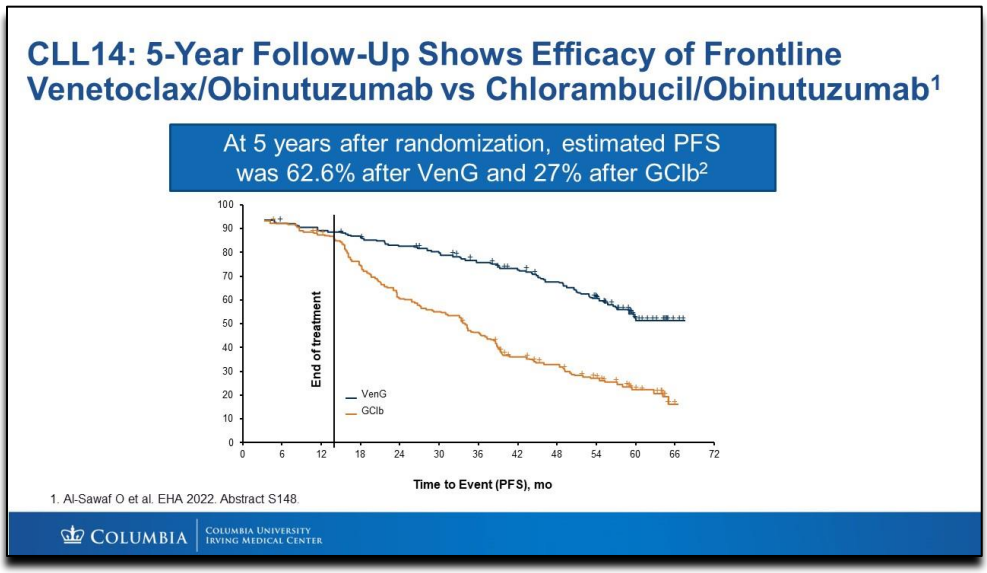
But, oftentimes, don't be surprised. Patients, depending upon where you are in your journey, if you're very young, you might be seeing both of these therapies during your lifetime. And so, it is not uncommon--so, when I think about when I'm starting a patient, they're always thinking about what we're going to get now. But, I'm always thinking about the next line, the next line, the next line. So, you always have to think ahead for all of you as well.



Longer Follow-Up Confirms Efficacy of Continuous BTKi Versus Traditional Chemoimmunotherapy

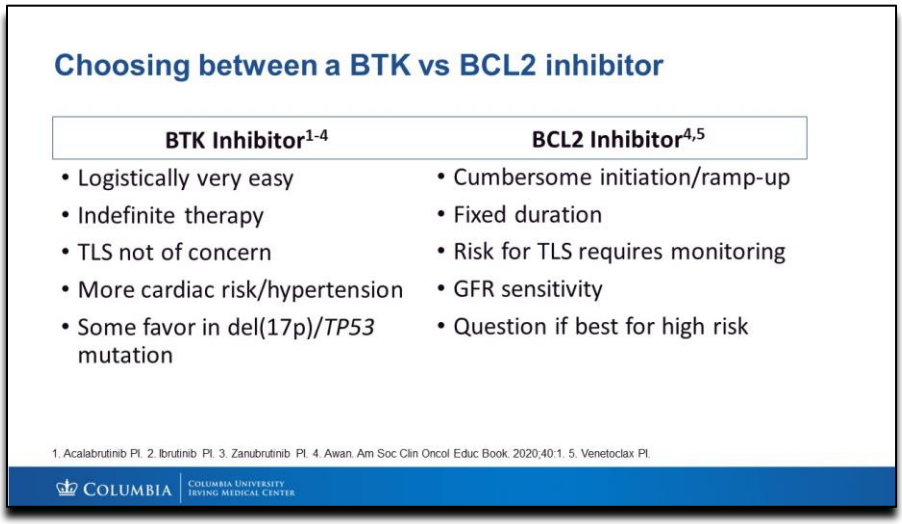
So, just to give you a little bit of data to say why BTK inhibitors have been so efficacious is that, again, ibrutinib was the first to market back in 2013. So, we have 10 years of data now on BTK inhibitors. And when they were compared to the more traditional therapies that we had, that was in the era of chemoimmunotherapy, the progression-free survival--and what that means is, progression-free survival is the length of time during and after treatment that somebody is living with the disease and has not progressed.

And so, when we compare the BTK inhibitors compared to chemoimmunotherapy, the BTK inhibitors did better with progression-free survival than traditional chemoimmunotherapy. And that's why you'll see that there's been a move away from chemoimmunotherapy for patients with CLL in favor of these targeted therapies, such as the BTK inhibitors. And this is just some of the summaries on all of the different BTK inhibitors, ibrutinib, acalabrutinib, and zanubrutinib. They've all shown superiority with regards to progression-free survival in patients with CLL.



CLL14: 5-Year Follow-Up Shows Efficacy of Frontline Venetoclax/Obinutuzumab Versus Chlorambucil/Obinutuzumab[1]

Now, flip side, the venetoclax and CD20 monoclonal antibody, obinutuzumab, also had a randomized study looking at that in comparison to traditional chemoimmunotherapy with chlorambucil and obinutuzumab. And, you can see here that after five years, the PFS [progression-free survival] was again better with venetoclax and obinutuzumab versus chlorambucil and obinutuzumab. And, so again, a move away from traditional chemoimmunotherapy in favor of these targeted approaches.



Choosing Between a BTK versus BCL-2 Inhibitor

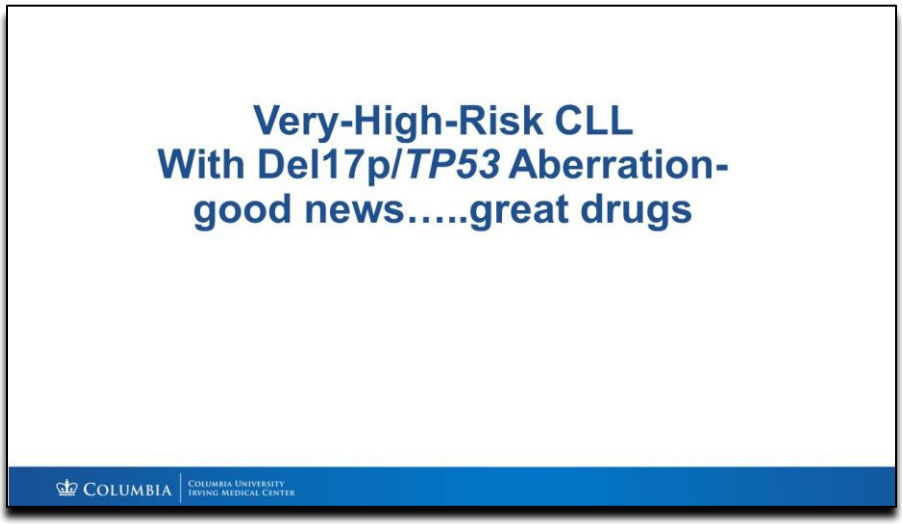
So, how do you choose between the two? And this is where we start nitpicking a little bit. So, one is a BTK inhibitor, ibrutinib, acalabrutinib, and zanubrutinib, are logistically very easy to start. It's a pill. There's not a lot of monitoring that is required when it comes to blood issues, blood monitoring.

Tumor lysis, that's the rapid breakdown of your leukemia cells that sometimes can then play havoc with your kidney function and your electrolytes is rare to happen with a BTK inhibitor. So, again, not a lot of monitoring. There are more cardiac risk factors and hypertension, and we'll talk about that. And, some of us favor BTK inhibitors as chronic, continuous therapy in patients with high-risk disease based on what we currently have from some of these clinical trials.

What about the BCL-2 inhibitor, venetoclax, and a combination of venetoclax and an antibody? It's a little bit more cumbersome to start. So, this requires much more monitoring of your blood counts and much more frequent visits to the doctor's office. If somebody has a lot of bulky disease, sometimes it even requires hospitalization even though it is a pill, ~~but it does--~~it causes a lot of tumor breakdown very quickly. And that havoc can cause a derangement in your electrolytes, like your potassium and your kidney function. And that can cause problems for you.

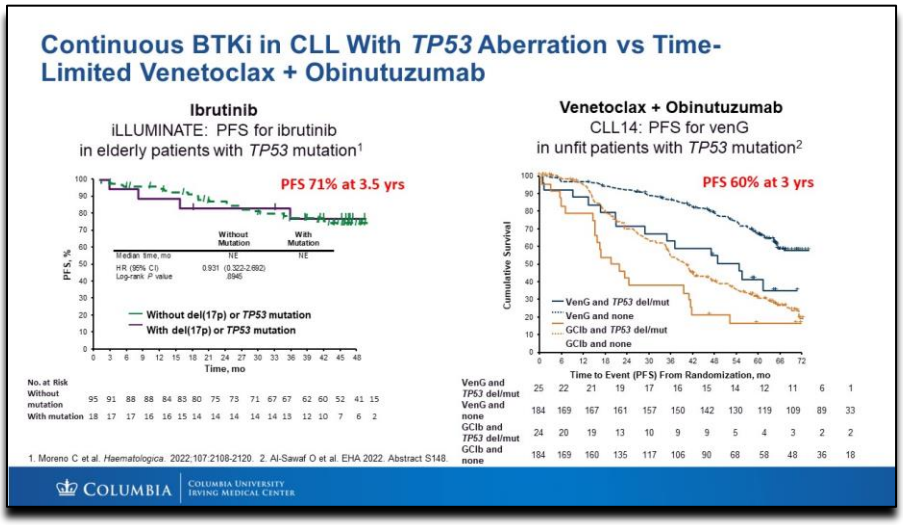
So, the best way for us to monitor you is by doing frequent blood work but mostly by actually giving you intravenous hydration with just saline to flush everything out and to give you some drugs that help keep those electrolytes in check, so that the tumor lysis doesn't become something that is threatening. And so, in the beginning, there is a ramp up of the venetoclax that happens over five weeks.

And so, there's a lot of visits to the clinic. Again, some might require, initially, a hospitalization in the visits to the clinic. And so, for the first two to three months of BCL-2 inhibitor plus antibody combination, there is a lot more work that needs to be done. Now, the payoff is that it's time-limited. So, at the end of 12 months, you're done. But, at the beginning, there's a lot more work. And so, that has to play a factor and a role when we discuss that with patients.



Very-High-Risk CLL with Del17p/TP53 Aberration—Good News … Great Drugs

So, what about patients with high-risk disease? So, patients with deletion 17p or p53? Because I know that there are those of you out there, and you read about this, and you read that you're high-risk. Well, the good news is these therapies work wonderfully well. And you have become a better-risk patient over the years because of these targeted therapies.

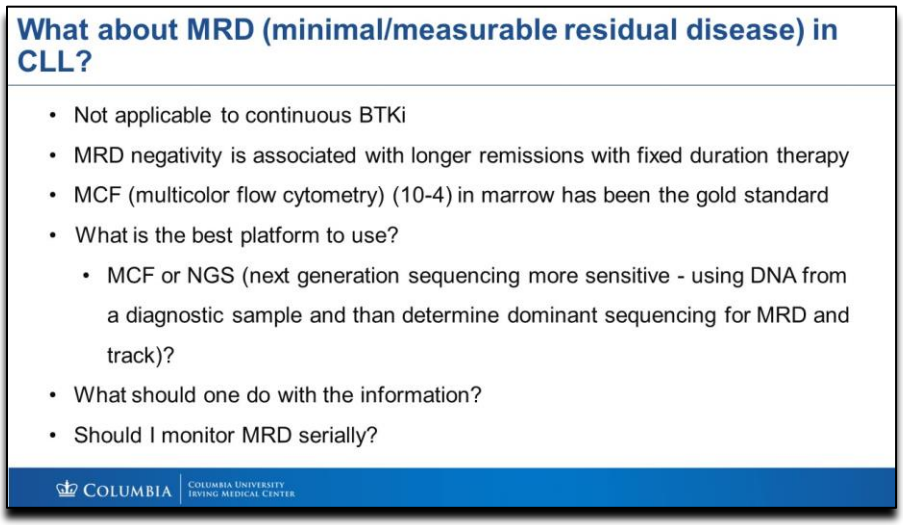


Continuous BTKi in CLL with TP53 Aberration Versus Time-Limited Venetoclax + Obinutuzumab

I'm just comparing ibrutinib and venetoclax + obinutuzumab, in this slide, just so you can see, but you guys are doing remarkably well. You can see on the left with chronic, continuous ibrutinib, whether you have the mutation or deletion or do not, you're doing just as good as other people. And so, we will tell--that anybody who has a 17p or p53 should not get chemoimmunotherapy for their disease at all, you should be getting a targeted agent. And that's where knowing that is important.

Venetoclax and obinutuzumab, that time-limited approach, also does really well for patients with high-risk disease. You can see on the right curve here. But, the PFS curve is a little shorter than that with chronic, continuous therapy. Now, mind you, these are not randomized studies. These are separate trials. So, we don't know--we haven't randomized to see, is it really, really different between patients with 17p?

But this is that notion that some of us will say, "Well, given this data, we're going to be really picky, even though everybody does great on a targeted therapy." Patients with 17p or p53, I often will recommend they get chronic, continuous therapy for now, until we have more data that talks more about the patients who are getting ven-obi or even oral-oral combinations. And, I'll talk about that in a little bit.



What about MRD (minimal/measurable residual disease) in CLL?

Patients also ask and read about minimal residual disease, or measurable residual disease. What is this? So, what this means is that we have sophisticated ways of looking at your disease when you're done with therapy, if you're on a time-limited approach. It's irrelevant for somebody who is taking a pill every day. If you're going to stay on a pill every day until the disease progresses, there's no need to check for MRD.

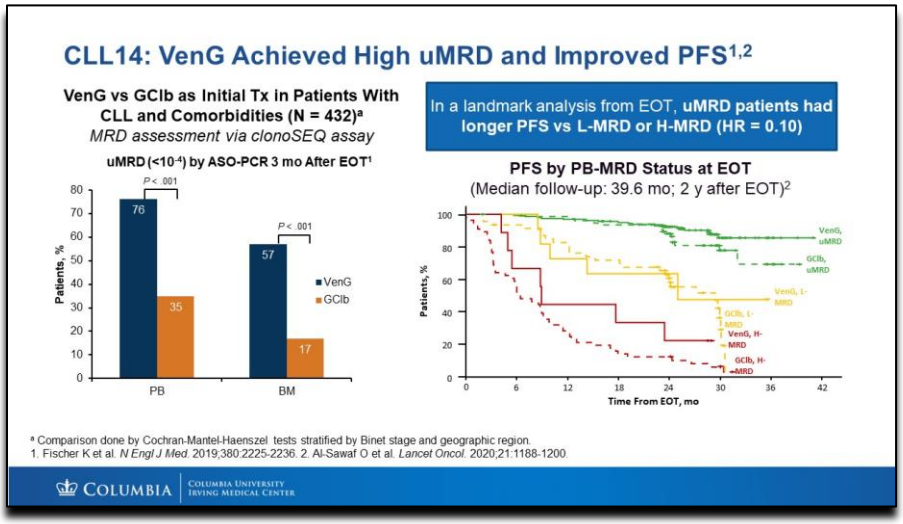
But, what we do know when we talk about time-limited approaches like venetoclax and obinutuzumab, is that if you're going to stop at a year, oftentimes, we're trying to get a sense--so this is on clinical trials right now--we're trying to get a sense of: Does somebody still have a little bit of evidence of disease? Who might be patients that we should think about, maybe they should be on it a little longer? Are there some where that matters? Are there other patients where it doesn't matter at all, and everybody should be stopping at 12 months or at 24 months of therapy?

So, this is an evaluation of your disease after you're done with therapy to see if there's any CLL cells remaining. In traditional or standard techniques, we use multicolor flow cytometry. That's that same test that we use to diagnose you in the first place.

And it's gotten more sophisticated in terms of the number of residual cells that we're able to detect, anywhere from 10^{-4} to 10^{-6}. So, different labs may have different cutoffs and techniques. And standardizing these needs to be done globally because it's important. Because we're not all talking about the same MRD, depending upon where you're getting tested.

There are newer platforms that are also looking to test minimal residual disease. One is called next generation sequencing, or NGS, and they're using DNA of your CLL, of your leukemia cells, from when you had disease.

And, then, following that, they can actually clone the dominant sequence. And, then, they follow it in a much more sensitive fashion and so, again, not yet sort of done in mainstream or approved, but the level of technology is improving, that we're able to get deeper and deeper into finding little remaining CLL cells. And, then, trying to use that in clinical trials to figure out how we can tailor therapies for patients with CLL in a time-limited fashion. So, stay tuned. So, what should one do with this information? Should I monitor MRD serially? I'm going to talk about that shortly.

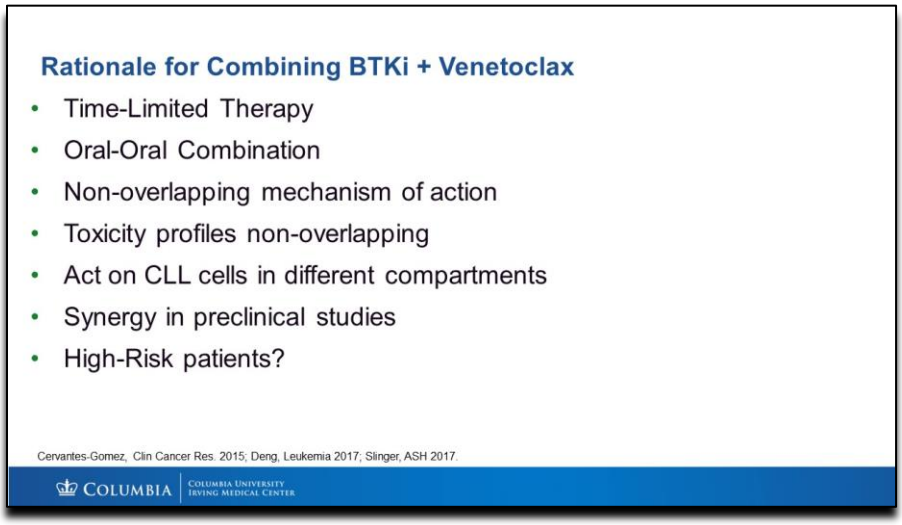


CLL14: VenG Achieved High uMRD and Improved PFS[1,2]

This came from a study like this with ven- obinutuzumab, where you can see that, in green, patients who don't have any disease, undetectable, and this study was by 10^{-4}. But, if you--whether you got

ven-obinutuzumab or even chlorambucil-obinutuzumab if you were undetectable, your progression-free survival was better than if you had a little bit of low-level disease or if you had a lot of disease left.

And so, that's where we're going to try to look forward in the future to look at MRD into figuring out which patients, where we might be able to tailor time-limited therapy better in certain disease--in certain subtypes of CLL patients. So, it's not yet ready for prime time.

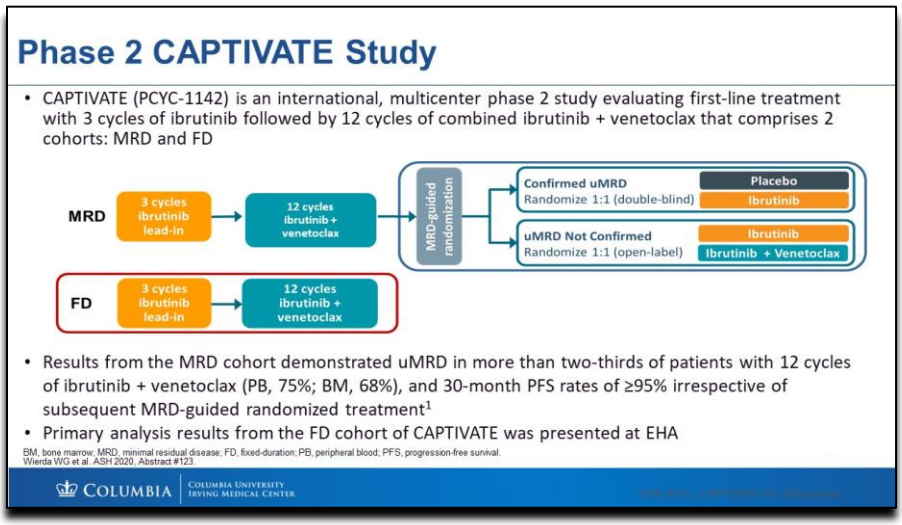


Rationale for Combining BTKi + Venetoclax

So, what about oral-oral combinations? So, if I just told you we'd have venetoclax and a CD20 monoclonal antibody, what about combining a BTK like ibrutinib or acalabrutinib or zanubrutinib plus venetoclax? Then you have an oral-oral rather than an oral-IV combination. They slightly work differently. Remember, I told you they have different mechanisms of action.

And the toxicities between the drugs are different. There are some overlapping toxicities; but most of the part, they're not overlapping. And they act in different compartments. As I said, the venetoclax works really good at mopping up the bone marrow. The BTKs do a great job at shrinking the lymph nodes. And, so then, you could combine them in that sense.

And there's definitely pre-clinical studies that have shown that these are very active together.



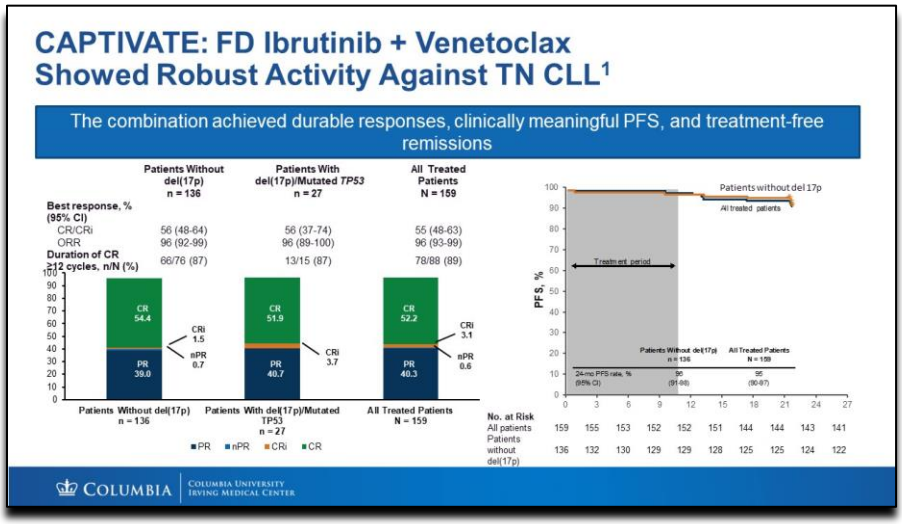
Phase 2 CAPTIVATE Study

And what about for high-risk individuals? Maybe then we can give people a time-limited approach if their high-risk with an oral-oral combination if the data is better. So, there are many studies looking at this combination now, I just want you to know.

This is one of them, called the CAPTIVATE study. And, so, patients get ibrutinib as a lead-in. They take the pill first for three months. And then, they're started on the combination with the addition of venetoclax. And that also helps to de-bulk patients, so that they don't have a high-risk of tumor lysis when they start their venetoclax.

And then, they're on it for the combination 12 cycles, so 15 months of therapy. And there is a fixed-duration cohort, meaning everybody stops after 15 months and is monitored. And there's actually an MRD-guided cohort, so patients will, then, get randomized, dependent upon if they still have detectable disease after the 15 months.

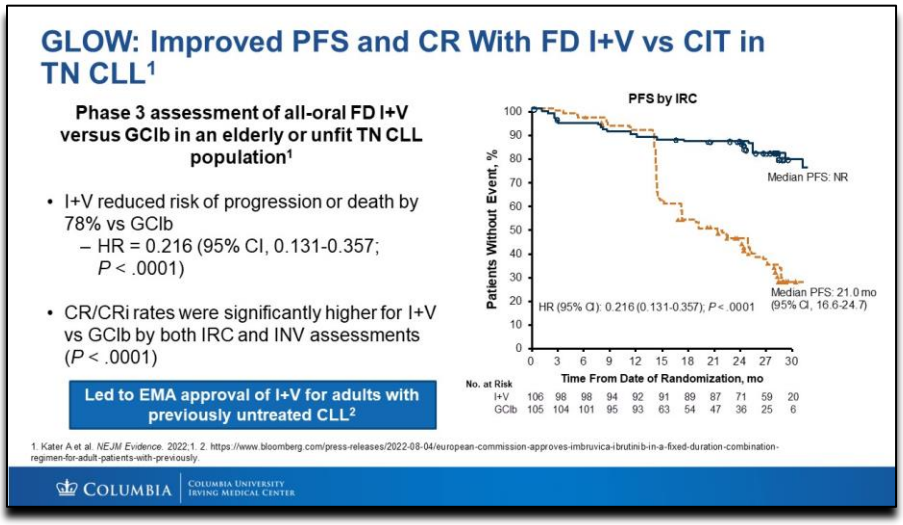
If they're undetectable, there will be a cohort of patients who get randomized to either placebo or to continue ibrutinib. If they have detectable MRD, they'll either continue ibrutinib or both pills at the same time. And, so, stay tuned.



31 CAPTIVATE: FD Ibrutinib + Venetoclax Showed Robust Activity Against TN CLL[1]

So far, this is some of the data on the fixed-duration cohort, the one that everybody stops after 15 months. So, it's a little immature. We have about two years of follow-up.

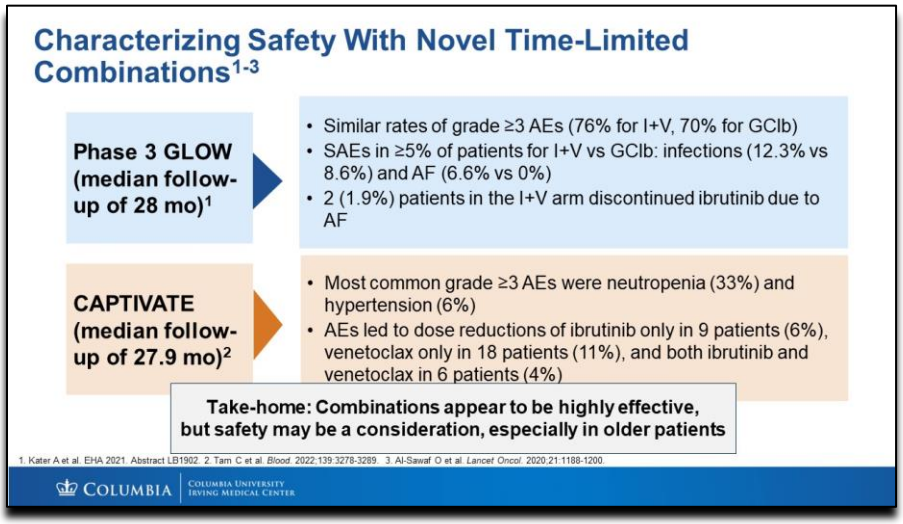
So, think about -- so after 15 months, we have about two years of extra follow-up here on the curve on the right. Then you could see whether you have a 17p deletion or not. Look how good the PFS curve is for everybody so far, almost two years out. So, everybody is doing very, very well on the oral-oral combination.



GLOW: Improved PFS and CR with FD I+V Versus CIT in TN CLL1

This was a study done by our European colleagues that looked at this fixed duration of ibrutinib and venetoclax versus chemoimmunotherapy with chlorambucil and obinutuzumab. And, just to have you note, not surprising, the PFS--we already knew that ibrutinib did better than chlorambucil and obinutuzumab, so not surprising the combination of ibrutinib and venetoclax also is doing better than chlorambucil and obinutuzumab.

But, this actually led to the EMA European Medicines Agency] approval of the oral-oral combination in Europe.

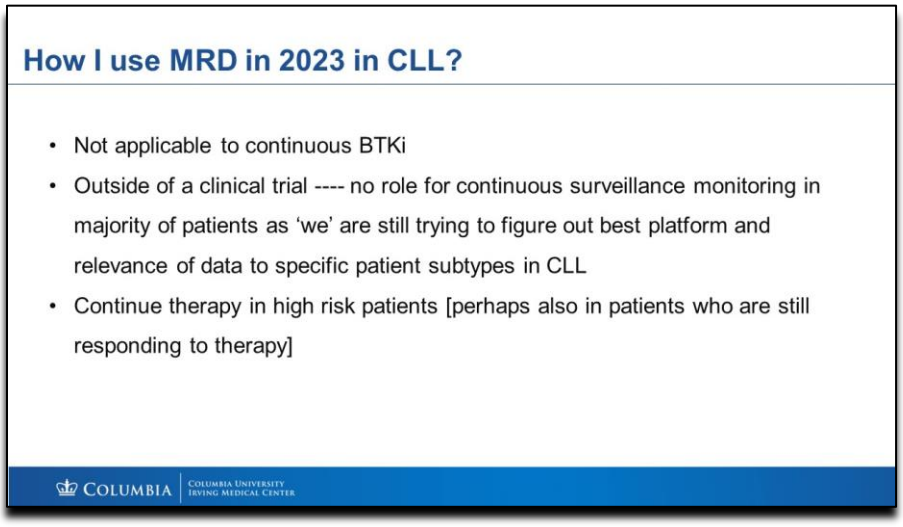


Characterizing Safety with Novel Time-Limited Combinations [1-3]

So, I want you to know it has not yet been approved here in the United States, but it is currently approved in Europe. Now, whether or not financially it will be accessible there--my colleagues are still going through that because they have different constraints. And, so, we'll have to see how readily available it will be because it just got approved. But, I'm sure there will be uptake soon.

The issues that we have with this combination is that there's no doubt when you add drugs together, there's increased toxicity. And, so, with the combination, even though it's time-limited, there's definitely increased cytopenias that can occur. There's some increased cardiac issues that have evolved.

There's increased infectious issues. And, so, the FDA here has not yet approved the oral-oral combinations. I suspect it's going to require some more randomized Phase III studies here in the U.S. that are currently running, for us to provide data that the oral-oral combination is safe in a time-limited fashion.



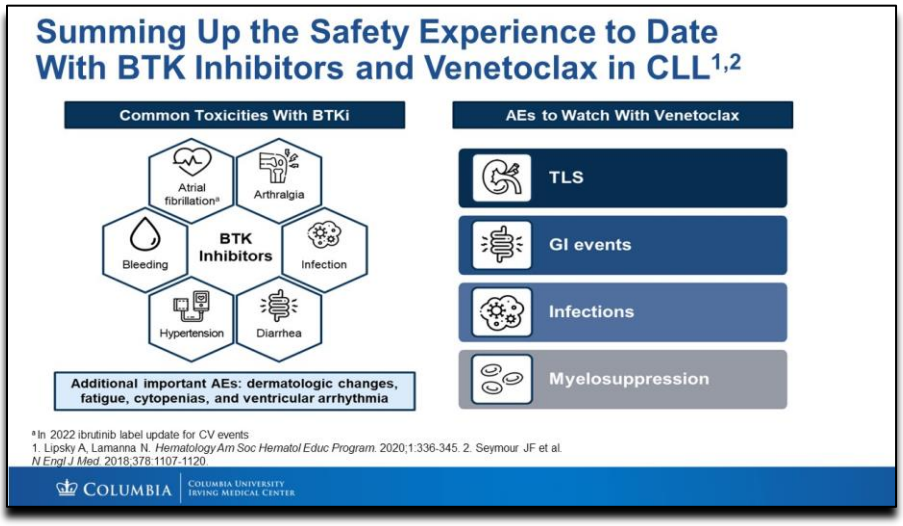
How I Use MRD in 2023 in CLL?

So, to get back, how do I use MRD in 2023? Again, if you're on a chronic, continuous BTK, there is absolutely no role for it. And outside of a clinical trial, there is no role for continuous surveillance of MRD in the majority of patients. Until we figure out what's the best platform, so that we're all testing in the same way, because you may think you're MRD-negative, and you may not really be MRD-negative on a more sensitive testing platform. And, is there relevance there might be some subtypes of patients with CLL high risk, not high risk, where it matters, in other words, to continue therapy or not continue therapy?

There may be some people who will always have a little MRD, no matter how long you continue that therapy. Those individuals should just be stopped. So, I think that, talk to your healthcare providers. But, in most mainstream, we are not telling docs to follow MRD currently outside of a clinical trial. There are certain subsets where your doctor may say "I want you to continue therapy because I think you're high risk." Those are individual conversations to have. But, MRD is not for prime time just yet.

What about Intolerance or Resistance to Therapies?

Now, what about if you are intolerant, or you're having side effects to therapy? Or what about if you're developing resistance, the drug stops working?



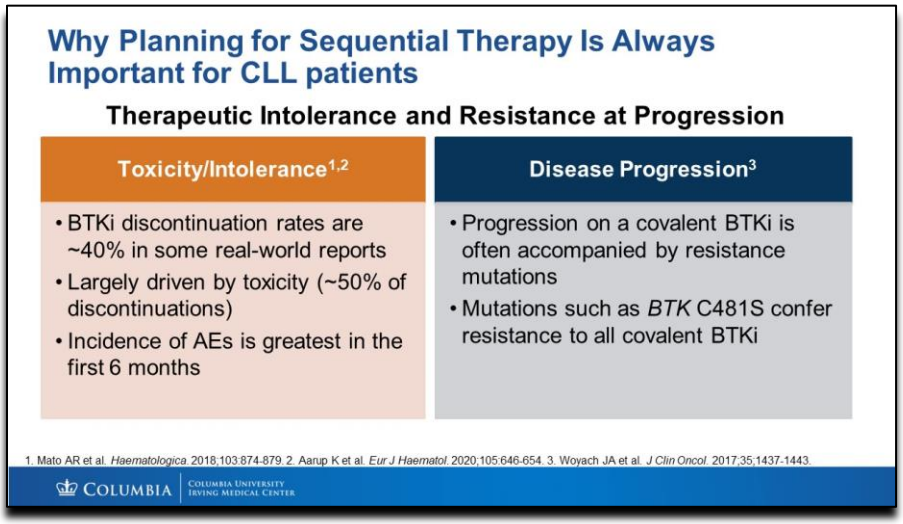
Summing Up the Safety Experience to Date with BTK Inhibitors and Venetoclax in CLL [1,2]

So, let's talk a little bit about that. We know that there are side effects to all of these therapies. With the BTK inhibitors, typically we talk about cardiac side effects and irregular heartbeat, atrial fibrillation. There can be other arrhythmias as well.

We talk about increased bruising or bleeding, increase of blood pressure, some GI side effects, diarrhea. Infection I see whether people are on or off therapies. It applies to all therapies, so we're in tune with that, with all the drugs. And, then, some people have arthralgia or joint pain. And then, with regards to venetoclax, we've talked about tumor lysis, so rapid cell kill where it can cause electrolyte issues that we're concerned about that we've got to monitor you to keep you safe from cardiac or heart or kidney issues when you first start the drug.

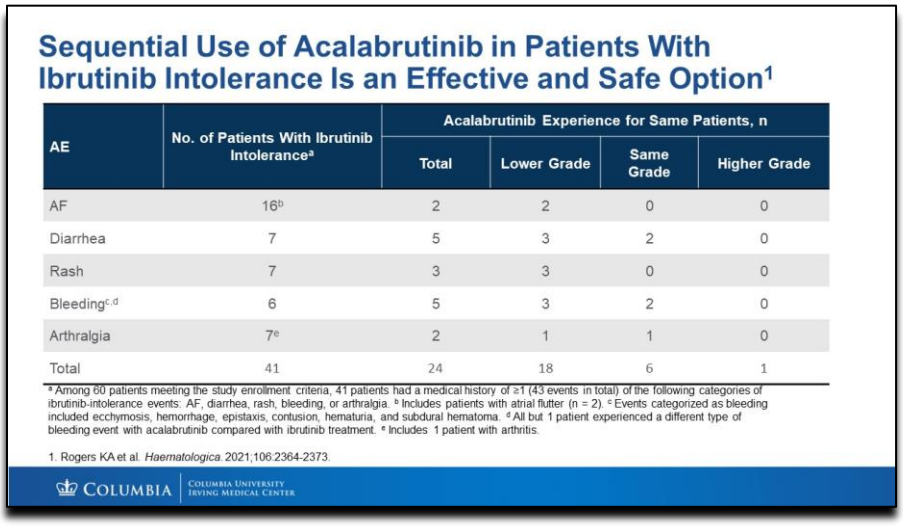
There can also be some nausea and diarrhea or GI issues, infections, as noted. And, because it does a better job at mopping out the bone marrow, your counts can actually--your good counts can dip too. So, sometimes, patients need dose reductions or injections to help boost their neutrophils, or even

withholding drug temporarily until their blood counts are better, depending upon how far their counts drop.



Why Planning for Sequential Therapy Is Always Important for CLL patients

So, when we talk about these therapies, it's important to talk about tolerance and toxicity as well as disease progression. We know that patients can come off either of these agents due to toxicity. But certainly, we know that patients can progress on both of these drugs as well. We're starting to identify resistant mutations that exist for both the BTK inhibitors but even for venetoclax. So, we know that people can progress on these agents.

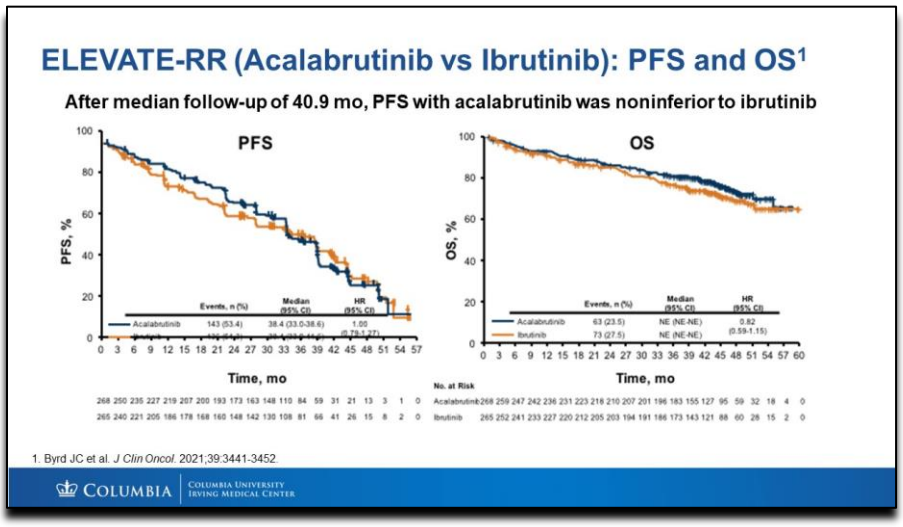


Sequential Use of Acalabrutinib in Patients with Ibrutinib Intolerance Is an Effective and Safe Option [1]

And, so, there are differences, then, what we would do with that individual.

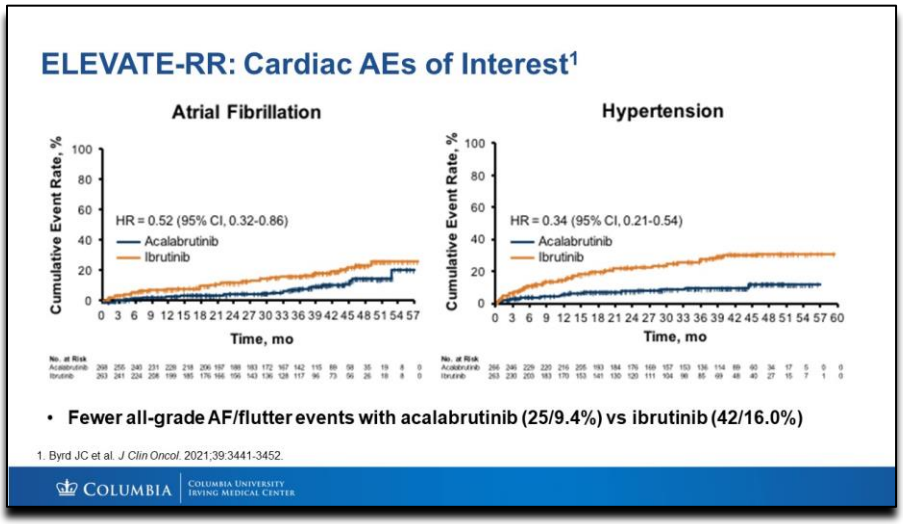
So, for patients who develop an intolerance, and some of you might have been on a BTK inhibitor, there are some data that perhaps you can change to a different BTK. So, this is work done by my colleagues at Ohio State looking at acalabrutinib after patients had an intolerance to ibrutinib.

And many of those individuals were able to be rechallenged on acalabrutinib. And their intolerance issue, whatever their side effect was, was at a lower grade or did not recur, and they were able to, then, maintain--because they were already--meaning they were responding well to ibrutinib. They just had a side effect. So, that's important. So, some patients could be rechallenged on a different BTK inhibitor.



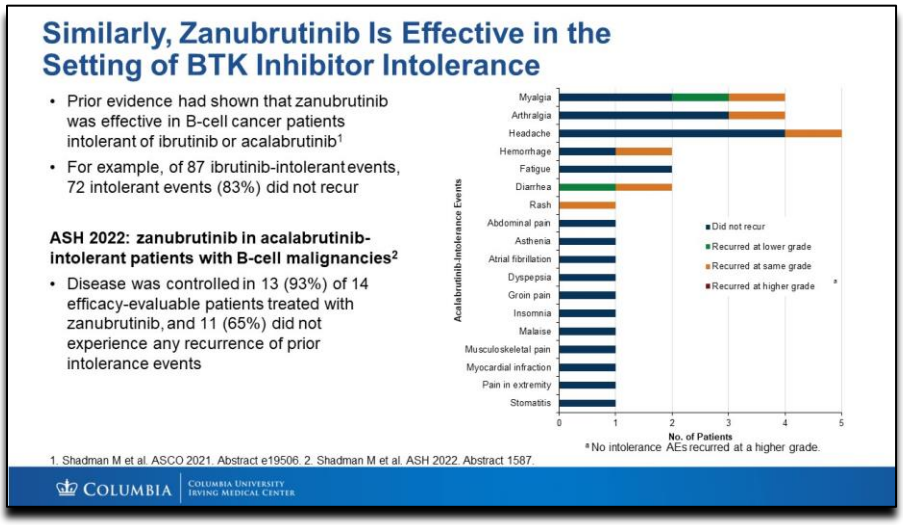
ELEVATE-RR (Acalabrutinib Versus Ibrutinib): PFS and OS[1]

There's also been some head-to-head data looking at acalabrutinib versus ibrutinib, showing that they're equal in terms of efficacy. So, there's no difference in terms of how they work or do in patients.



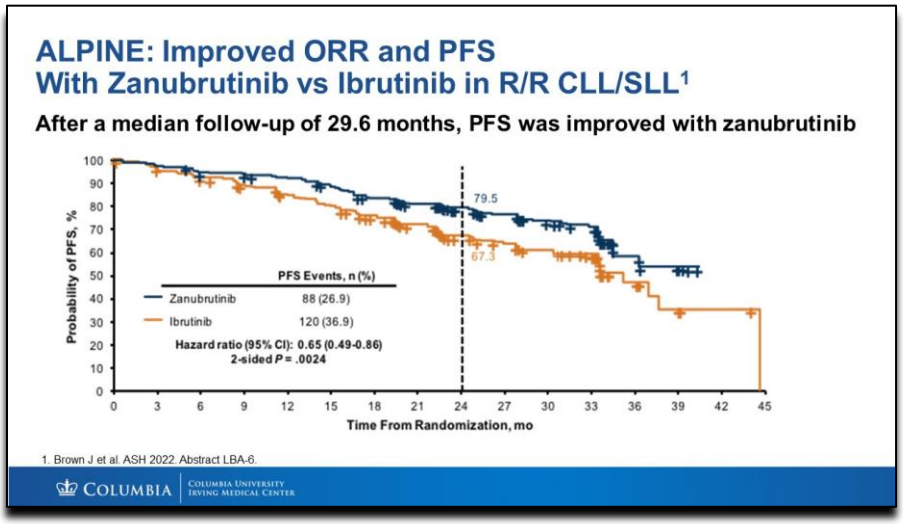
ELEVATE-RR: Cardiac AEs of Interest [1]

But, there's less cardiac toxicity with acalabrutinib as compared to ibrutinib in this study so, specifically, less atrial fibrillation and less hypertension.



Similarly, Zanubrutinib Is Effective in the Setting of BTK Inhibitor Intolerance

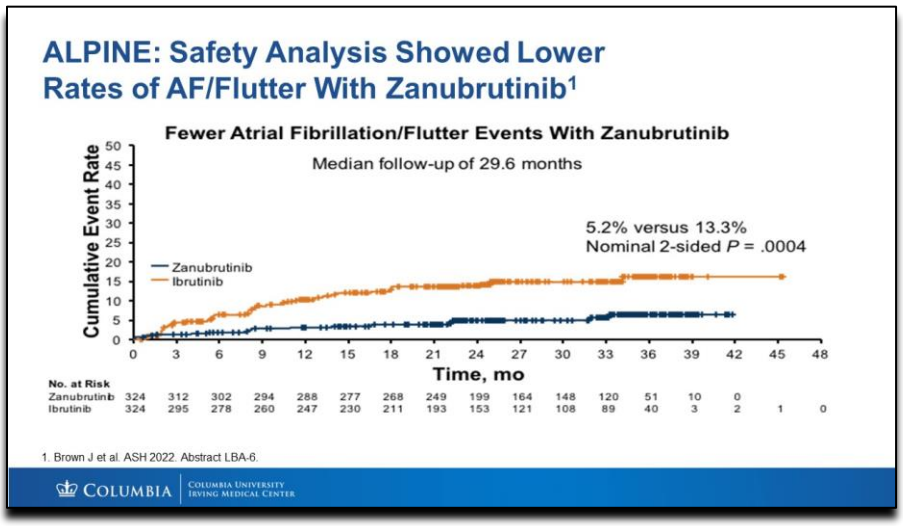
Similarly, zanubrutinib, which is the newer BTK kid on the block, also looked at intolerance. And so, patients who had either ibrutinib or acalabrutinib and might have had some side effects were, then, rechallenged with zanubrutinib. But, again, many of those intolerance issues did not recur when they were rechallenged on a different covalent BTK inhibitor. And so, they were able to extend the uses of this class. And I do think that's important.



ALPINE: Improved ORR and PFS with Zanubrutinib Versus Ibrutinib in R/R CLL/SLL[1]

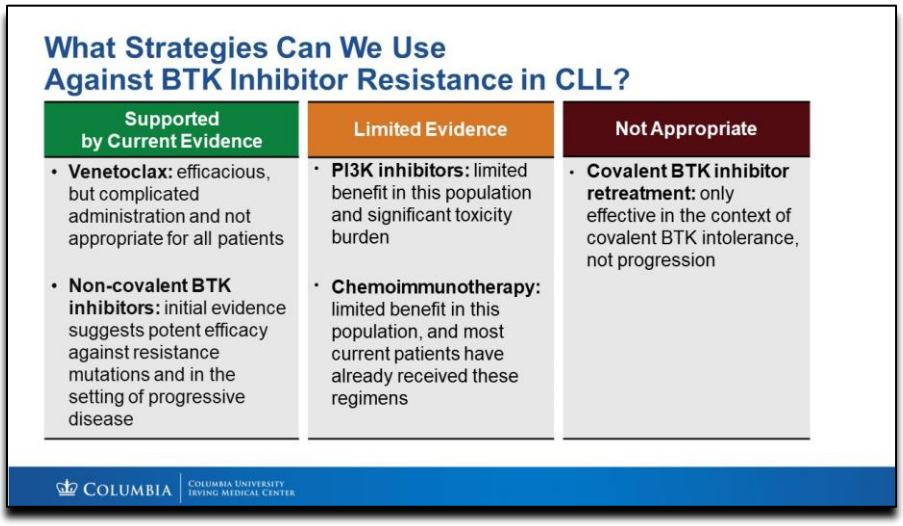
There was also head-to-head data called the ALPINE study in relapsed patients with zanubrutinib versus ibrutinib. There was a slight difference here in progression-free survival with zanubrutinib versus ibrutinib, which was not what we saw in the other study I just showed you with acalabrutinib. We're obviously very keen, because normally, we wouldn't think that these agents worked differently. They are all covalent BTK inhibitors.

But, we're going to be watching this split in the curve to see if this is still maintained the further out that we follow these curves, to see if they're truly different or not.



ALPINE: Safety Analysis Showed Lower Rates of AF/Flutter with Zanubrutinib[1]

But, what is important that we took home from this study as well is that there was also less cardiac issues with zanubrutinib, less atrial fibrillation and cardiac events with zanubrutinib versus ibrutinib.

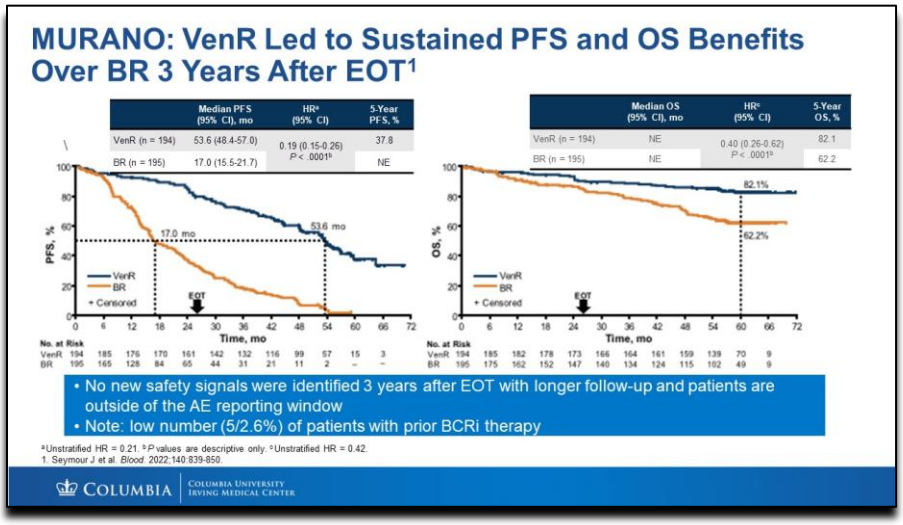


What Strategies Can We Use Against BTK Inhibitor Resistance in CLL?

Now, what about if you develop resistance to one of these agents? Certainly, if you have a BTK inhibitor that you've developed resistance to, most of the data supports going to venetoclax. I'm going to talk about that. There's also newer agents we're going to talk about, non-covalent BTK inhibitors.

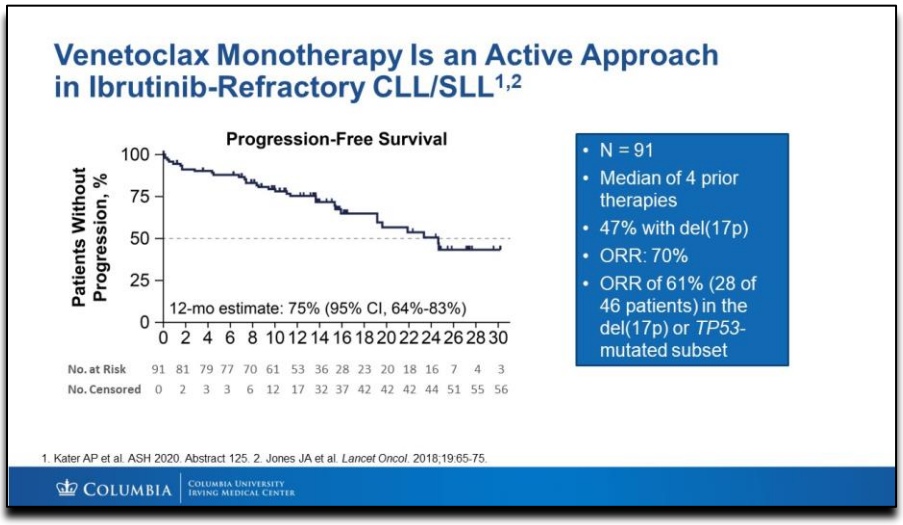
PI3 kinase inhibitors are another drug that I told you were FDA-approved in the relapsed setting. There are limited data that showed that if you go from covalent BTKs to PI3, the response duration probably won't be very long because the PI3s are also part of that B-cell receptor pathway that I showed you earlier. It doesn't mean you couldn't do that. It's just that we know it will probably be a bridge to another therapy. In other words, it may not last as long as we'd like.

There's little data with chemo. So, we probably won't be going back to chemoimmunotherapy if you've already been on targeted therapies because there's more side effects. And you're not going to go--like I just showed you that intolerance data. If you didn't tolerate ibrutinib, you can go to acala. Well, that's fine for intolerance. But, if you're progressing on ibrutinib, you're not going to go to acala because they work the same. So, we would not do that.



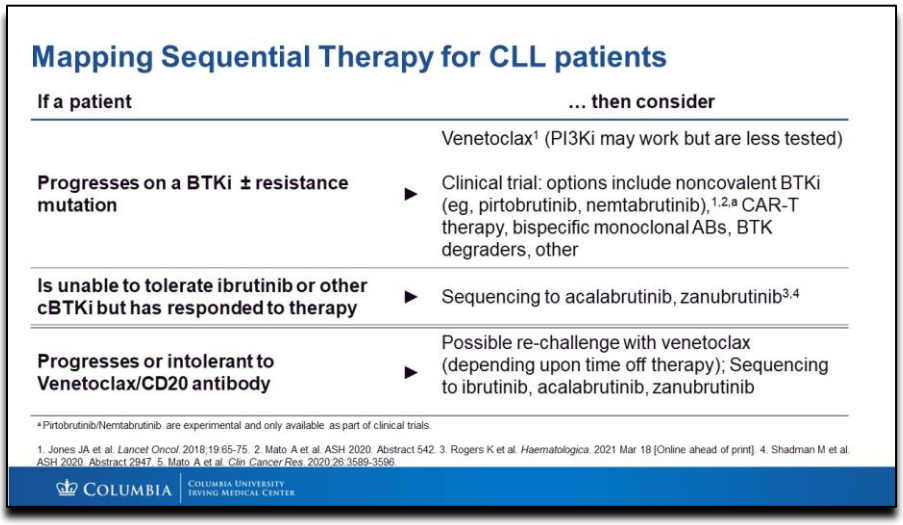
MURANO: VenR Led to Sustained PFS and OS Benefits over BR 3 Years after EOT[1]

The MURANO study--so this is a study that looked at venetoclax-rituximab in the relapsed setting. And, so, this is--if you've had a BTK in the front line, this is something that you could go to in the relapsed/refractory setting. This is time-limited. It is longer therapy than in the frontline setting, which was 12 months with obinutuzumab. This is 24 months. But, it did better than chemoimmunotherapy with regards to progression-free survival. And, so, this is absolutely an approved indication for going to venetoclax-rituximab in patients who had had prior BTK.



Venetoclax Monotherapy Is an Active Approach in Ibrutinib-Refractory CLL/SLL[1,2]

Venetoclax is also approved as monotherapy. I mean, we've been using it as time-limited to give people a break off of therapy. But, there's no doubt that in certain patients, perhaps staying on venetoclax might be applicable. And, so, this actually first got approved as chronic monotherapy in patients who are ibrutinib refractory. And so, this is again, if you failed a BTK inhibitor that's covalent, you could go to venetoclax in the relapsed setting.



Mapping Sequential Therapy for CLL patients

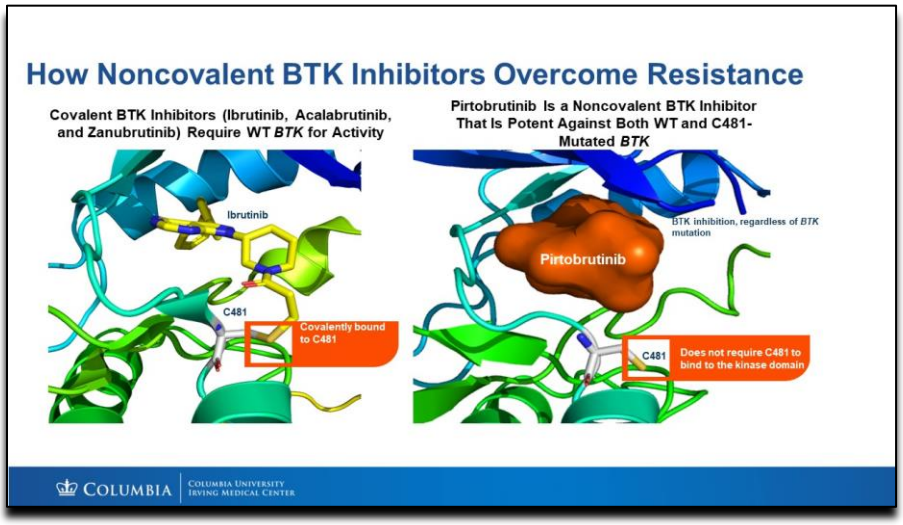
So, how do we think about this if somebody has developed a resistant mutation on a BTK? We would often give them venetoclax. But, we're going to talk about clinical trials and new drugs in a second. If you are unable to tolerate a BTK inhibitor, I think it's worth trying and talking to your doc. It does depend on the side effects. Not every side effect I'm going to want to try to change to a different BTK. If somebody has a major bleeding event on a BTK inhibitor, I'm probably going to switch them off the BTK because a re-bleeding could occur with one of the other ones too.

So, it depends--it does depend--on the side effect. But, if it's a mild side effect, something that's not life-threatening, absolutely, I think trying to switch around between the covalent BTK inhibitors is a good idea because if you're doing well on a drug, you can extend the life of the drug before needing another drug like venetoclax.

And, certainly, if you progress on venetoclax, you can certainly then go to a BTK inhibitor and vice versa. And, certainly, part of that there's also some rechallenging of venetoclax because it's time-limited. So, some individuals might also be able to restart venetoclax, depending upon when they progress after they first finished it.

Other Therapies on the Horizon for CLL patients

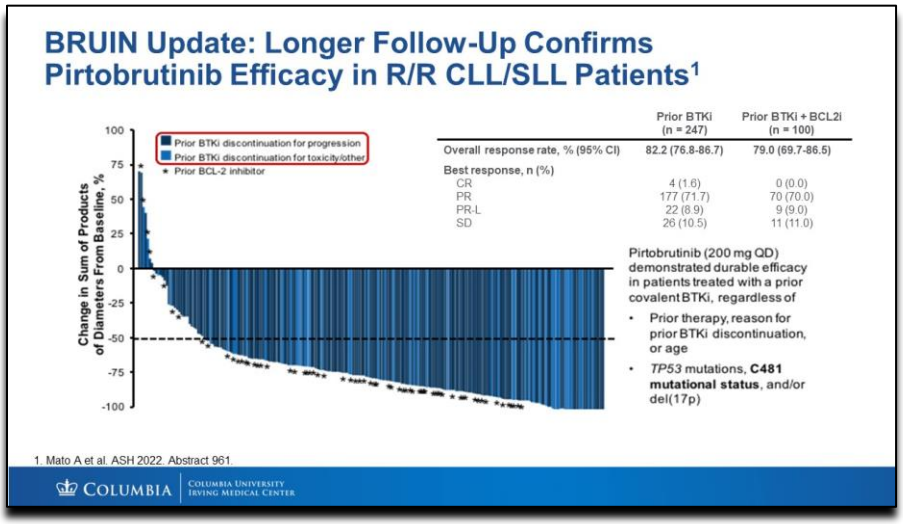
So, let's briefly talk about, before I conclude, because I know you have lots of questions.



How Non-Covalent BTK Inhibitors Overcome Resistance

Let's talk briefly about some new agents. We're going to talk about the non-covalent BTK inhibitors.

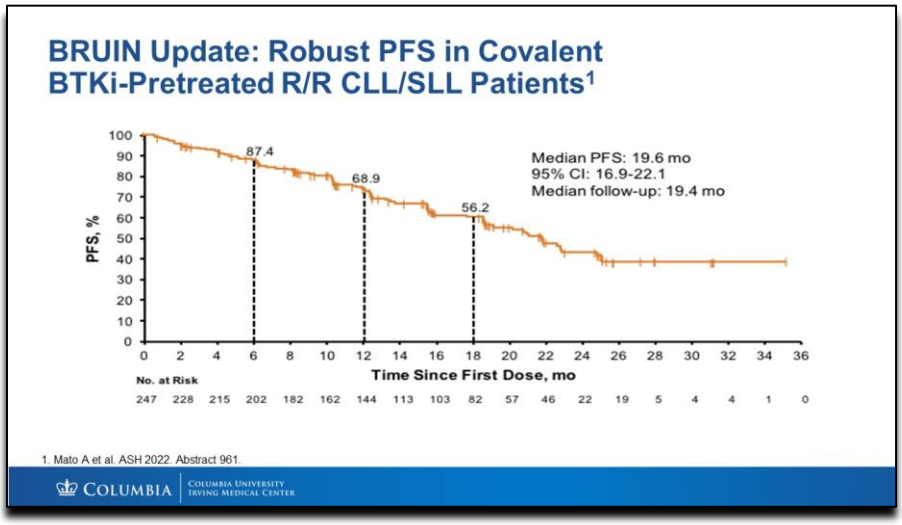
So, we have the covalent BTK inhibitors, ibrutinib, acalabrutinib, and zanubrutinib. But, I told you they can develop resistant mutations, particularly in the C481S. And, so, pirtobrutinib and nemtabrutinib—these are the newer, non-covalent BTK inhibitors that are not yet approved for CLL—they are effective in both the wild type but also in C481-mutated BTK because they don't require C481 to bind to the kinase. So, they can overcome and still be useful in patients who develop that resistant mutation on covalent BTK inhibitors.



BRUIN Update: Longer Follow-Up Confirms Pirtobrutinib Efficacy in R/R CLL/SLL Patients[1]

So, this is a study called the BRUIN study that looked at this in patients who all had prior covalent BTK inhibitors, whether it be ibrutinib or acalabrutinib or zanubrutinib. I don't think there were probably many zanu at the time we did this study. But, if you had a prior covalent, either if you had a toxicity to it, or you progressed, you were eligible to go on this study of 247 patients.

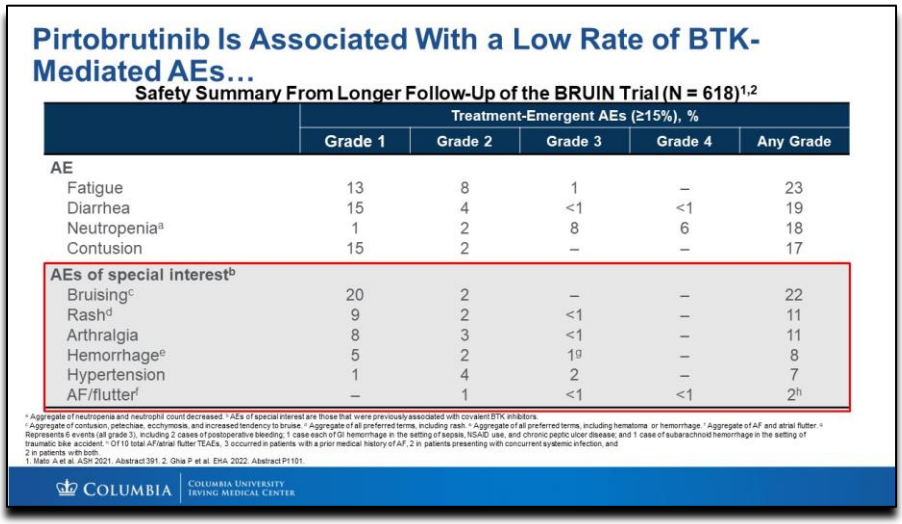
And, actually, 100 of those patients already also had venetoclax. In other words, they had both BTK and BCL-2. So, think about that. They've had both of their frontline therapies.



BRUIN Update: Robust PFS in Covalent BTKi-Pretreated R/R CLL/SLL Patients[1]

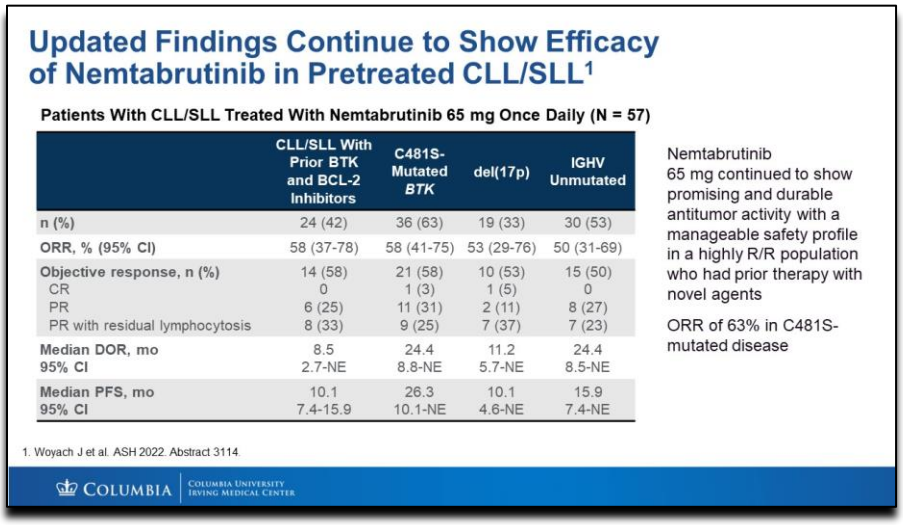
And what you can see here is those patients, many of them, were able to re-respond to therapy, even though they failed a prior covalent BTK inhibitor.

And so, this is a good sign because we might, then, also have another drug we can use in patients who are developing resistant mutations to the covalent BTK inhibitors.



Pirtobrutinib Is Associated with a Low Rate of BTK-Mediated AEs …

Similar to the other BTK because it's still a BTK, the adverse events that we talk about, that I alluded to earlier, seem manageable. They seem more like acalabrutinib and zanubrutinib, so very tolerable in terms of the side-effect profile.



Updated Findings Continue to Show Efficacy of Nemtabrutinib in Pretreated CLL/SLL[1]

Patients With CLL/SLL Treated With Nemtabrutinib 65 mg Once Daily (N = 57)

	CLL/SLL With Prior BTK and BCL-2 Inhibitors	C481S-Mutated *BTK*	del(17p)	IGHV Unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95% CI)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%)	14 (58)	21 (58)	10 (53)	15 (50)
CR	0	1 (3)	1 (5)	0
PR	6 (25)	11 (31)	2 (11)	8 (27)
PR with residual lymphocytosis	8 (33)	9 (25)	7 (37)	7 (23)
Median DOR, mo	8.5	24.4	11.2	24.4
95% CI	2.7-NE	8.8-NE	5.7-NE	8.5-NE
Median PFS, mo	10.1	26.3	10.1	15.9
95% CI	7.4-15.9	10.1-NE	4.6-NE	7.4-NE

Nemtabrutinib 65 mg continued to show promising and durable antitumor activity with a manageable safety profile in a highly R/R population who had prior therapy with novel agents

ORR of 63% in C481S-mutated disease

1. Woyach J et al. ASH 2022. Abstract 3114.

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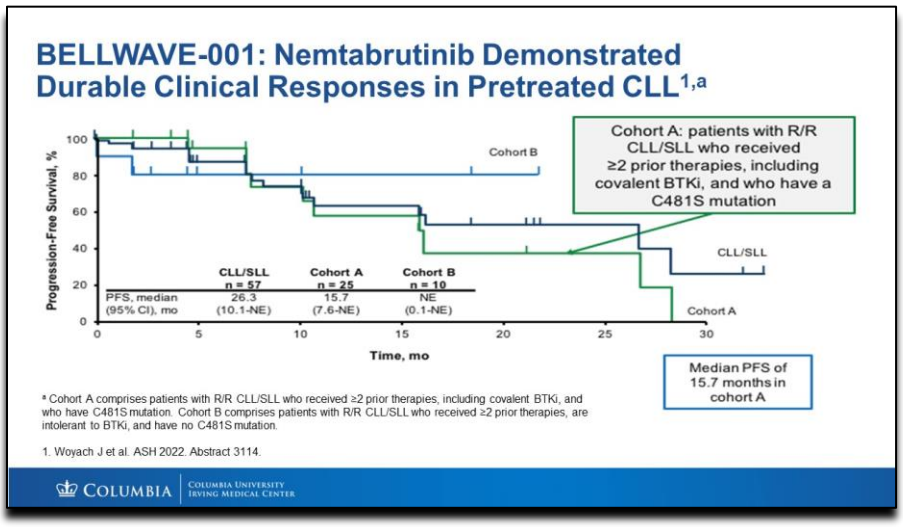
Updated Findings Continue to Show Efficacy of Nemtabrutinib in Pretreated CLL/SLL[1]

Nemtabrutinib is another non-covalent BTK. It's just a little bit more immature with regards to the data, but it's catching up. Also, has responses in patients who have failed both prior covalent and BCL-2 and who have developed a resistant mutation.



BELLWAVE-001: Nemtabrutinib Demonstrated Durable Clinical Responses in Pretreated CLL[1,a]

[a] Cohort A comprises patients with R/R CLL/SLL who received ≥2 prior therapies, including covalent BTKi, and who have C481S mutation. Cohort B comprises patients with R/R CLL/SLL who received ≥2 prior therapies, are intolerant to BTKi, and have no C481S mutation.

1. Woyach J et al. ASH 2022. Abstract 3114.

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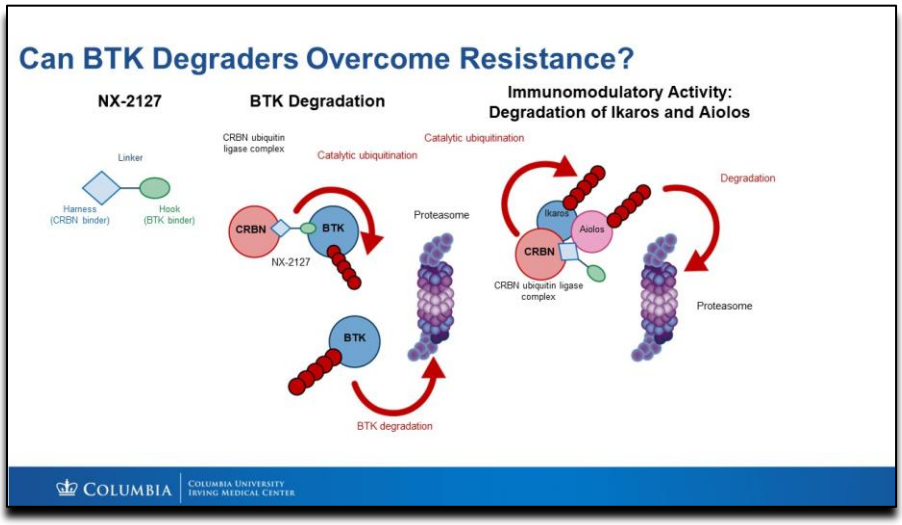
BELLWAVE-001: Nemtabrutinib Demonstrated Durable Clinical Responses in Pretreated CLL[1,a]

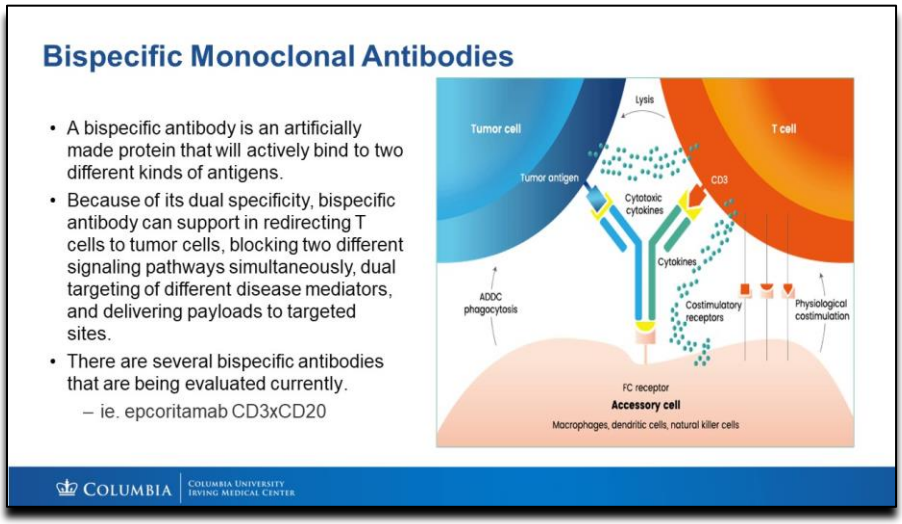
And this is the curves for those individuals, so about--median PFS here--about 16 months and about 63 percent of overall response in patients with prior C481S mutation. So, stay tuned to the non-covalent BTK inhibitors.



Can BTK Degraders Overcome Resistance?

And then, there are some newer, really early Phase 1, 2 studies of some compounds that look really interesting. One is called the BTK degraders. This is just one particular example. There are many that are being evaluated that are early. And, essentially, what this is--it's a molecule that consists of two parts. There is a hook that is linked to a kinase. And, in this case, it happens to be BTK. But, you could use--if you think about it—you could use another kinase. So, this might be applicable to other cancers as well.

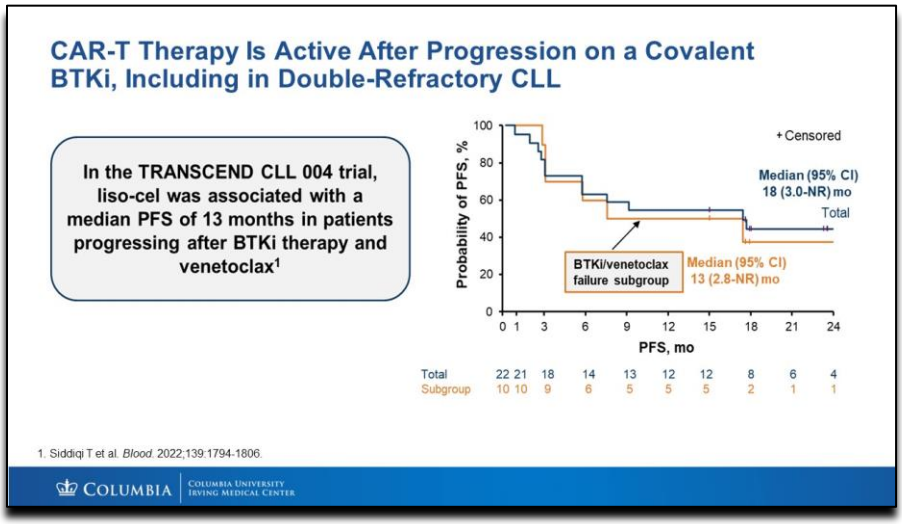
So, it hooks onto BTK. And, then, the whole molecule is sort of shuttled to an E3 ligase. In other words, this whole complex is degraded. And what that allows for--what does BTK degradation do? It allows for suppression and signaling and proliferation of your cancer cells, of the CLL cells. And, so, this would then be applicable to patients who may have resistance to the covalent BTK inhibitors because, then, you can cause BTK degradation and cause dying of your cancer cells. And, so, for patients who have failed covalent BTKs, this would be possibly a good therapy, another strategy for them as well. So, these are really early-phase development.



Bispecific Monoclonal Antibodies

We also have bispecific monoclonal antibodies. I talked about CD20 monoclonal antibody, rituximab and obinutuzumab. This is bispecific. In other words, it will bind to two antigens, not just CD20. You can actually pick different antigens. So here, you could pick CD3 and CD20. What that does is--by

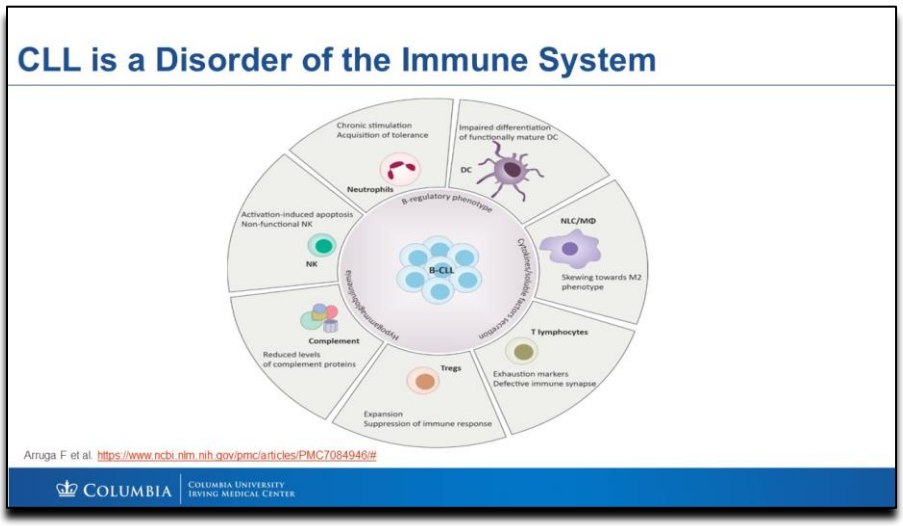
picking two antigens, it's trying to reengage your T cells to fight your CLL cells so that you can have better targeting and, as I said, reengage your T cells and redirect them to kill the B cells. And, so, these are also in early-phase development. Studies are ongoing now, which is very exciting.



CAR-T Therapy Is Active after Progression on a Covalent BTKi, Including in Double-Refractory CLL

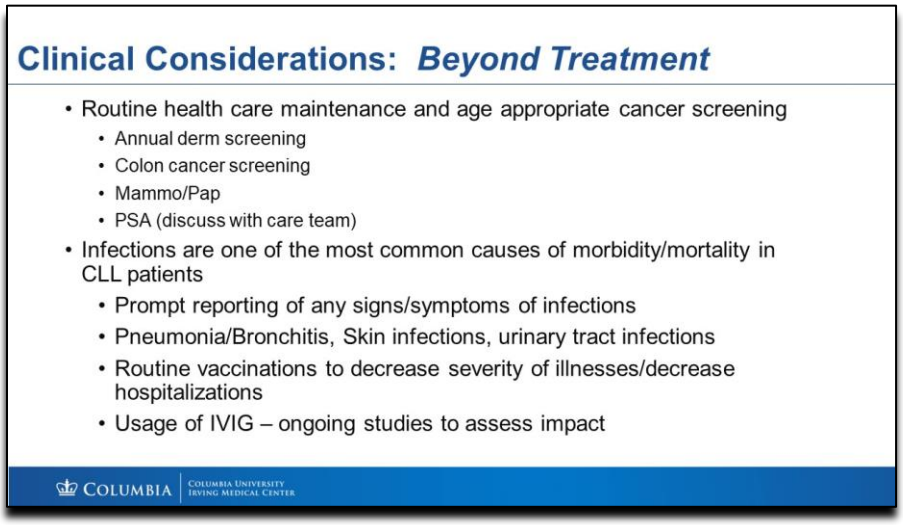
And then, we have CAR T-cells. And so, obviously, this has been ongoing for a long time. You guys have heard about this story. It is not new. And certainly, it has come a long way. You've heard about some of the toxicities that are associated. Because it is a T-cell immunotherapy, that can always play havoc with our patients with CLL, so increase cytokine release syndrome and neurologic toxicities. But, the toxicity profiles have gotten better, and there's no doubt that there's some durable response durations in patients, particularly in patients who have failed BTK inhibitors and venetoclax and in patients with Richter's [transformation into an aggressive lymphoma]. So, I think that CAR T-cell is evolving.

The reason why it hasn't come to the forefront is because of all these other targeted therapies that have come along with less toxicity that have just worked so well that it has not gotten pushed up front in terms of treatment with CLL patients because of the availabilities of effective therapy. But, I do think that this therapy is important, particularly in some of our really refractory patients or in patients with Richter's. So, stay tuned. Hopefully, there will be, at some point, an approval for CAR T in the near future for CLL like it is for lymphoma.



CLL Is a Disorder of the Immune System

Now, to step away from therapy and end this, I'd like to remind you all the CLL is a disorder of your immune system, and it impacts multiple cells in your body. Everybody thinks about the B cell and the CLL cells, but there are other cells that support the proliferation and survival of your CLL cells and help, but, at the same time, they can also cause dysregulation, which impacts other parts of your body. And this is why you guys, as a CLL population, may have other autoimmune or immune manifestations and infectious issues that are different from patients with different diseases.



Clinical Considerations: Beyond Treatment

And, so, beyond the treatment, again, we really want to recommend that you make sure you stay up-to-date with your healthcare maintenance and taking care of your body. See your primary care, your internist. Get control of your other comorbidities because that impacts your immune system, too. Do follow up on age-appropriate cancer screening, your annual dermatologist. One of the most common things I see is skin cancer, squamous cell, basal cell, melanoma. They are curative. Go for your annual derm screenings.

Also, remember, other cancers that are curative, if they're picked up early, they are removed. They are curative. Colon cancer screening; mammo; paps; PSA, that's a moving target because PSA, depending, prostate cancer is also somewhat similar to CLL in that some patients actually don't need to be treated

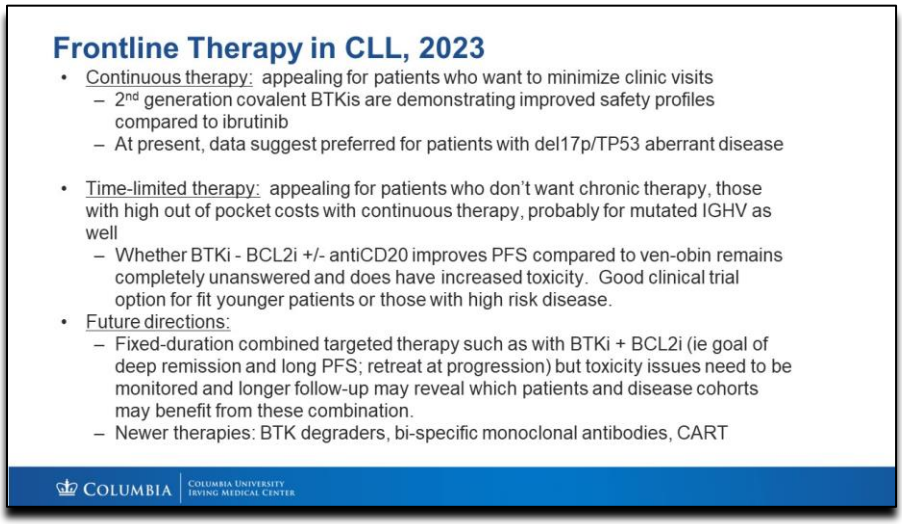
with low-risk disease. Talk to your care team about that, depending upon your age, and whether or not you should be tested for PSA. Because it shouldn't be annually in everybody.

And then, infections are the most common cause of morbidity and mortality in CLL patients. Promptly report your infections to your care team. Pneumonia, bronchitis, skin infections, urinary tract infections, we see all of these things. Again, vaccination use is really to decrease severity of illness and decrease hospitalizations.

They do not take away the fact that you cannot get the flu or COVID just because you got vaccinated. The point is to prevent you from getting really sick by trying to see if your body will recognize that virus. And then, you can mount some sort of immune response so you won't get so ill or die from that virus.

So, routine vaccinations are recommended and then the use of gamma globulin. So, it is not uncommon to have patients at diagnosis; 25 percent have low immunoglobulin levels. And that increases as you go on your CLL journey. The problem is that not everybody--as I showed you in this picture before, the immunoglobulin levels are just one part of your immune system. And so, not everybody with low levels gets sick all the time. And, on the contrary, that's why you don't--not everybody is receiving IVIG [intravenous immunoglobulin] or immune replacement.

But, there are some patients who are constantly getting ill all the time and needing oral antibiotics or constantly hospitalized. And that's where we'll talk about the use of IVIG or immune replacement to help, sort of, decrease their risk of infection, if possible, and boost their immune system. There are actually ongoing studies to assess the impact of IVIG uses in CLL patients, so I encourage you to be on those studies.



Frontline Therapy in CLL, 2023

So, just to summarize, so I give you guys time for questions, the therapy, CLL future, is bright in 2023. There is continuous therapy for patients who want to minimize clinic visits and who are okay with taking a pill every day. It's very effective therapy. The newer generation seem to have less side effects than the original. However, if you've been doing great on ibrutinib, stay on ibrutinib. There are no reasons to change if you're otherwise doing fine.

And, at present, we think that for the high-risk individuals, I like to do continuous therapy right now until I see more data on the oral-oral combination. Time-limited approach for many patients, a great appeal for those who don't want to be on chronic therapy. But, just remember, the first two months, there's a lot of work to do, and you need to follow up and make sure that, to keep you safe, we've got to

monitor you frequently. So, the first two to three months is a big committal, but you'll be off of therapy by a year or, in the relapsed setting, in two years.

And then, the future direction, obviously, we have more clinical trials on some of these novel agents that I showed you before, such as the non-covalent BTK inhibitors, BTK degraders, bispecific monoclonals, CAR T-cells. And then, of course, there will be more data on the oral-oral combinations to look at side effects and toxicity issues to see if that's something that eventually we will get FDA approved, although we will also have to think of how we salvage patients.

Hopefully, they will be re-sensitive. If they come off the oral-oral, we can rechallenge them back on one or both of those agents later on down the road if they get a lot of response duration. So, we still have a lot of work to do. I hope I was able to kind of, in a nutshell, summarize a lot of data for you with regards to CLL.

Thank You

And so, with that, I just want to say, thank you. And then, we can take it over and go for questions.

Lizette Figueroa-Rivera
Well, thank you so much, Dr. Lamanna, for your very informative presentation. You had so much information. I know a lot of the folks online have been saying, "She has so much information. Can we have the slides?" I just want to remind folks that the slides are on this platform as well as on our LLS website, LLS.org/Programs, where you could find the program page, and the slides are up for you right now.

Question & Answer

So, as you said, Dr. Lamanna, it is now time for our question-and-answer portion.

Lizette Figueroa-Rivera
And we'll take the first question from the Web. Dr., Jackie asks, some of the chemo pills affect the bones, causing severe pain. Is there any way around it? And, is there anything that can alleviate the pain?

Nicole Lamanna, MD
So, I'm thinking that this person is talking about the BTK inhibitors, specifically, because that's a side effect of the BTK inhibitors. If that isn't correct, again, I'm sorry if I'm trying to sift through what somebody is meaning. Sometimes, we will try some supportive measures. In other words, that sometimes--and it does depend on your kidney function and your platelet count, too. So, sometimes, we'll try short, brief courses of anti-inflammatory agents, so Advil® and ibuprofen (Advil®, Midol®, Motrin®, etc.), again knowing that that can increase slightly the risk of bruising when you're on the BTK inhibitors.

It's not something we'll do chronically but just to see if it works, sometimes a short course of steroids, like a Medrol® (methylprednisolone) pack. Oftentimes, the arthralgias are in the beginning of the drug, in other words, the first couple of months, and actually improve over time. However, if they don't, and you're really having a lot of discomfort, that talk that I said earlier about, can you change to a different BTK inhibitor, that's what I would talk to your provider about.

Because if you're having a lot of joint pain, you can try to see if it's due to the drug. You give the other--besides supportive measures, sometimes we'll just hold the drug to see if that's what's really causing it. Then, you talk to your provider: Should you be trying a different covalent BTK inhibitor to help?

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

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

Frederick
Yes, I was diagnosed in 2003 with CLL and have not had to have any treatment up until about two weeks after I got my second COVID vax. And, I was just wondering if anybody has seen any uptake.

And I had a--I think I had a white blood cell count in the 42, 43 about a month and a half before I had to be hospitalized. And it just seemed coincidental.

Nicole Lamanna, MD
Sure. I guess on a general sense, has vaccinations or has COVID infections caused a change in patients with CLL? There's no doubt, unfortunately, COVID infections I've seen have a lot of change in CLL patients. As you all know, in 2020, in fact the highest mortality of cancer patients was in CLL patients with COVID. So, there was no doubt that our CLL patients got the most impact with morbidity and mortality due to actual COVID infection and COVID-related complications due to the virus itself.

Now, have patients who have gotten the vaccine--have they had increases in their blood counts or increase in their lymph nodes flares? And can certain rare things happen? Absolutely. I will not say never. I have seen all of it and any of it. I would still--the downside of not getting vaccinated is obviously the concern of what we saw and dealt with on our end on the Leukemia Service was that obviously there were many more patients who passed away due to COVID and COVID complications that still sort of negate the--I would still--the risk/benefit ratio, I would still be recommending vaccinations in CLLs, given your immune dysfunction. But, we've seen lots of differences. I've had patients with COVID infection whose blood counts, then, tanked after their infection, so, and even had some rare immune, like pure red aplasia or autoimmune hemolytic anemia after getting COVID infection. So, there's lots of different things that we're still evaluating with the impact of COVID on patients with CLL. So, yes, it certainly--I would say we've seen everything. It has run the gamut.

Lizette Figueroa-Rivera
And, to continue this discussion on vaccines, Michael is asking, do BTK inhibitors have an effect on vaccines, such as the flu vaccine, COVID (as we were speaking about), or even the shingles vaccine?

Nicole Lamanna, MD
Yeah. So, just in general, this is a great question, and I'm so glad both of you gentlemen asked about these issues. The impact, in general, is that CLL patients have an impaired ability to mount immune responses to vaccines. And so, we know that, in general, forget--we'll get to therapy in a second--but the flu vaccine, pneumonia vaccine, COVID vaccine, shingles vaccine, that most patients--there may not be 100 percent of the same immunity that if we were to give those vaccines to a non-CLL patient. We still recommend them, again, because the most common morbidity and mortality in CLL is actually due to infections.

Yes, it's underpinned by the disease, but your inability to fight those infections off. And so, if there's any way to decrease severity of those illnesses, if we can give you guys vaccines to try to prevent you, hopefully, from getting too sick from the flu or toCOVID, we do recommend that you get it because we might stimulate some antibodies that, hopefully, you'll recognize whatever that vaccine is supposed to do.

Now then, I just told you that you're a little bit impaired due to the disease itself. Then, throw on therapies on top of that. So, there's no doubt that therapies, more particularly monoclonal antibodies, so rituximab and obinutuzumab, can impact the vaccines in general. So, oftentimes, if somebody is receiving a course of obinutuzumab or rituximab, we'll say, "You're likely not going to mount much of an immune response this year to the vaccines you receive." I still think it's fine to get, but just know that, right? So, you'll still be more at risk for infections because the vaccines may not work as well the year, even six months to a year, after the antibody.

Similarly, with BTK and venetoclax, you might have a dampened response, although probably not as prominent. It's one of those things that we're actually trying to get more data and learn more about the immune response in patients with CLL. So, stay tuned. There's lots of laboratory work going on in this area with regards to vaccines in CLL patients to see if there's different ways that we can try to help improve our vaccinations and the response of vaccinations in patients with CLL on therapy. So, stay tuned.

So, still get your vaccinations because the complications that we see--thankfully, COVID and CLL, you guys have done much better as the years have gone on. And, hopefully, that's because of the decreased variants being so vicious and also due to the immunity that's been generated over the past several years with many patients getting COVID. But, there's always a handful of patients every year who come in the hospital from COVID or flu or RSV [respiratory syncytial virus], admitted to my Leukemia Service because of CLL.

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

Operator
Our next question comes from Marie, calling from Maryland. Please state your question.

Marie
I read that in Imbruvica® if stopped completely. Survival is only eight months. My survival would only be eight months. Is that true?

Nicole Lamanna, MD
So, that was the original data, so careful what you all read. So, that was data that was generated a really long time ago when ibrutinib was first used. Remember, I said ibrutinib has been around now 10 years. When it first started in the clinical trials, it was used on patients who had only prior chemoimmunotherapy, so they had no available options of therapy. And when they went on ibrutinib, because that was their last available choice, they responded. But, if you stopped them off therapy, they would relapse very quickly, and their median survival was very poor.

Now that these agents have all been moved up, and chemoimmunotherapy has moved--has gone away--that is not the same anymore. In fact, as you saw, I guess I didn't show that slide, the PFS actually, the progression-free survival of patients who are treatment-naive who have been started on ibrutinib is well over--at seven years--well over 70 percent; in other words, that most patients are still on ibrutinib and doing well.

If they stop ibrutinib for various reasons because, remember, sometimes we tell you to stop it. You're going for a surgical procedure, or we don't want you to bleed, or maybe you were sick and we told you to hold it for a while. So, the median survival is not eight months now that you hold ibrutinib.

What you do have to pay attention to, though, is sometimes when the BTKs are held, sometimes people do get a flare of their disease. So, their lymph nodes might grow, not all, but to be aware of that. But, that median survival that you just quoted was from a really old study in multiply-relapsed, heavily pretreated patients. So, that data doesn't apply today.

Lizette Figueroa-Rivera
Thank you. And our next question is from Elizabeth. Elizabeth is asking about the differentiation between age-related fatigue and as a sign of disease progression in those who are stable for a long time.

Nicole Lamanna, MD
That's a great question. If I had the answer about fatigue and CLL, we're going to go play lotto. There is no doubt fatigue is one of probably the most troubling nondescript symptoms that we have, which is difficult to kind of characterize because it could--I'll never say it couldn't—be related to your CLL. But, it's really hard if your CLL--if the numbers look good, and they're stable, and your physical exam is stable, it's really hard to then go, Oh, my gosh, is this all related to the CLL? Or is there other things going on?

So, I, for sure, encourage you to try to talk to your care team because they should look for--if your fatigue is getting so great, let's say, it may prompt a workup for other things, too, whether it's related to

CLL or not. In other words, sometimes if I think that somebody is having a lot of fatigue that seems out of proportion to their disease, sometimes, I might do some imaging then or check your thyroid. Or is there something else going on?

So, I think that it's a very difficult symptom to have. And I do think that CLL, for sure, can cause fatigue. But, we always want to try to see, how is it in relationship to your numbers and your physical exam? And is there anything else going on that could be playing a role and, then, adding more to your baseline fatigue from the CLL? So, definitely talk to your care provider. It's one of the most difficult symptoms we deal with because it's not so straightforward.

Lizette Figueroa-Rivera
Thank you. And our next question from Mary, who is on active surveillance, or watch-and-wait or watch-and-worry. Mary is asking, are there any vitamins or minerals that can help during that time?

Nicole Lamanna, MD
So, that's a really good question when we talk about diet and exercise and supplements. And so, I do think, so people always ask me, is there anything I can do? The closest thing that we had was a study by my colleagues at the Mayo Clinic involving green tea. It was run many, many, many years ago. They're hoping to do a follow-up study--stay tuned--if they have some finances.

But they used really high doses of green tea, which is a great antioxidant. And it definitely did some shrinking of some lymph nodes, a little softening, and a little bit reduction in the absolute lymphocyte count, not necessarily anything that constituted a complete--a response that we talk about when we talk about how to do responses with therapies that we use. But, certainly, it's something that could have a benefit. And there's a lot we don't know about supplements and CLL.

What may be a supplement that might be good for one disease is not necessarily good for another disease. So, I always encourage patients, if they're not on active therapy, and they want to take some vitamins, I have no problem with that. But, please, please tell your provider what the supplements are. Anything that is prescription or over-the-counter that you ingest in your body could have impact to other things that you might be unaware of. Or, there could be drug-drug interactions for medicines that you might be taking for a different reason, from your cardiologist, for example.

And so, you want to make sure that they're safe for you, and they don't cause undue organ toxicity to your kidney or liver. But I have no problems with a multivitamin. I have no problems with green tea. I tell everybody, moderation. Don't do high doses of any one supplement because, again, you have to process--either your kidney, liver, or both organs--process most of the either prescription drugs or over-the-counter drugs. We want to keep your organs safe. And we also want to make sure there's no drug-drug interactions with anything else you're taking.

That's the closest clinical trial we have when we talk about CLL and a supplement, is with green tea. But I do think that moderation. Exercise is important, stimulates your immune system and cytokines, which help fight off infections. There's lots of ways that CLL folks can help themselves by taking care of their body on a routine basis—getting proper sleep, and proper exercise, and eating well, that probably if it helps your other medical problems, will go a long way with your immune system, will probably help your CLL if you should ever need treatment.

Lizette Figueroa-Rivera
Thank you so much. And our next question comes from the telephone audience, please.

Operator
Thank you. And our question comes from Rocko, calling from New York. Please state your question.

Rocko
Hi, Dr. Lamanna. It's a pleasure listening to you. I was diagnosed seven years ago with CLL. The reason I was diagnosed was I went into the hospital with a kidney stone. And, as they did blood work, they said, "Oh, boy, your white blood counts are high. You may have some form of cancer." And I was totally shocked because I'm in perfect health. And there was no treatment needed at the time. And it's been seven years. I still don't need treatment.

I'm in perfect health. I work out six days a week. And the only question I really have about my CLL, so they say, is that it seems like I understand it more than even my doctors here because I'm following you.

Lizette Figueroa-Rivera
So, Dr. Lamanna, when folks may not be near a larger cancer center, what can they do to get more information?

Nicole Lamanna, MD
Yeah. I mean, I think that's a great question. And, Rocko, you're revealing my age if you're following Dr. Byrd and Dr. Kipps. So, I'm feeling a little old here. But, it is true. Remember, you guys are rare individuals. When we talk about cancers, most docs are dealing with solid tumor malignancies--breast and colon and prostate and things like that. And the leukemias as a whole, not just CLL, there are other leukemias, too, represent the minority of cancers.

And so, many doctors are not as familiar with these diseases, or go, "Oh, you need to be monitored, and I don't want to spend much time talking about this because I'm busy taking care of this patient who has got breast cancer." And so, I apologize for my colleagues in the field. I understand where they may be coming from. I always think it's a good idea to get an opinion regarding your CLL, particularly if somebody tells you, you need therapy.

What they may offer might be different than what some of us are doing. And so, that's a very good time to get a second opinion. But, certainly, these kind of avenues online, LLS. As you know, many of you are involved in a lot of patient advocacy networks, CLL Society, Patient Power, as I said, LLS, that provide ample opportunity.

LLS Education & Support Resources

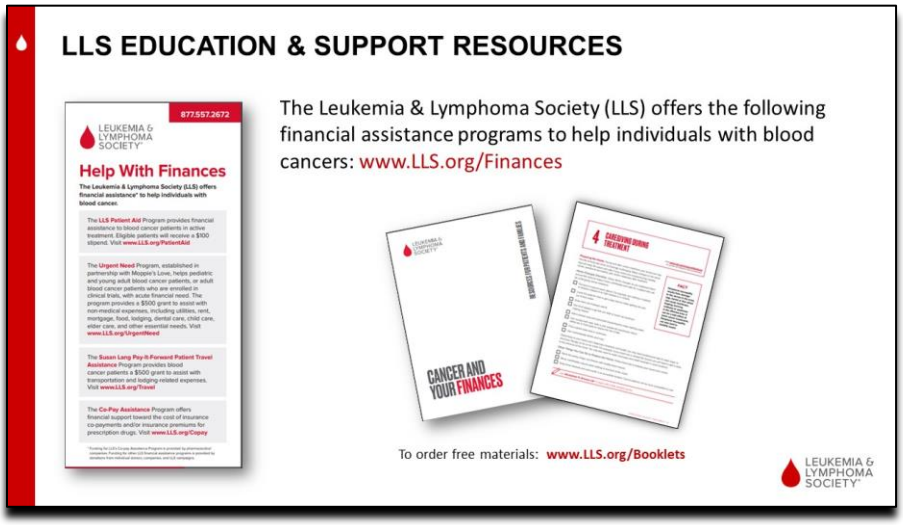
There are opportunities to get telemedicine visits if you live far and don't have access to somebody who is a CLL specialist. There are different ways that we can support you to at least get an opinion that way. So, I do think it's important to speak to somebody who is a specialist at least one point. And,

again, sometimes it's more critical when there's something acute going on versus if you're just in the active observation and monitoring, and you know that you're okay.

But, I would advocate that you can use any of these services available to help with learning about your disease, so you're your own advocate for doctors who may not be--less knowledgeable about that. I'm sorry to hear that, Rocko. But, it's not uncommon that I hear this. But, there are avenues for patients to get access to one of us for a consultation.

LLS Education & Support Resources

Lizette Figueroa-Rivera
Yes, definitely. And thank you, Rocko, so much for your question, which was our final question today. And, as Dr. Lamanna explained, we can assist folks in getting second opinions and looking for more information about their disease, their diagnosis, clinical trials, and treatment as well as other resources, financial resources, and support.



LLS Education & Support Resources
Again, thank you so much, Dr. Lamanna, for sharing your expertise with us and your dedication, your continued dedication to our blood cancer patients. Thank you so much.

Nicole Lamanna, MD
You're very welcome. Again, I hope this was a little bit for some of you, it was to try to hit everything for CLL, to give you a little sort of refresher course and also to talk about some of the newer therapies that some of you might have been interested in as well.

LLS Education & Support Resources

Lizette Figueroa-Rivera
Thank you. And if we weren't able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9:00 a.m. to 9:00 p.m. Eastern Time, or you can go to us at lls.org/informationspecialist to chat online or e-mail us at lls.org/contactus. We also do have a Clinical Trial Support Center where we have Clinical Trial Nurse Navigators to personally assist you throughout the entire clinical trial process. And you can reach them at lls.org/navigation.

The Leukemia & Lymphoma Society is proud to partner with Dollar For, a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free. So, please visit lls.org/dollarfor, that's lls.org/dollarfor for more information.

Thank You

And, again, we'd like to thank AbbVie, Inc.; BeiGene; Eli Lilly & Company; Pharmacyclics, an AbbVie Company; and Janssen Biotech; and the Thomas D. Oxley Fund for CLL Patient Education and Support.

Again, on behalf of The Leukemia & Lymphoma Society, thank you so much for joining us. And please consider sharing your story with us. Your words of encouragement can bring hope and confidence to others. You may submit your stories at www.lls.org/voices-of-lls-submission.
Thank you so much and take good care.