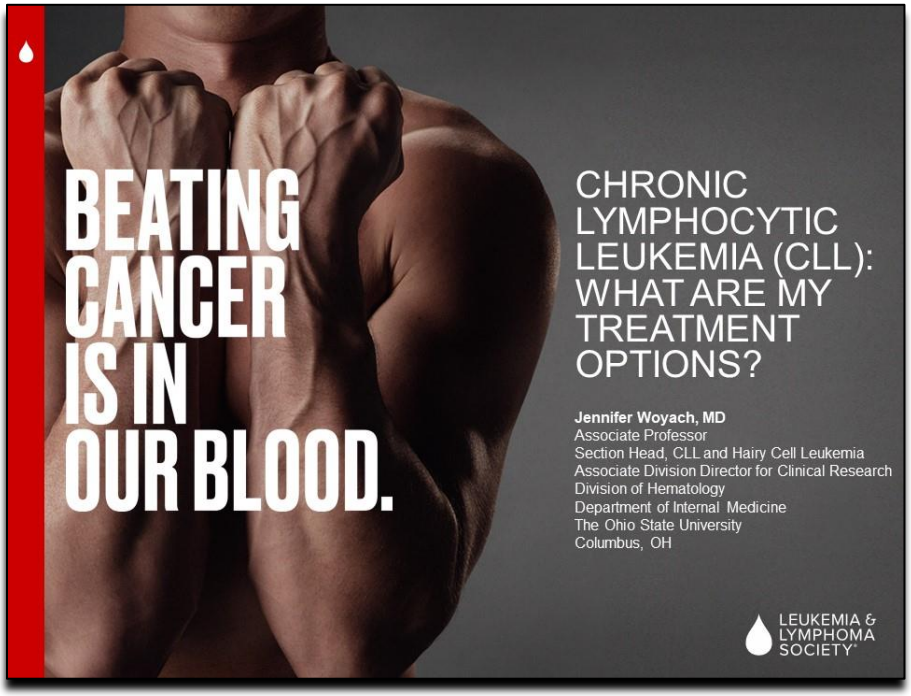


Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options?

Operator
Greetings, and welcome to Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options, a live telephone and web education program. It is now my pleasure to introduce your moderator, Ms. Lizette Figueroa-Rivera. Thank you. You may begin.

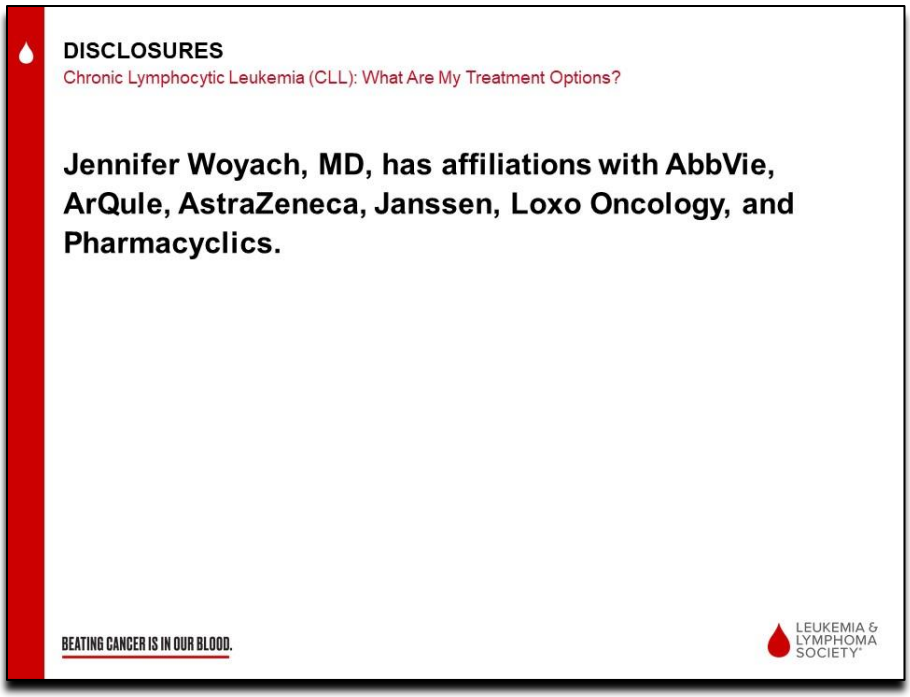
Ms. Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Jennifer Woyach, MD for sharing her time and expertise with us today.

I want to take this time to thank everyone for participating in today's program during these uncertain times. A cancer diagnosis is scary and overwhelming, and having cancer amidst the coronavirus pandemic is even tougher. So, LLS is laser-focused on helping blood cancer patients, their families, and healthcare providers during this pandemic, and continue to drive breakthrough research to accelerate better treatments and cures and ensuring patients have access to the care, support, and resources that they need.

All of our support services, including webcasts, podcasts, online chats, as well as our new COVID-19 patient financial aid program and information regarding COVID-19, are on our website at www.LLS.org/coronavirus. If you want to speak to us directly, please call us at 1-800-955-4572. Let us be here for you.

Support for this program is provided by Genentech & Biogen; Pharmacyclics, an AbbVie Company; & Janssen Biotech; and The Leukemia & Lymphoma Society.

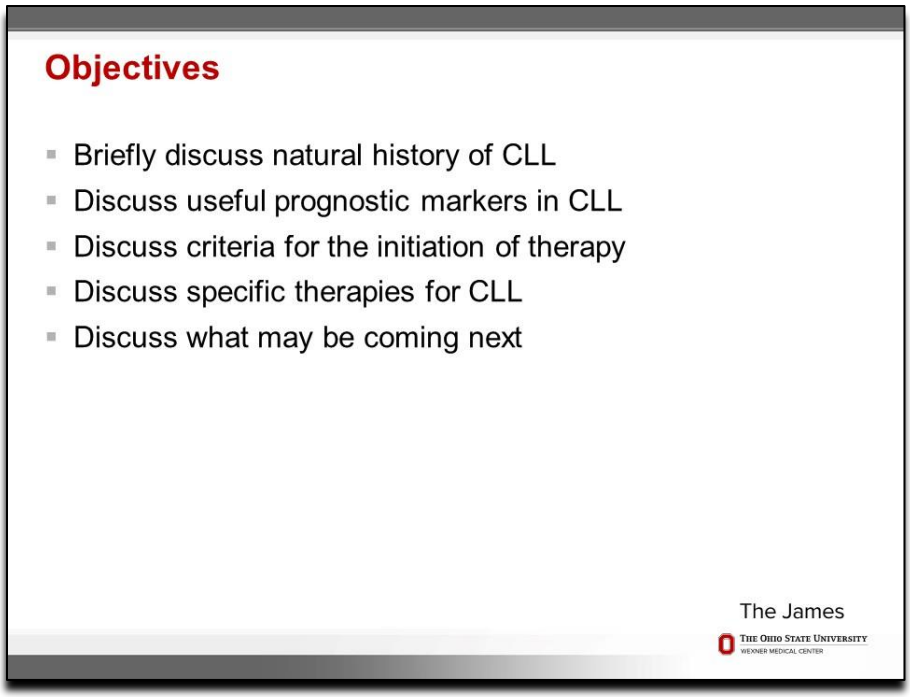
I'm pleased to introduce Dr. Jennifer Woyach, Associate Professor, Section Head, CLL and Hairy Cell Leukemia, and Associate Division Director for Clinical Research, Division of Hematology, Department of Internal Medicine at the Ohio State University in Columbus, Ohio. On behalf of The Leukemia & Lymphoma Society, thank you today, doctor, for volunteering your time and expertise with us. And now, I'm privileged to turn the program over to you.



Disclosures

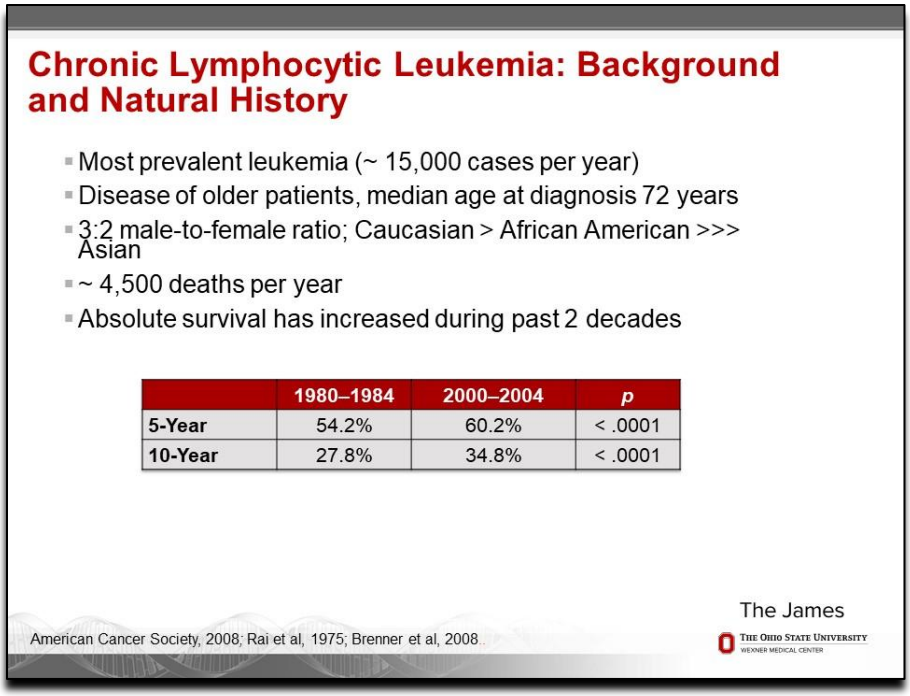
Current Treatment of CLL

Jennifer Woyach, MD
Thank you so much, Lizette, for the introduction. And welcome, everybody. I'm delighted to be here with you today to discuss the current treatment of CLL. We'll have about an hour discussion with a talk, and then I'm really happy to take any questions from the audience.



Objectives

So, during the talk today, I'm going to start by briefly discussing the natural history of CLL. We'll talk about some of the useful prognostic markers, why we start therapy when we do. We'll talk about specific therapies for CLL. And then I'll end with a short discussion on what is coming next in terms of new trials and new treatment paradigms.



Chronic Lymphocytic Leukemia: Background and Natural History

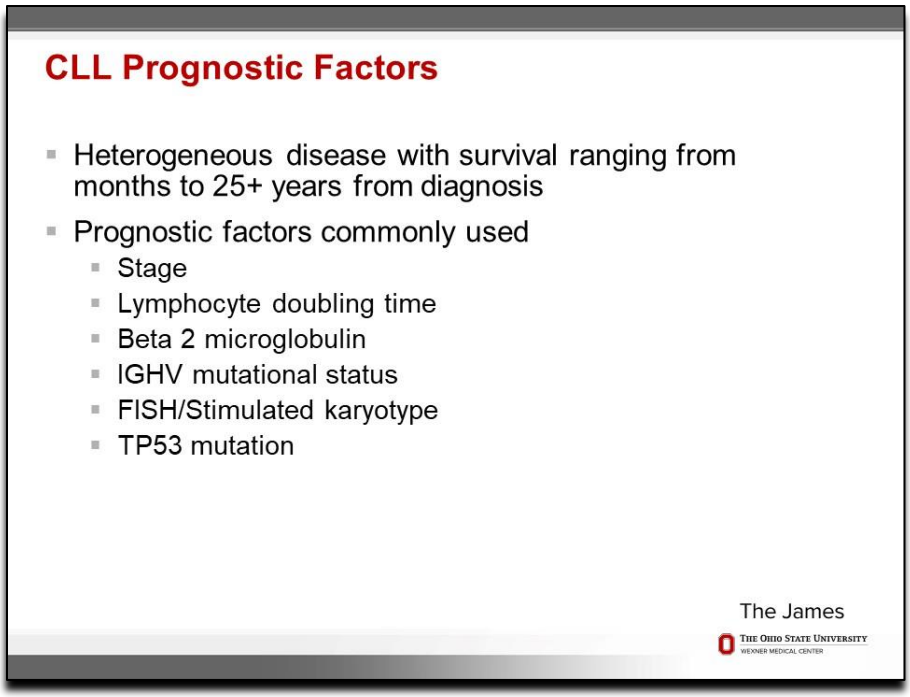
So, just a brief background for those of you who are less familiar with the disease. Chronic lymphocytic leukemia, or CLL, is the most prevalent leukemia in adults with about 15,000 new cases diagnosed per

year. It's traditionally considered to be a disease of older patients, and median age at diagnosis is about 70 to 72 years. About three-quarters of patients are diagnosed at age 65 or older.

That certainly doesn't mean that younger people can't get CLL as well and maybe there are even some younger people on the call today. We certainly see people even as young as their 20s and 30s who have the disease. And people are actively looking at how age plays a role in the natural history of the disease and how different treatments work.

CLL has a little bit of a male predominance at 3:2 male-to-female ratio. It is much more common in Caucasians than in African Americans. And much more common in those two racial groups than in Asian. There are about 4,500 deaths per year due to CLL, and hopefully that number is going to continue to decrease each year as our therapies get better and better.

We've seen that absolute survival in CLL has increased very dramatically during the past 2 decades with the introduction of new therapies, as well as better supportive care in terms of managing infections, managing side effects, etc. One of the first things that I tell patients when they come to see me in clinic with a new diagnosis of CLL is to not look at anything on the Internet related to survival because even the most updated literature really does not take into account the great strides that have been made in the treatment of CLL recently.

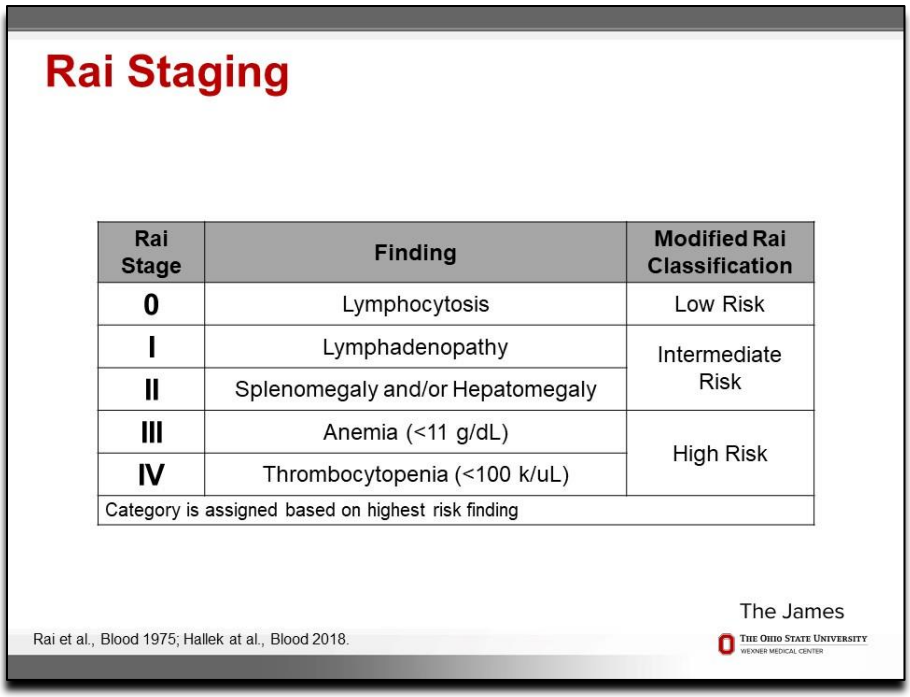


CLL Prognostic Factors

So, CLL is a very heterogeneous disease, which means that there is a lot of difference from person to person in how people present, how long it takes before people need treatment, and how they will ultimately do. Survival ranges from months, unfortunately, in some cases, to 25 or more years from the time of diagnosis.

There's a lot of prognostic factors that are commonly used in medicine right now for CLL, which really can help somebody with a new diagnosis understand if they're likely to be somebody who is going to need treatment within the first few years of diagnosis. Or maybe somebody who might never need treatment in their lifetime.

We're going to talk about a few of these in more detail, but the factors that we commonly think of are stage: lymphocyte doubling time. And what that means is whether or not the lymphocyte count doubles within the course of a year. Beta-2 microglobulin, which is a marker that can be tested in the blood where higher levels indicate more aggressive disease, IGHV mutational status, FISH and stimulated karyotype, and TP53 mutation.



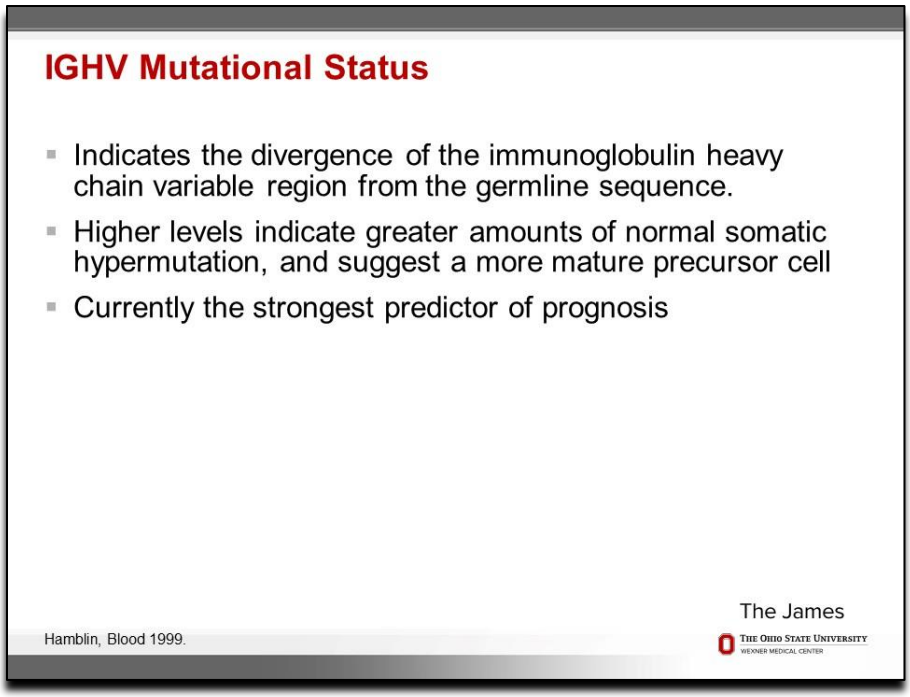
Rai Staging

So, the staging of CLL is done according to either the Rai staging system, which is primarily used in the United States, and the Binet staging system, which is used in many other countries, especially in Europe. So, both of those staging systems are similar in that they take into account burden of disease and use that to assign a stage.

So, with the Rai staging system, it has started out as a 0 through IV stage, and now we call it low risk, intermediate, and high risk. And you can see on this slide here how those specific slides relate to the new modified stage. So, basically, people who are diagnosed and have only a high white blood cell count without any evidence of enlarged lymph nodes or other-disease related features are considered Rai stage of 0.

Those that have lymphadenopathy or enlargement of lymph nodes anywhere are stage I. The presence of either an enlarged spleen or an enlarged liver is a stage II. Patients who develop anemia, which is a low red blood cell count with a hemoglobin of less than 11, are stage III. And stage IV includes patients who have a low platelet count with a platelet count of less than 100,000.

Importantly, the stage III and IV: So, the anemia and thrombocytopenia are predominately describing people who have these blood counts because their bone marrow is taken up by CLL cells. So, people who have autoimmune or their own cells breaking down their red blood cells or their platelets are not considered to be the higher stages.



IGHV Mutational Status

So, one of the most important prognostic factors that we have right now is something called the IGHV mutational status. And basically, what this means is that every CLL cell and indeed every normal D cell, which is the normal count or part to a CLL, has a receptor on its surface. And when the B cells are first produced in the bone marrow, every one of those receptors is exactly the same. So, if you did DNA sequencing of each of those receptors, they're all going to be identical.

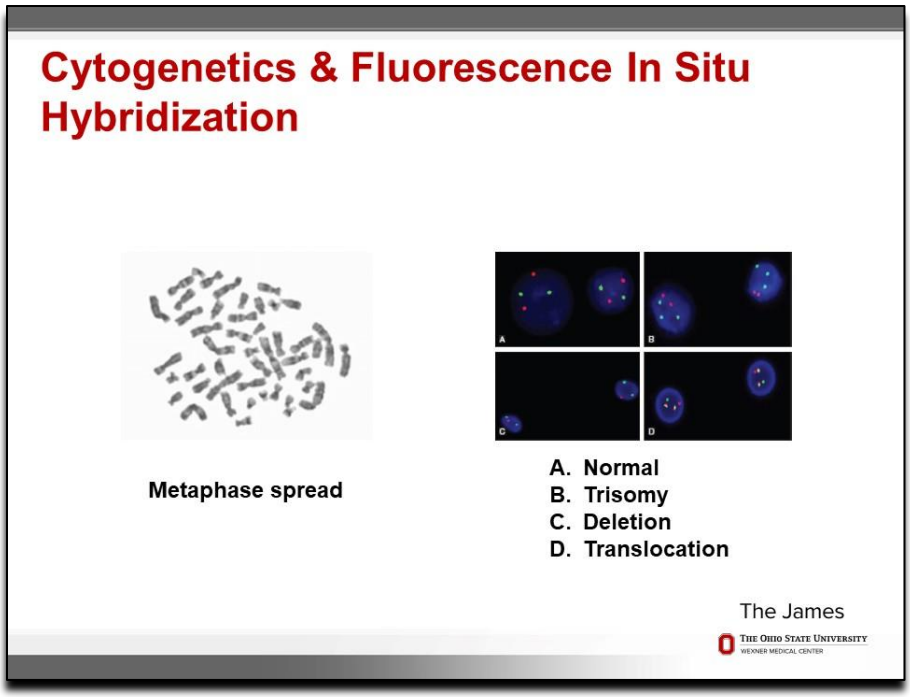
So, as a normal B cell matures, it undergoes this process called somatic hypermutation, which is where the DNA in that receptor randomly recombines for the purpose of creating a whole group of normal B cells that have different receptors. And this is really important for immunology or immune surveillance. So, if a bacteria or a virus or something comes into the body that's not supposed to be there, one of those B cells should have a receptor that randomly recognizes that as foreign. And so, that's just kind of the normal way that B cell would work.

In CLL, every one of a patient's CLL cells will have the exact same receptor on their surface. So, if you do DNA sequencing, they're all exactly the same. And about 60% of the time, those receptors on the surface of the CLL cells are different than the newly born B cells in the bone marrow, and we call this IGHV mutated. And what we think that indicates is that, that type of CLL is rising from a mature B cell and those tend to be less quick to growing or they're more slow growing.

In contrast, the IGHV-unmutated CLL, if you look at the receptors on the surface of those B cells, they're identical to the newly born B cells. And we think that that means the precursor cell to IGHV unmutated CLL is a more primitive or premature cell, and those tend to be more aggressive.

What this means clinically is those patients who are in the IGHV mutated group, about half of those people will never need treatment during the course of their lifetime. Certainly, that's not that applicable to somebody in their 50s. But, somebody in the average age range of 70, those people may never need treatment. The average time from diagnosis to first treatment in that group is about 10 years.

In contrast, in the IGHV-unmutated group, basically everybody is going to need CLL treatment within the course of their lifetime. And average time from diagnosis to first treatment is about 3 years.

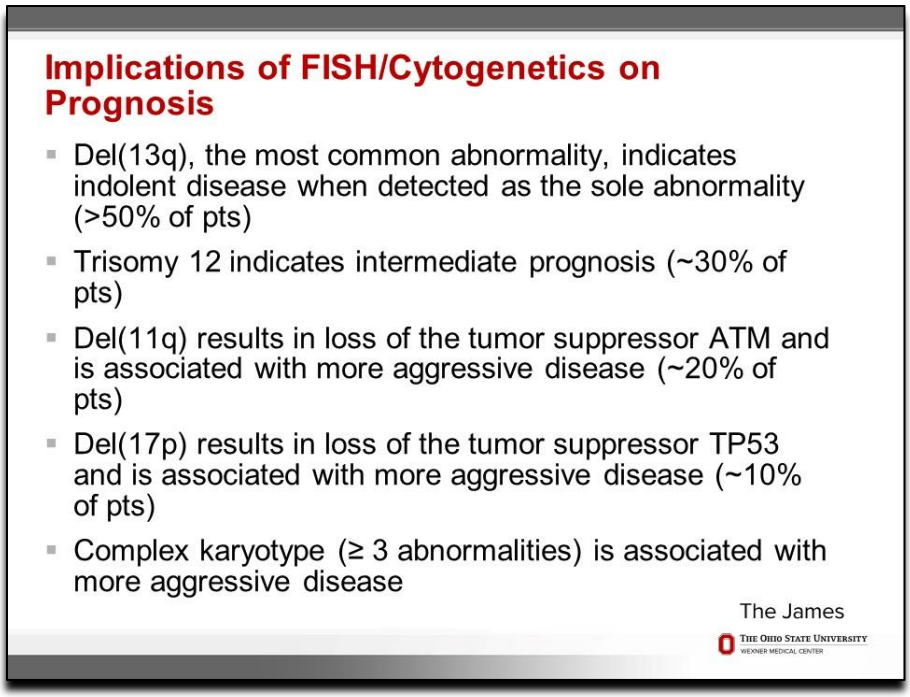


Cytogenetics & Fluorescence In Situ Hybridization

Another very important prognostic factor is cytogenetics and fluorescence in situ hybridization, which is known as FISH testing. And both of these refer to the fact that in CLL, there are a number of recurrent abnormalities in the chromosomes that can be used to predict prognosis.

What I have here on this slide is just an example of what we're talking about. So, on the left here that says metaphase spread, that's looking at a conventional cytogenetics spread or a conventional karyotype where all of the chromosomes are just laid out and somebody by hand is going to look at them and say, "This chromosome doesn't look like it's supposed to." The reason that that's important is we know that people who have three or more abnormalities in their chromosomes, which is called a complex karyotype, tend to have a little bit more aggressive CLL.

On the right there is just an example of what FISH testing looks like. And in FISH testing, we take antibodies that recognize specific abnormalities that are recurrent in CLL and then we can look for those specific abnormalities. So, it's a lot more sensitive of a test than the karyotyping, but you can only find what you're looking for.



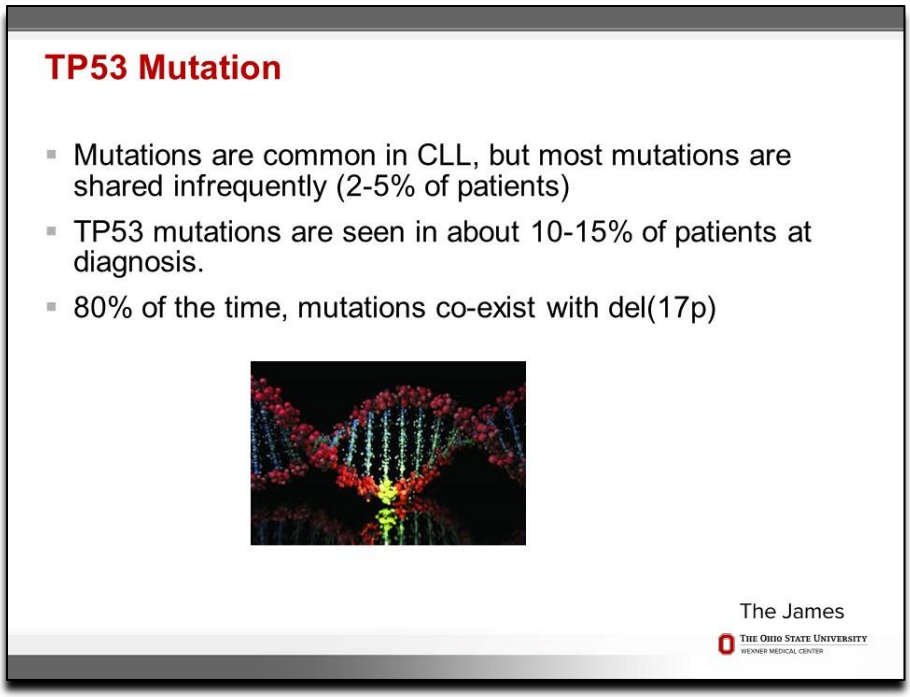
Implications of FISH/Cytogenetics on Prognosis

So, on this slide, I've put down some of the most important of the FISH and cytogenetic abnormalities that really help us with prognosis. The first four there are ones that most CLL FISH panels are going to test for.

The first one, a deletion of part of chromosome 13 or 13q deletion, is the most common abnormality that's seen in CLL. And it's present in over half of patients. When it is the only abnormality, it is a very good prognostic indicator and indicates somebody who's likely to have very slow-growing CLL.

Trisomy 12 means an extra copy of chromosome 12, and that's an intermediate prognostic marker. I'm talking about 30% of people at diagnosis. A deletion of a portion of chromosome 11, called an 11q deletion, results in the loss of a gene that's very important tumor suppressor and it's associated with more aggressive disease. This is seen in about 20% of people who are newly diagnosed.

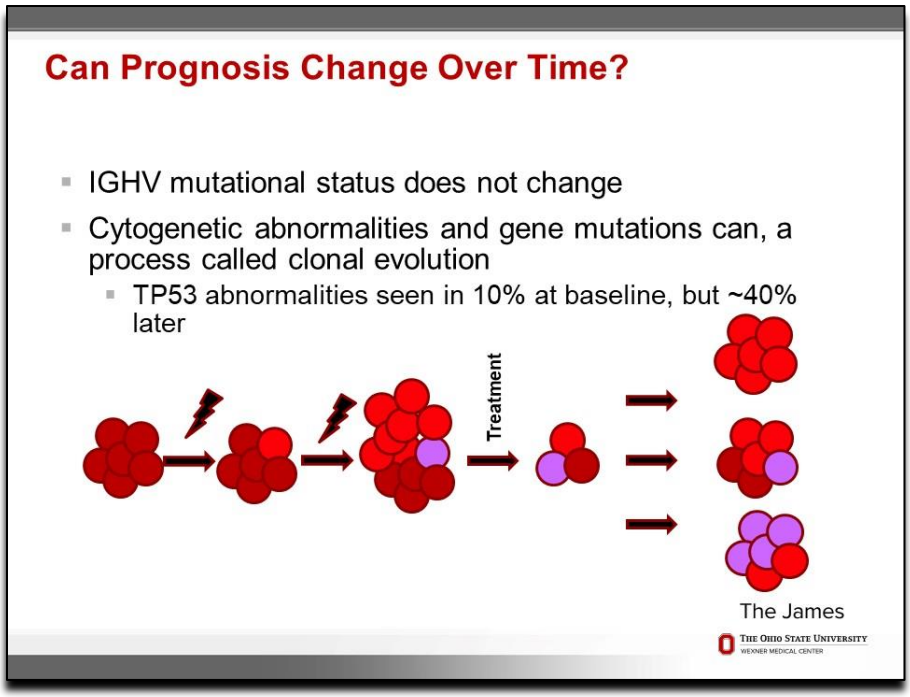
And a deletion of 17p right now indicates people who have the most aggressive type of CLL, which is because of a loss of a tumor-suppressor protein called TP53. This is seen in about 10% of people at the time of diagnosis or first treatment. And seen in a little bit higher amount in people who have CLL that's relapsed after treatment.



TP53 Mutation

The TP53 mutation is another prognostic factor in CLL that is becoming increasingly important because it's easier and easier to test for a gene mutation. And this is really right now the only mutation that we use specifically to help us with prognosis in CLL. There's a lot of mutations that you can find in CLL cells if you look at enough patients. Most of the mutations are very uncommon.

TP53 mutation, though, which is related to the 17p deletion in most patients, is seen in about 10% to 15% of people at the time of diagnosis.

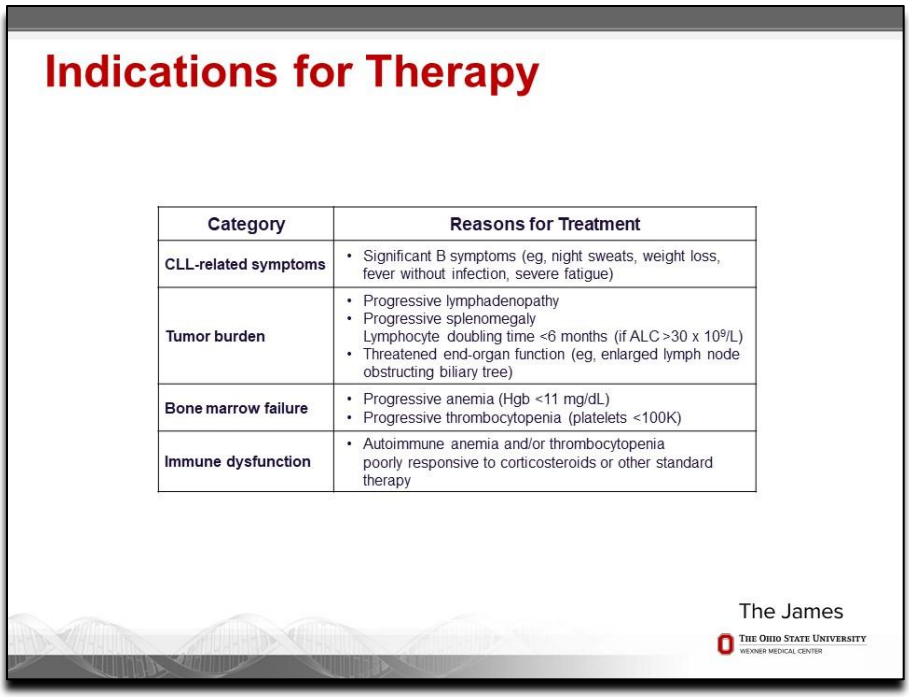


Can Prognosis Change Over Time?

So, one big question that people have is if we do this FISH testing, IGHV, things like that at the time of diagnosis: Are these things going to change over time? So, we think from the IGHV status is something that does not change. And typically, we would never test this again in somebody who's already had it checked.

The cytogenetic abnormalities, the FISH abnormalities, the gene mutations like TP53 can. And this is a process that's called clonal evolution, whereby cancer cells just by virtue of being cancer cells can acquire new mutations as they divide. And sometimes those mutations don't do anything and they just carry on. And sometimes those mutations can be important, and those mutations can select for a group of cells that are going to continue to proliferate.

One of the things that accelerates this process that's called clonal evolution is treatment, especially things like chemotherapy that are directly damaging DNA.



Indications for Therapy

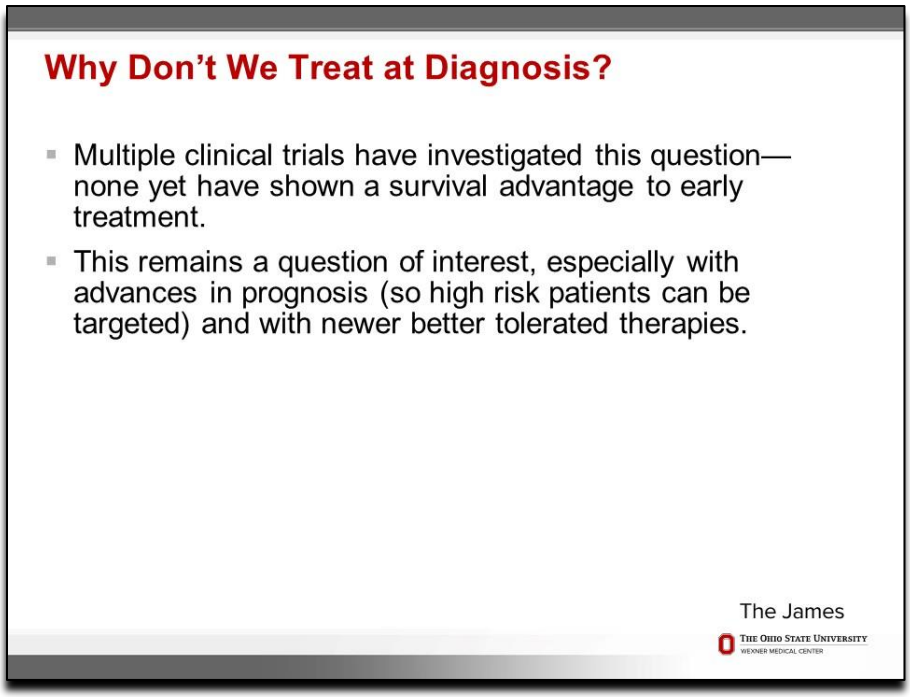
So, when we talked about starting therapy for CLL, we really need a reason to do so. And so, our indications for therapy currently come in four separate categories. And one of those, which is really the most common reason why we start treatment, are CLL-related symptoms. So, these are kind of constitutional or whole-body symptoms that are happening just because the disease is more active.

The most common of these is going to be fatigue. And when we think about this, we think of fatigue that is severe enough that it is limiting what people want to do during the day. So, are they needing to take a nap and not able to do their work, not able to do things around the house? People also less commonly can develop other symptoms, like night sweats, weight loss, and fever without an infection. We also think of an indication for therapy in terms of higher amounts of CLL or increased tumor burden. And by this, we mean things like increasing in size of lymph nodes, increasing in size of spleen, when the white count goes up very quickly.

And then, less commonly, if the enlarged lymph nodes are just in a place that is bad placement. So, if there's an enlarged lymph node that's around the liver and the bile ducts, that can cause symptoms. It can cause problems with liver function.

If there's a big group of lymph nodes that's pressing on the ureter, which is the tube that connects the kidney to the bladder, that can cause problems. Again, in CLL, that's actually not that common. It's much more common with other types of lymphomas.

Bone marrow failure is another indication for therapy. And so, this is when the bone marrow gets so full of CLL that it can't produce normal cells. And then, immune dysfunction, which usually are things like autoimmune anemia, where the body breaks down red blood cells, or autoimmune thrombocytopenia, where the body breaks down platelets.



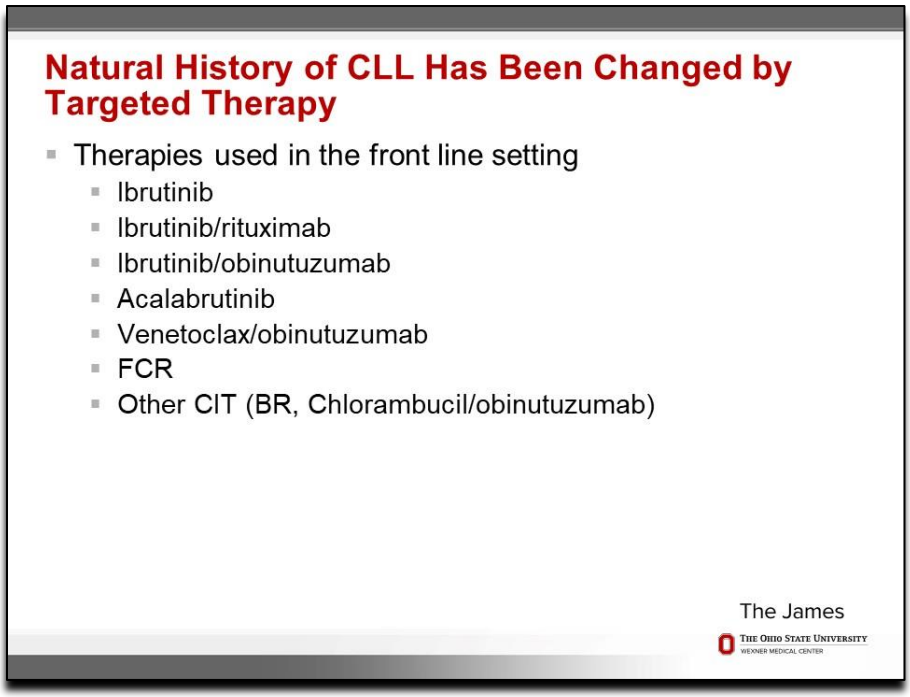
Why Don't We Treat at Diagnosis?

So, a big question most people have at diagnosis is, "Why don't we just treat it at diagnosis and do something about the cancer?" For CLL, since most of our therapies are not considered to be curative, one reason not to do this is because if somebody is feeling fine and you give them a treatment that's not going to cure them, all you really have done is give them symptoms, unless we show that that therapy actually is going to give people survival advantage overall.

There's been a lot of trials investigating multiple different types of therapy, and so far none have yet shown a survival advantage to treating people at diagnosis rather than waiting until they developed symptoms. Though, this is still a question that is of a lot of interest, especially as we're getting therapies that are better and better tolerated and more and more effective. And also, better ways to do prognosis.

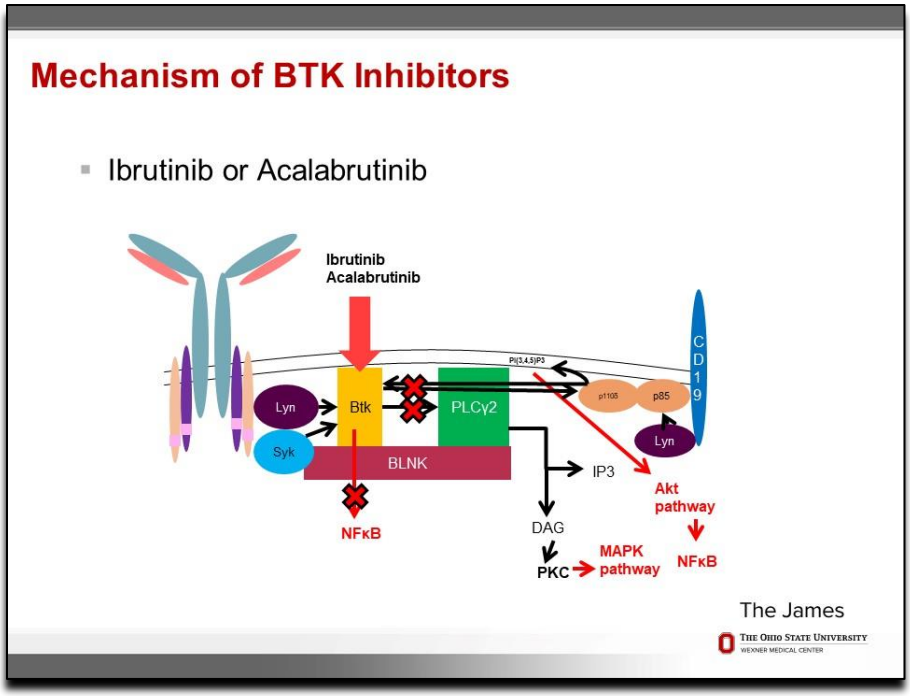
So, there's no reason to treat somebody who is never going to need therapy in the course of their lifetime. But if we did predict the people who are going to need treatment soon or have a high likelihood of developing more genetic abnormalities and being resistant to therapies, that might be a group that is really important to target early.

So, there are still lots of clinical trials that are investigating that.



Natural History of CLL Has Been Changed by Targeted Therapy

Now, the natural history of CLL or how people do over time has been changed very, very dramatically by the introduction of targeted therapies. And I'm going to spend a bit of time now talking about some of the therapies that we use in the frontline setting.



Mechanism of BTK Inhibitors

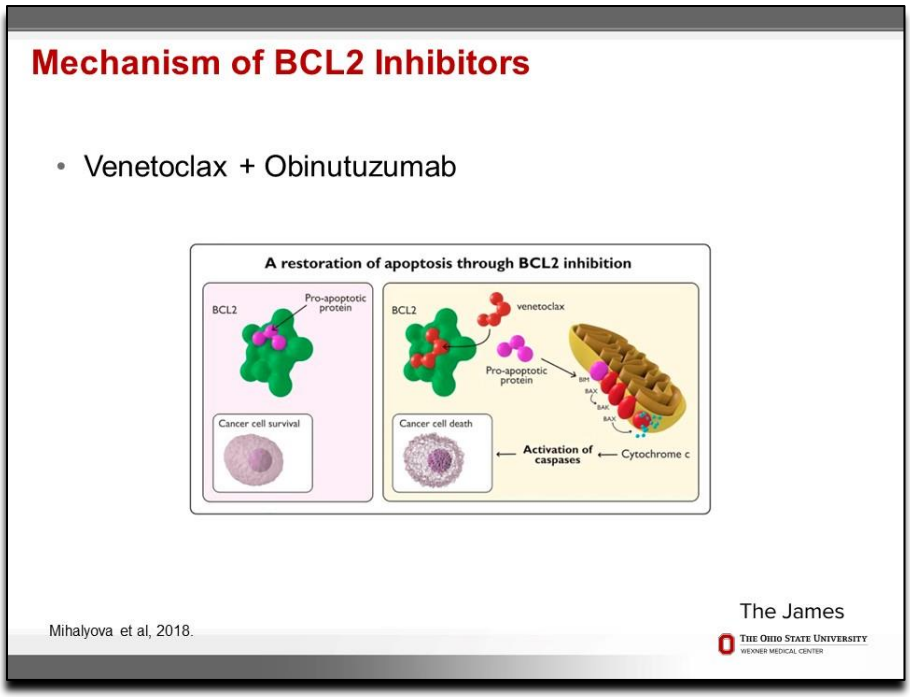
And these are the BTK, or Bruton's tyrosine kinase, inhibitors: ibrutinib (Imbruvica®) or acalabrutinib (Calquence®) that can be given either alone or with antibodies, like rituximab (Rituxan®) or

obinutuzumab (Gazyva®), the BCL2 inhibitor venetoclax (Venclexta®), which is usually given with an antibody as well.

And then there also are some chemotherapy regimens, such as fludarabine (Fludara®), cyclophosphamide (Cytoxan®), and rituximab (Rituxan®), or FCR, and then other chemotherapy drugs. And we'll talk about some of the studies that have been done that have kind of visioned these as our frontline therapies.

So, this is a pretty scientific mechanistic drawing here that is not important to memorize, but basically it is showing us the top of B-cell reflector signaling in CLL. And the basic explanation is that signaling inside of CLL cell is very dysregulated. So, it doesn't really do anything productive to a person. All that that signaling is doing is making extra copies of the cancer cells.

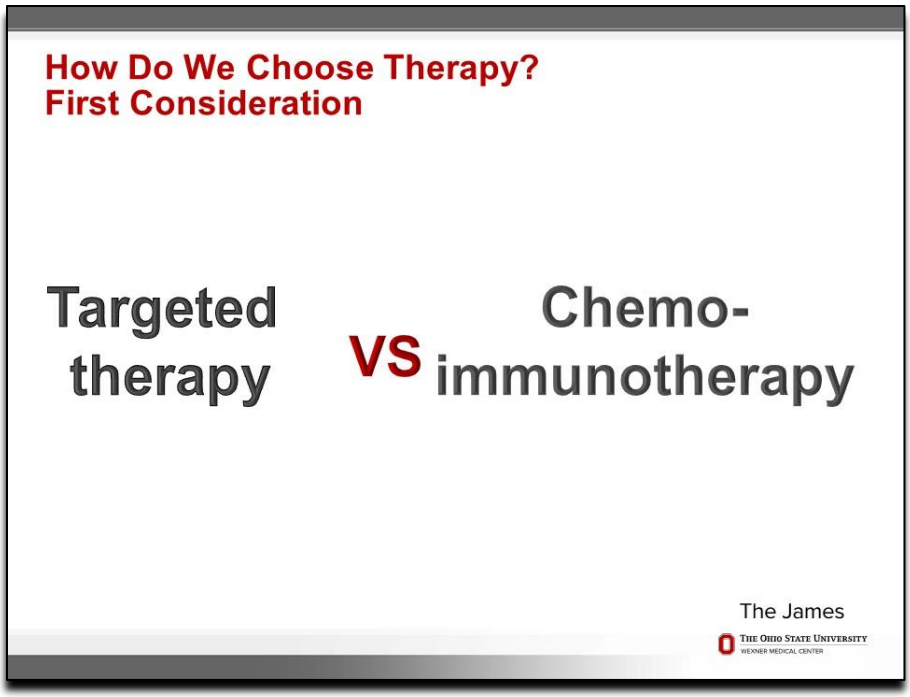
It is then demonstrated that BTK, or Bruton's tyrosine kinase, is a protein that is very, very important in the signaling. And if it is shut off, there's really not a good way for a cancer cell to get around that. So, it's kind of like flipping off a light switch to the CLL cells. And all of the signaling that is creating more cancer cells and doing other things that are bad for a person gets shut off with these inhibitors of BTK. The ones that are currently FDA approved for use in CLL are ibrutinib and acalabrutinib.



Mechanism of BCL2 Inhibitors

And then, we also have this newer drug, venetoclax, which is a BCL2 inhibitor. So, BCL2 is what's considered an antiapoptotic protein, which means that it keeps cells alive. And a lot of cancers, including CLL, the CLL cells will produce more and more BCL2 to keep themselves alive longer. And one of the things that extra BCL2 does is it keeps the proteins that are supposed to cause cell death or proapoptotic proteins from being able to work.

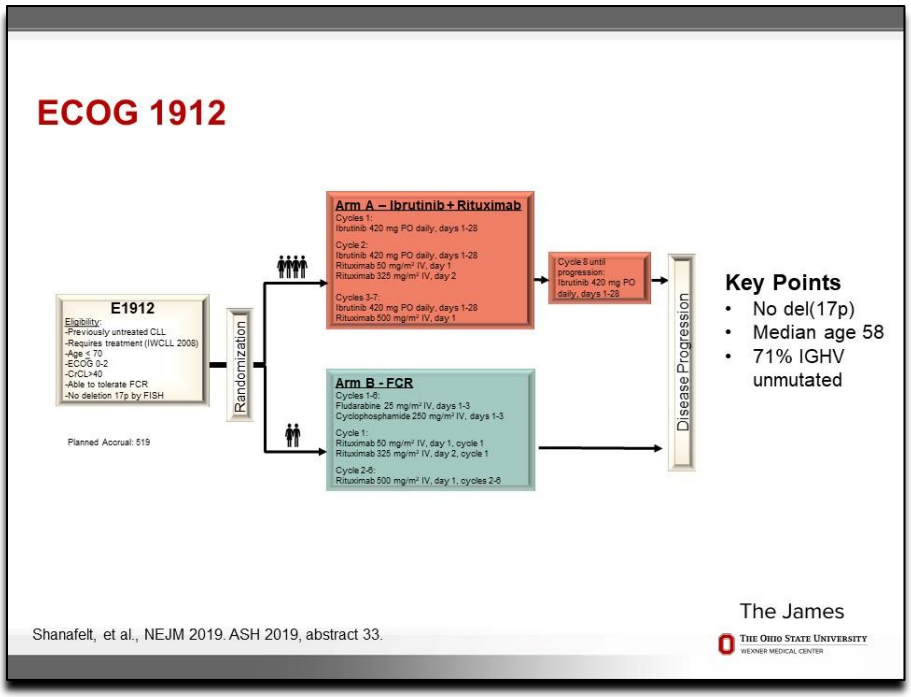
And so, what venetoclax does is it occupies that extra BCL2 so that the cell can undergo its normal process of cell death.



How Do We Choose Therapy? First Consideration

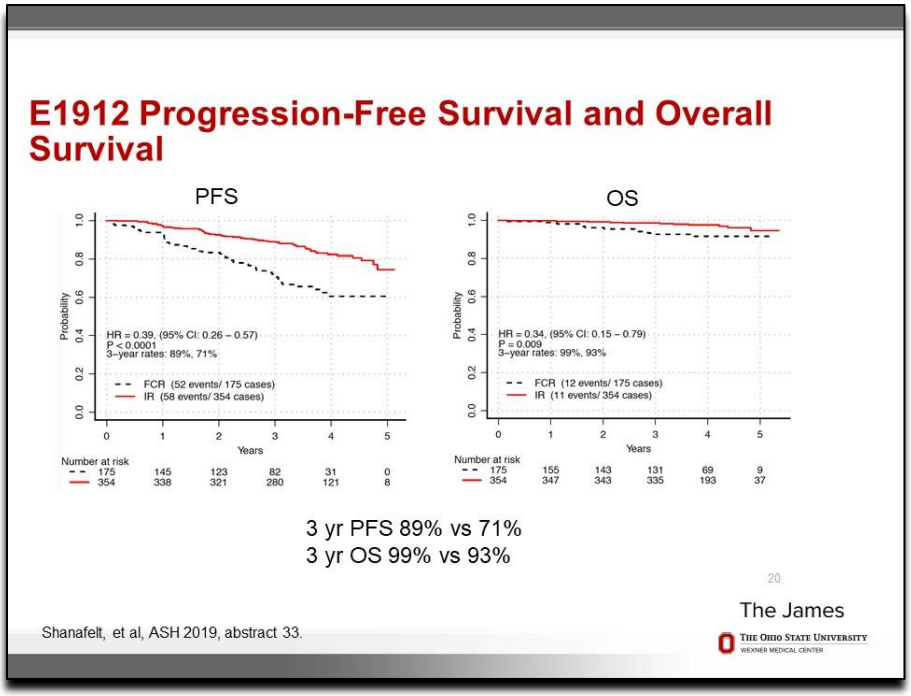
So, how do we choose therapy? And this is something that your doctor's thinking about a lot behind the scenes. In some cases, discussing it with the patient and, in some cases, these calculations kinds of take place and are already decided before even talking to somebody.

So, the first question is should we be doing a targeted therapy or chemotherapy with an antibody called chemoimmunotherapy. And I'm going to show you some data from clinical trials, and it's not really important to remember how these studies were designed or remember the exact intricacies of the outcomes. But hopefully I'll be able to get across some of the general points here, which are really relevant when you're thinking about therapies.



ECOG 1912

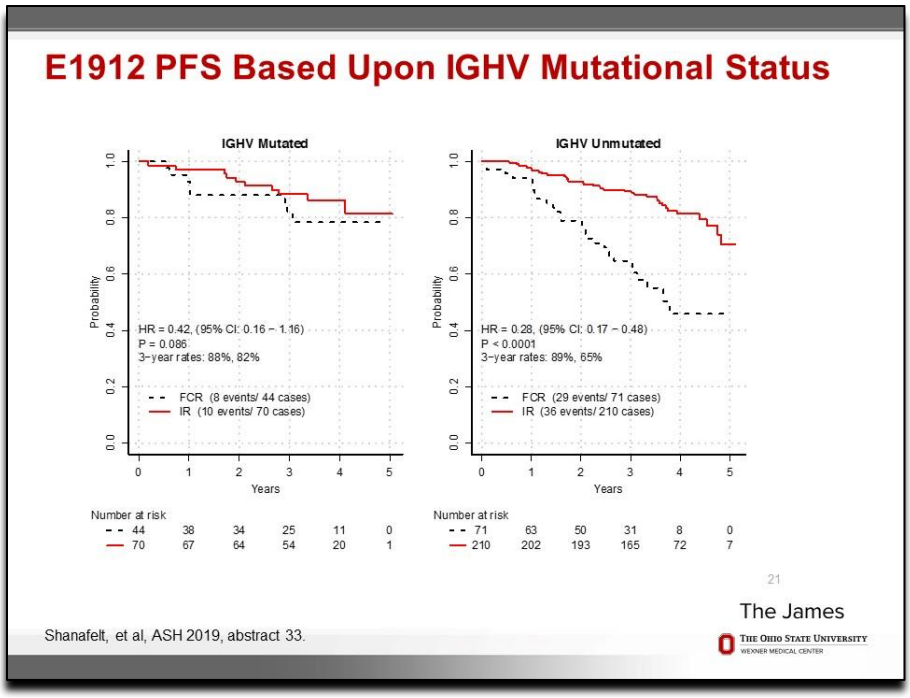
So, one of the big studies that has helped us decide chemotherapy or targeted therapy is the ECOG 1912 study. And this study was taking patients who were younger. So, in CLL, this is under the age of 70. And randomizing them to either receiving their first treatment, ibrutinib plus rituximab, or chemotherapy with FCR.



E1912 Progression-Free Survival and Overall Survival

And what this study showed is that those progression-free survival or time of remission as well as overall survival were better in people who received ibrutinib plus rituximab than those who received

FCR, which is very, very important and one of the only studies that has actually early on showed a survival advantage of one therapy over another. It's actually hard to do in CLL because there are so many good options for a second-line therapy, but I think that this just shows us how effective our targeted therapies are.

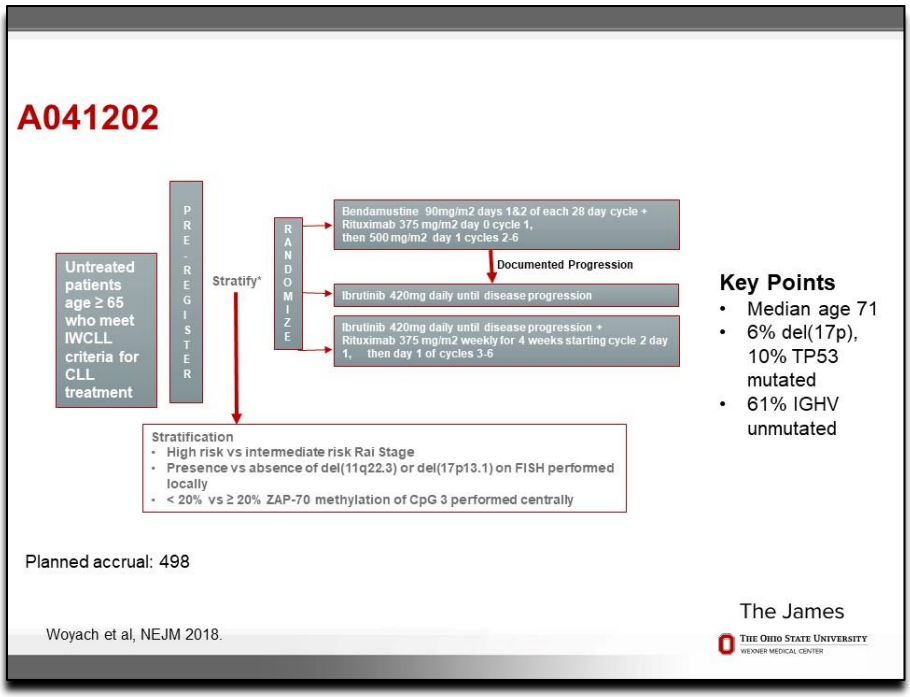


E1912 PFS Based Upon IGHV Mutational Status

I put this slide up here to show you how prognosis is different in the setting of targeted therapies based upon that IGHV mutational status. And what we see here is that most of the benefit of the targeted therapy or the ibrutinib is because of patients who have unmutated IgVH, where the FCR is not working as well.

In the patients with mutated IgVH, there is not much difference between those two groups. So, this could change over time. And really, the reason why there's no difference is a good one, which is that people are doing well whether they get the ibrutinib/rituximab or they get the FCR.

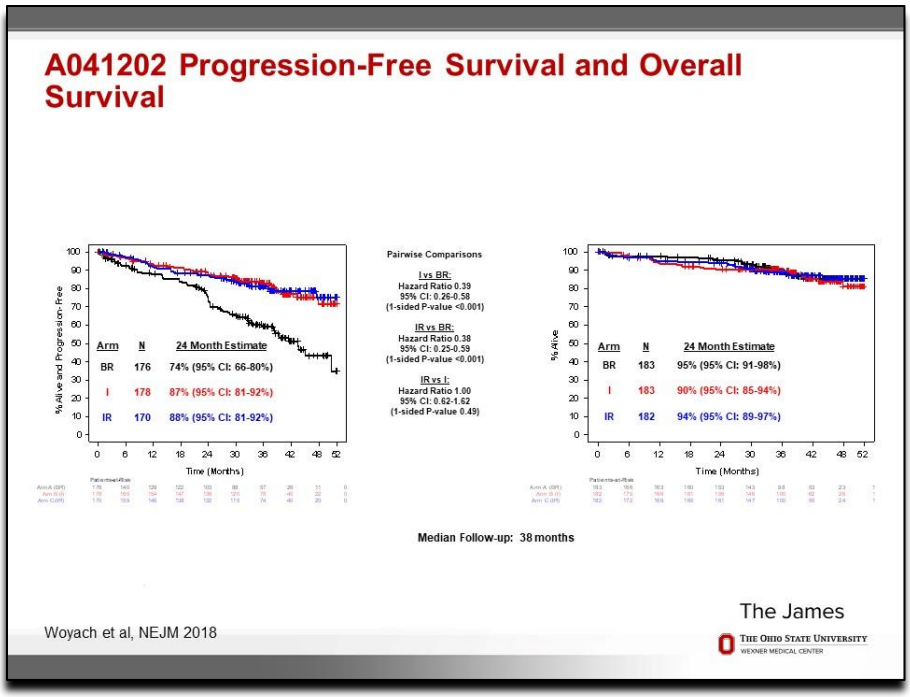
So basically, the way that people are interpreting this trial right now is that ibrutinib/rituximab is better than FCR. Although there might be some people who have mutated IGHV who are younger, who are fit, who would like to have a therapy that's going to stop in 6 months that might still be appropriate for FCR.



A041202

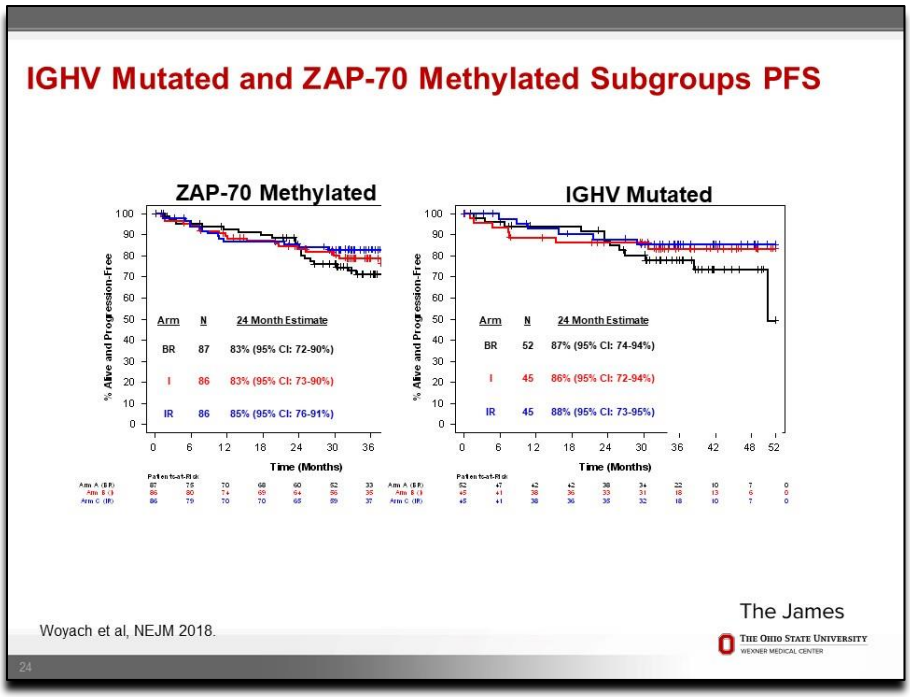
The other big study that helps us decide chemotherapy versus targeted therapy is A041202, which is a study looking at older patients. So, in this case, age 65 or older who are getting their first treatment for CLL. And in this study, we randomized patients to bendamustine plus rituximab or BR or to ibrutinib by itself or to ibrutinib plus rituximab.

This study also has a crossover design where people who were on the BR arm who have progression of their CLL can then move over and get ibrutinib at that point.



A041202 Progression-Free Survival and Overall Survival

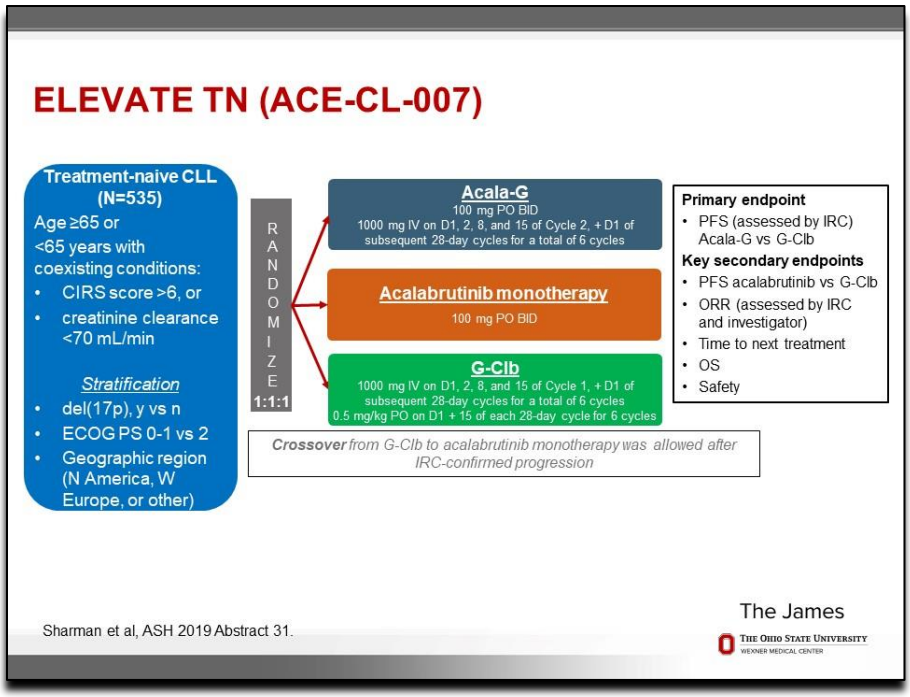
And similar to the study that I showed you before, we see a big advantage to using the ibrutinib or the ibrutinib plus rituximab when we're talking about remission duration. This study did not show a difference in overall survival at least at this point. And one of the big reasons for that is because of that crossover design. So, if people get the chemotherapy, they progress, they get ibrutinib, hopefully the ibrutinib is going to work at that point. And then, we're really not going to see a survival difference.



IGHV Mutated and ZAP-70 Methylated Subgroups PFS

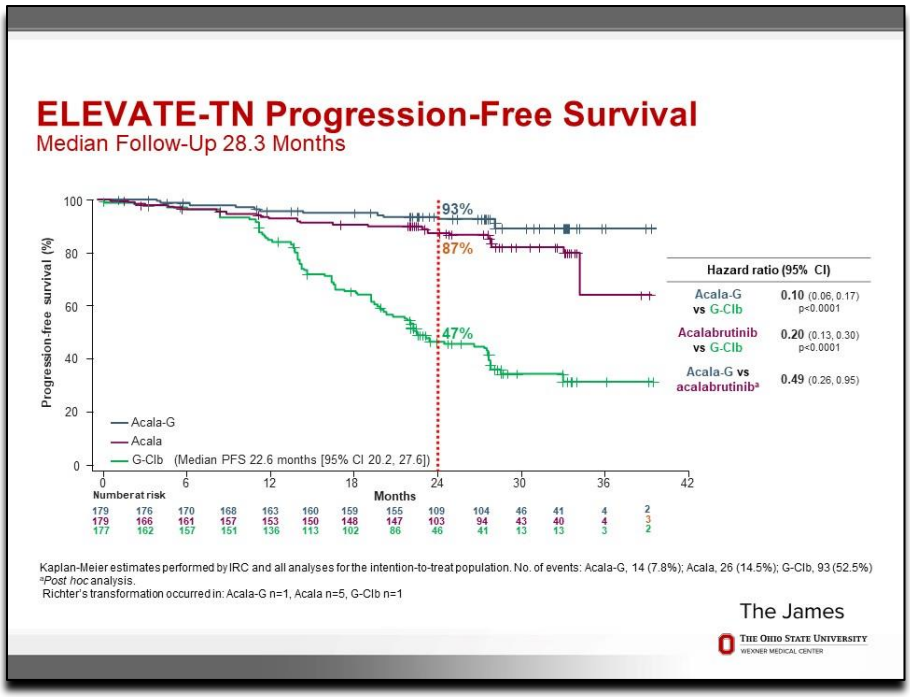
And again, in this study too when we look at the people who are expected to do very well, those with the IGHV-mutated disease. And in this case we also talk about ZAP-70 methylated, which is pretty similar. And we see that there is less of a difference among the different treatment regimens in this case, but it still does look like the targeted therapies do better than chemotherapy.

The other important thing we saw from this study is that there is not a difference between ibrutinib given by itself and ibrutinib given with rituximab. So, the rituximab, in this case, doesn't add anything. So, most doctors are offering ibrutinib by itself, except in specific circumstances.



ELEVATE TN (ACE-CL-007)

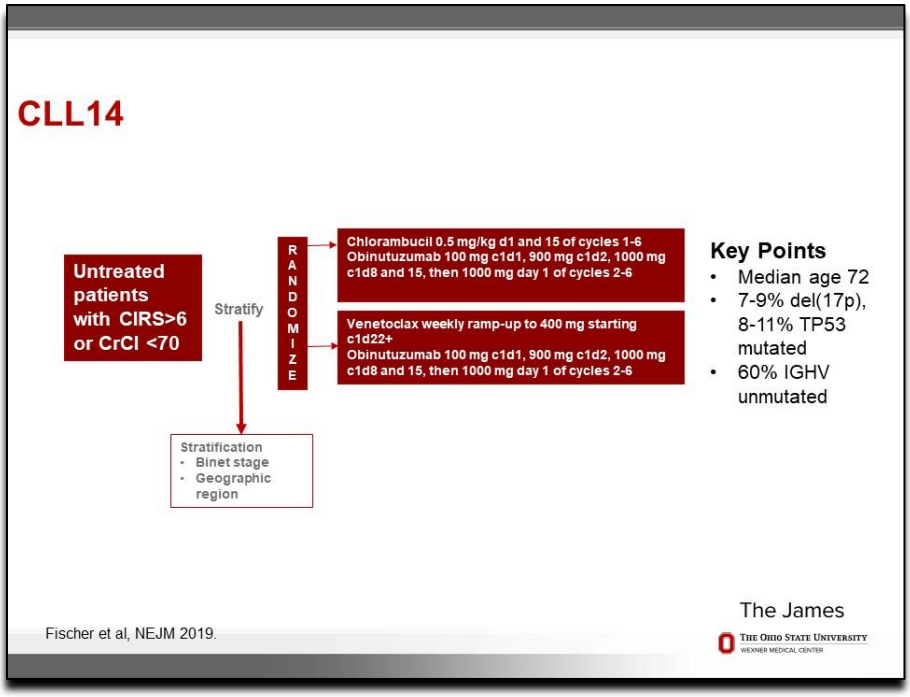
I also wanted to show you guys the data for the acalabrutinib study. So, this is a second-generation BTK inhibitor. It's a little bit more specific than ibrutinib. And for some people, it's better tolerated.



ELEVATE-TN Progression-Free Survival: Median Follow-Up 28.3 Months

So, this is the clinical trial that led to the approval of this agent for frontline treatment of CLL. And in this study, people who were age 65 or older or who were younger but had other comorbid medical problems were randomized to receive acalabrutinib by itself, acalabrutinib plus a CD-20 antibody called obinutuzumab, or a chemotherapy regimen called chlorambucil (Leukeran®) plus obinutuzumab.

Similar to what we see with ibrutinib, we see that patients that are treated with acalabrutinib either alone or in combination with the antibody have longer remissions than those treated with chemotherapy.

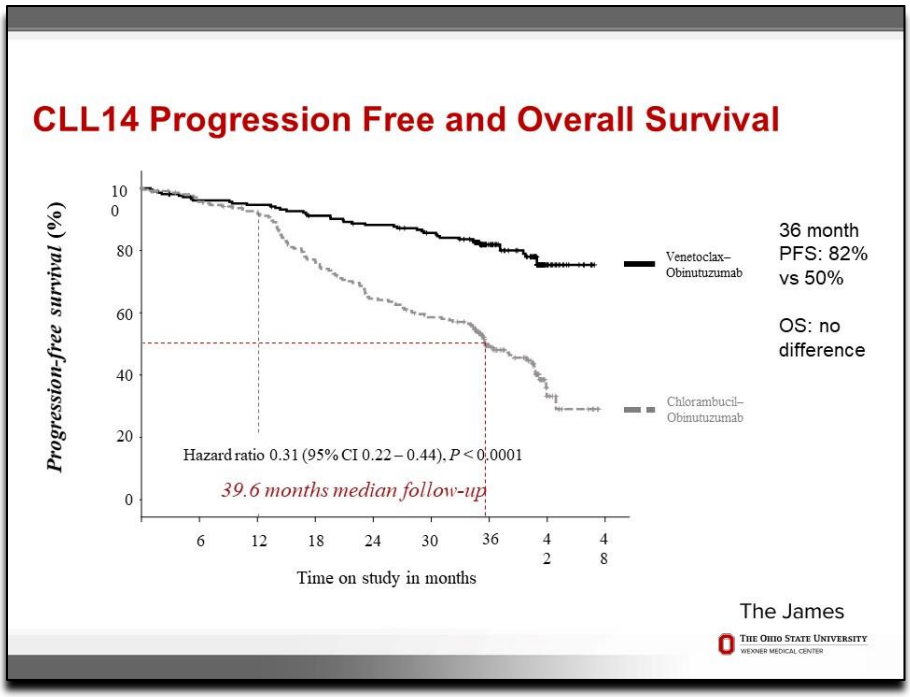


CLL14

I also want to show you a trial that was looking at that BCL2 inhibitor venetoclax in combination with the CD-20 antibody obinutuzumab. An important difference between venetoclax and the BTK inhibitors, like ibrutinib and acalabrutinib, is that those ibrutinib and acalabrutinib were meant to be given indefinitely. So, they're started when somebody needs treatment. And then, unless it stops working or people don't tolerate the drug, it's just continued potentially forever.

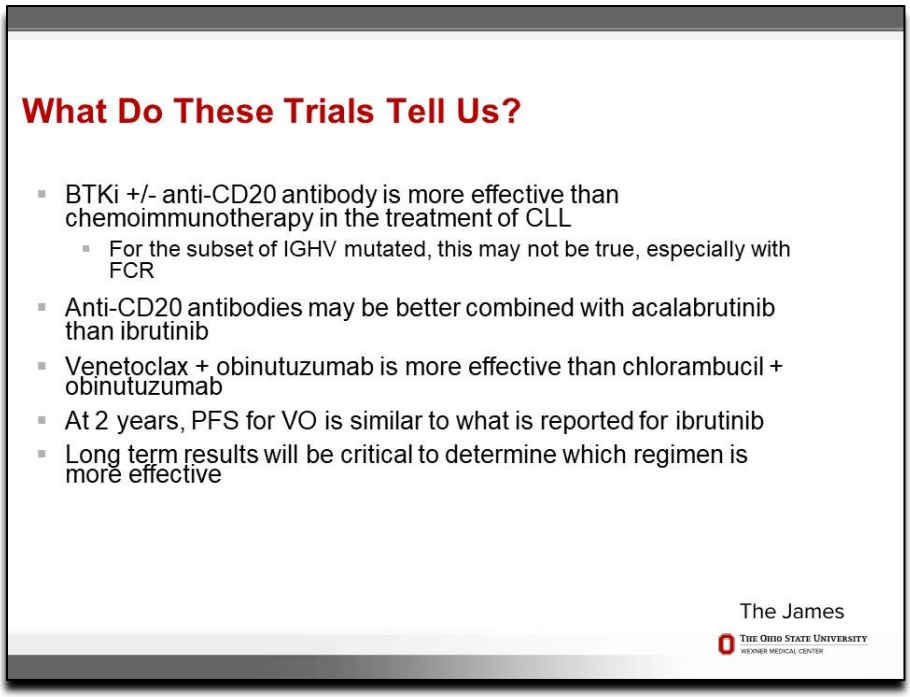
We, actually, at Ohio State started doing the first ibrutinib study back in 2010 and still have people who are on those same trials.

So, in contrast, venetoclax is meant to be given for a limited duration. So, in the case of people who have never had treatment before, it's 1 year. And that's in combination with about 6 months of the antibody obinutuzumab.



CLL14 Progression Free and Overall Survival

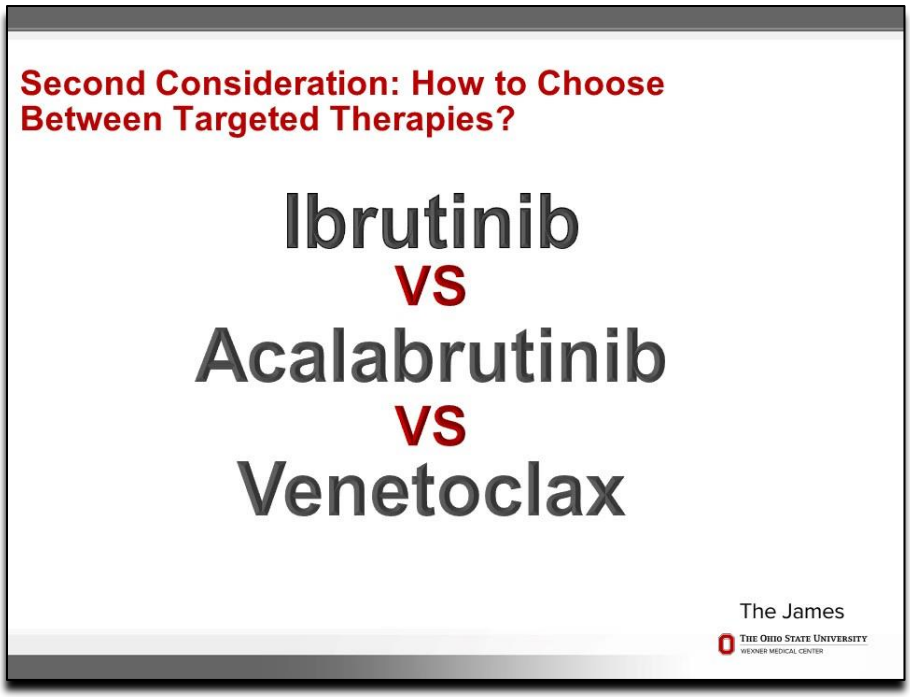
So, this study randomized patients to receive that venetoclax plus obinutuzumab combination versus a chemotherapy regimen: chlorambucil plus obinutuzumab. And we see, again, that patients who are treated with a targeted therapy do better overall than people who are treated with the chemotherapy regimens.



What Do These Trials Tell Us?

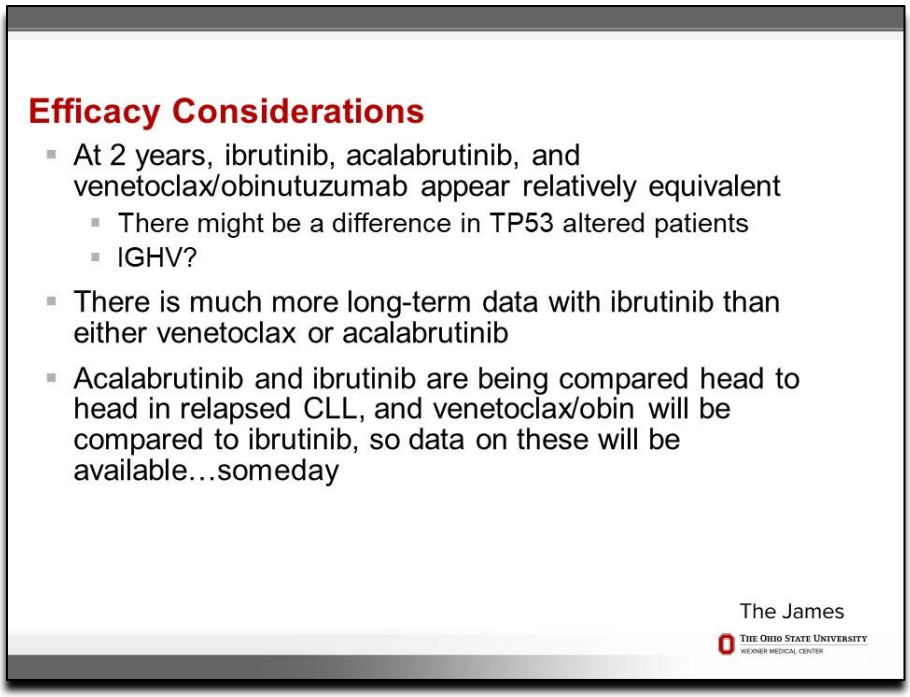
So, what did we learn from these studies? We see that BTK inhibitors, with or without antibodies, are more effective than chemotherapy. And this is one caveat that may be for patients with IGHV-mutated disease: there might still be some benefit to that FCR chemotherapy regimen.

I didn't really spend time talking about this, but the antibodies might be better combined with acalabrutinib than ibrutinib. We see the venetoclax plus obinutuzumab is more effective than chemotherapy. And really, what these short follow-ups, the remission durations for the venetoclax combination is pretty similar to what we see with ibrutinib and acalabrutinib. So, we're really going to need to wait longer to see if one of these regimens is more effective than the others.



Second Consideration: How to Choose Between Targeted Therapies?

So, the second consideration is how would you choose between these targeted therapies? So, we have ibrutinib, we have acalabrutinib, and we have venetoclax.



Efficacy Considerations

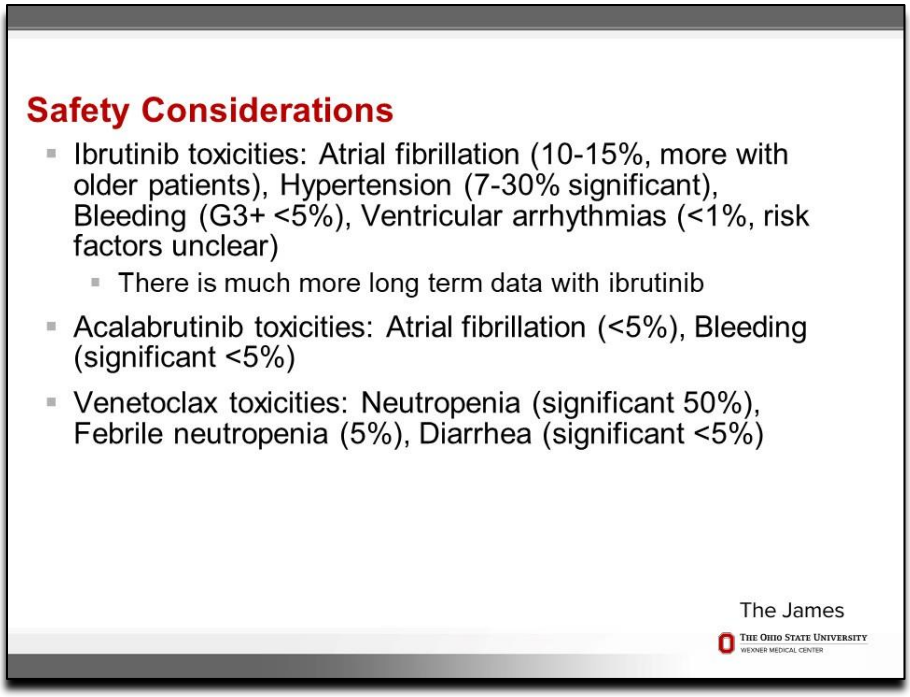
Now, I've already told you that at least in the short-term, these appear to be fairly similar. There's some suggestion when you look at all of the trials that have been done that patients who have 17p deletion or TP53 mutation might do better with BTK inhibitors than with venetoclax. So, that's not entirely

known for sure. And we don't really know yet whether IGHV mutational status is going to make a difference, too.

There's certainly much more long-term data with ibrutinib than either venetoclax or acalabrutinib, just because the drug has been around longer. And we do know that acalabrutinib and ibrutinib currently being compared head-to-head in a randomized study. So eventually, we'll know which one of those drugs is better. But, it's going to take us a while to find that out.

So right now, I think we can't really say that much differentiates those drugs in terms of how well they work.

So, the next consideration is, "Is one safer than the other?" Now, I'll start by saying, again, we have much more long-term data with ibrutinib, which is good because we know what those side effects are. They also make it seem like those side effects are much worse just because we know so much more about them.



Safety Considerations

So, with ibrutinib, we know that people can develop atrial fibrillation and that's seen in about 10% to 15% of patients. Much more common in older patients than younger patients. We see hypertension is something that occurs with more and more exposure to the drug. So, people who have been on it 3 years are more likely to get it than people who've been on it for 1 year.

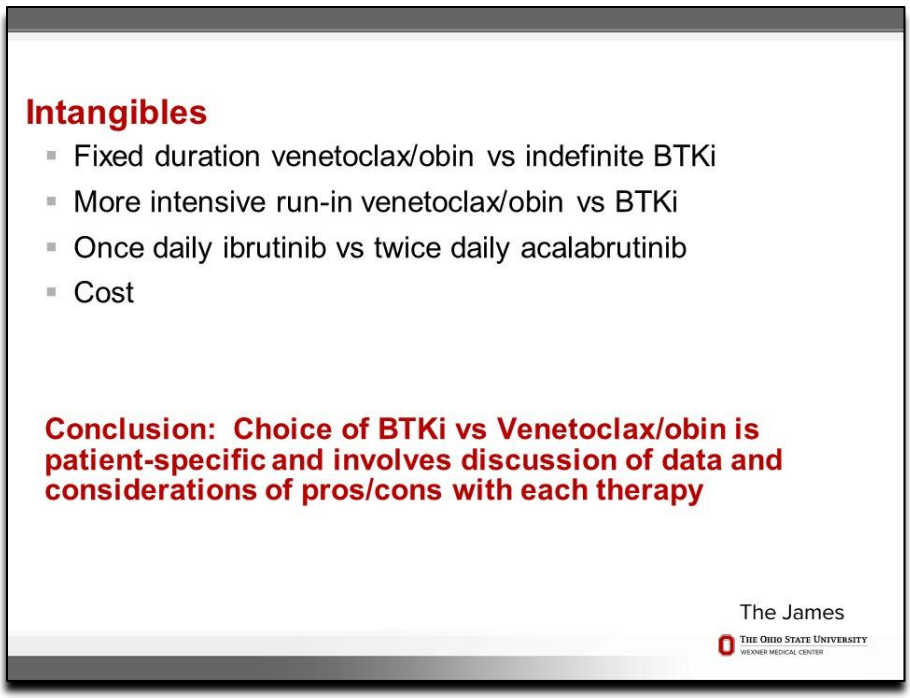
We see bleeding as a complication of ibrutinib as well. It's really very uncommon to have significant bleeding, but bruising is very common. And then, I mentioned atrial fibrillation already, which can usually be managed with medication. However, some patients will develop what are called ventricular arrhythmias, which are more dangerous but luckily a lot less common.

So, with acalabrutinib, much of the toxicities are the same because of inhibition of either BTK or other proteins that are similar in structure and are just inhibited by the drug along with BTK.

It seems like some of the side effects for acalabrutinib are less common than with ibrutinib. Like, atrial fibrillation seems to be less. Bleeding risk seems to be about the same. Hypertension seems like it's

less as well. However, I think we really need to wait until we get more data with acalabrutinib to say for sure that these toxicities are actually very different between the drugs.

Venetoclax works completely different and the side effects are completely different. It causes a lot more neutropenia, which is lowering of good white blood cell counts, which can put people at risk for infection. It causes some diarrhea, and so do ibrutinib and acalabrutinib. I think that the diarrhea with venetoclax in some patients can be worse, but it doesn't happen very often.



Intangibles

And then, I also like to think of some of the intangible differences between the drugs, which don't necessarily make a difference for everybody, for each patient, but for some patients are very important. So, I always like to talk about these with the patient.

The first big thing is that fixed duration. So, with venetoclax/obinutuzumab, it's 1 year of treatment and then stop, versus BTK inhibitors, which are started and then don't plan to stop. The converse of this, though, is that when you start venetoclax plus obinutuzumab, it is a lot more time intensive on the part of the patient than a BTK inhibitor.

So, with venetoclax, one of the things that we worry about is called tumor lysis syndrome, where the CLL cells actually can break down too quickly. So, patients have to come in for a lot of lab draws and many times stay in either the hospital or in the clinic all day to get their venetoclax dose plus some laboratory checks. They also have to come to get that antibody, which is given through the IV.

And in contrast to that with a BTK inhibitor, we write a prescription, patient gets a drug delivered to their doorstep, and then they just start taking it. They still have to come in for labs. They still have to come in for visits, but it tends to be a lot less time and a lot less effort on the patient.

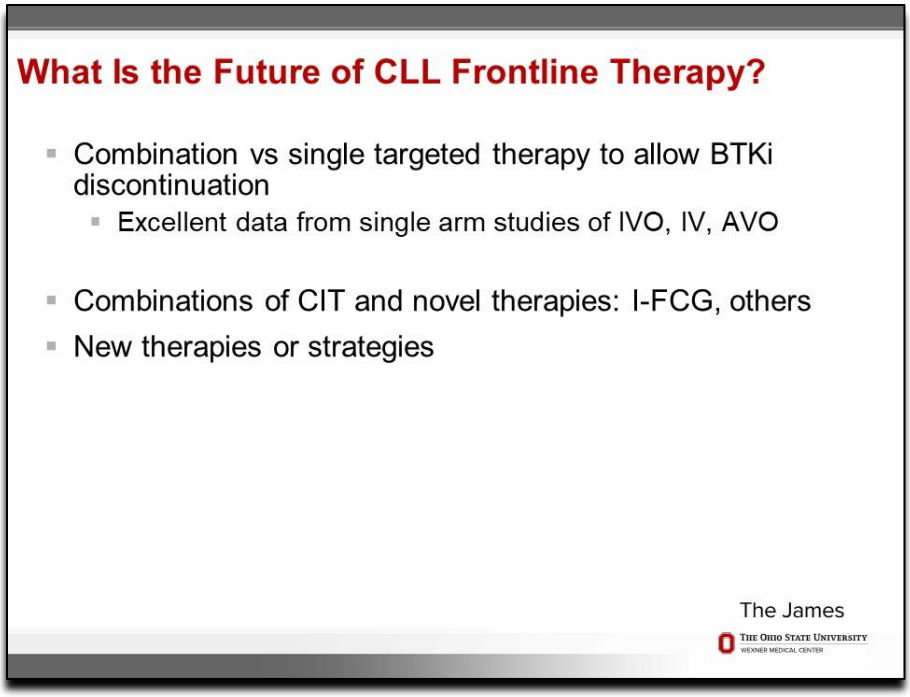
Between ibrutinib and acalabrutinib, ibrutinib is given once a day whereas acalabrutinib is given twice a day. And if somebody's already on other medications that are taken twice a day, that's probably not a big deal. If they're not, that can be a big difference in their lifestyle. And with these drugs, it's really important that they're taken every day. So, I always make sure if I'm going to give somebody

acalabrutinib that we really have an honest discussion about whether twice-daily medications is going to be something that they can do.

We're still trying to understand what is really the difference of cost of the regimen. So, the drugs all have fairly similar cost and they cost a lot. When you give an antibody, the cost is even higher. Obviously, if they all work the same, giving venetoclax is going to be less costly because the drug is only given for a year. But, we don't really know how long those remissions are going to last. So, if you have to give it again in 2 years, then you really don't have as much of a cost difference.

So, these are all things that are still being studied in a lot of clinical trials and in some of just the analyses of patients that are repeating the drugs.

So, I think really the choice of these BTKI inhibitors vs venetoclax plus obinutuzumab is patient specific. It involves a discussion of all these data that we talked about, considerations of some of the pros and cons of each therapy, and really understanding what's best for each individual patient.



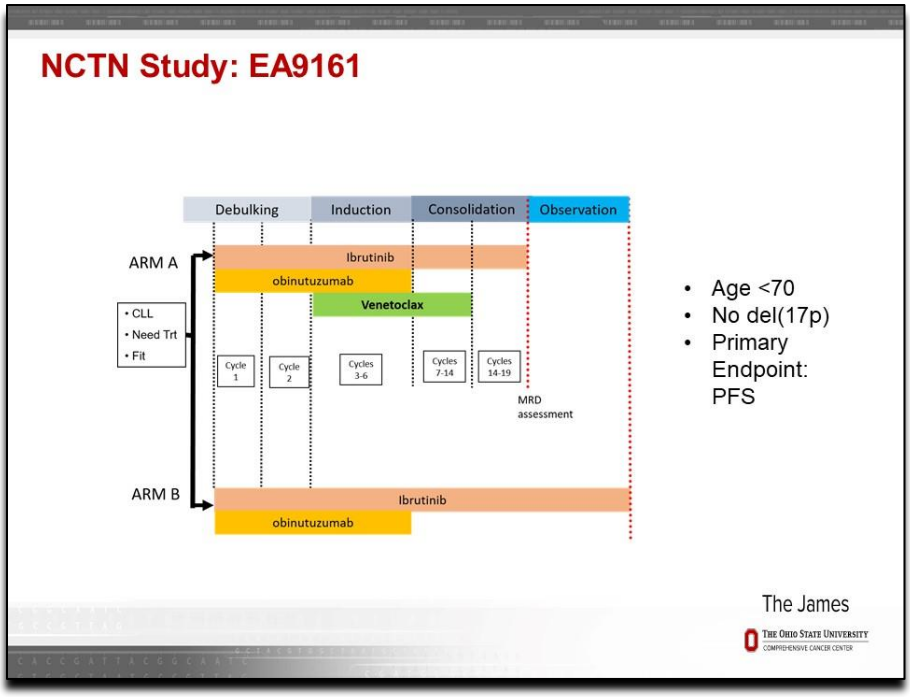
What Is the Future of CLL Frontline Therapy

So, what's the future of CLL frontline therapy? Things have been changing very, very rapidly and there's no reason to think that that's not going to continue to happen. There's a lot of interest right now and actually, combining all of these mechanisms so take a BTK inhibitor, and add a B-cell inhibitor, and maybe we can make them work even better. And in smaller clinical trials, this seems to be the case.

People are also interested in combining chemotherapy with ibrutinib or with acalabrutinib or even with venetoclax to see what you can shorten the amount of chemotherapy somebody gets and also shorten the amount of time they're on that therapy.

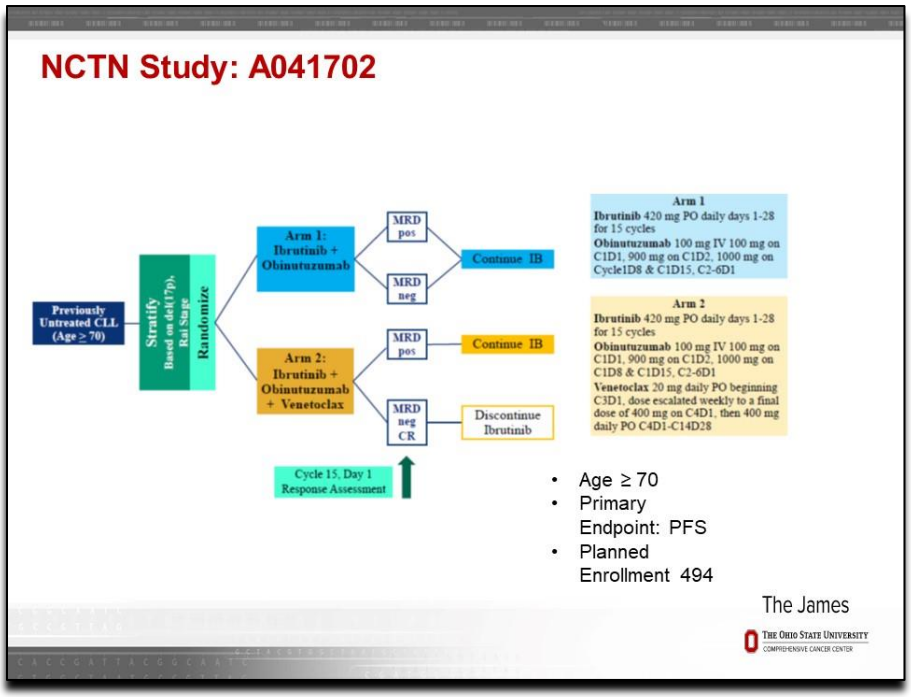
I wanted to just point out two ongoing studies that are countrywide studies. So, they are open to people in all different settings. So, it's community practices and academic centers that are really trying to get at the question of what is the best therapy for CLL patients right now. One other

advantage of participating in these studies is that all of the drugs are paid for by the study. So, neither a patient nor their insurance has to pay for these drugs.



NCTN Study: EA9161

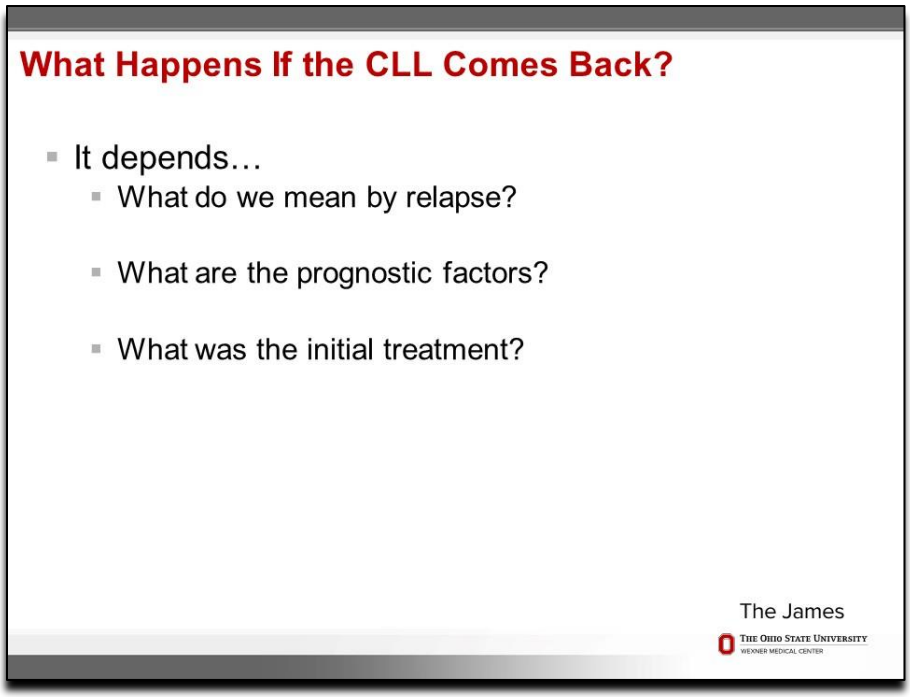
So, these are the successors to two of the trials I talked to you about before. And the first one is EA9161, which is for patients under the age of 70. And patients here are randomized to ibrutinib plus obinutuzumab, and that's our standard-therapy arm. Or ibrutinib plus obinutuzumab plus venetoclax. And in this study, at the end of about 18 months, anybody who was on the three-drug arm will stop all drugs, whereas those that are on the two-drug arm will continue ibrutinib. So, the goal of this study is to see which one of these produces longer remission.



NCTN Study: A041702

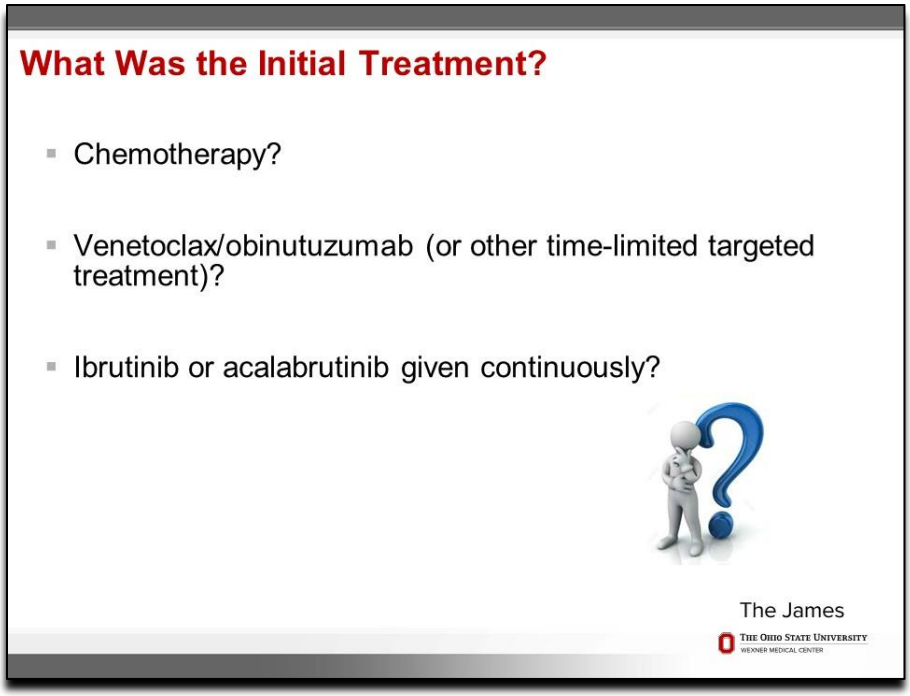
The successor to the Alliance study is A041702. And this is for patients aged 70 and older. And similar to that other study I showed you, people are randomized to ibrutinib plus obinutuzumab versus ibrutinib plus obinutuzumab plus venetoclax. In this study, people who are getting the two drugs will continue ibrutinib indefinitely. Those that are getting the three drugs, at the end of a year, will have their response evaluated. And those that are in a complete remission where we can't detect any CLL will discontinue all drugs.

So this, again, is designed to see whether the two-drug or three-drug regimen is better.



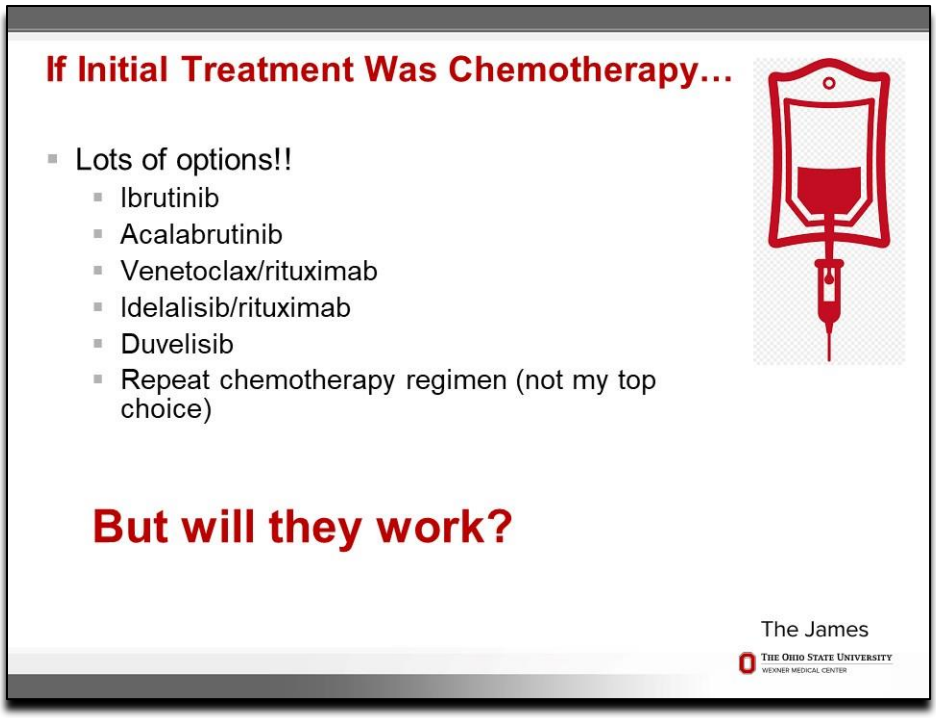
What Happens If the CLL Comes Back?

Another big question is what happens if the CLL comes back? And it depends on what we mean by the relapse. What does it mean when the CLL comes back? What are the prognostic factors? And what was the initial treatment that the patient got?



What Was the Initial Treatment?

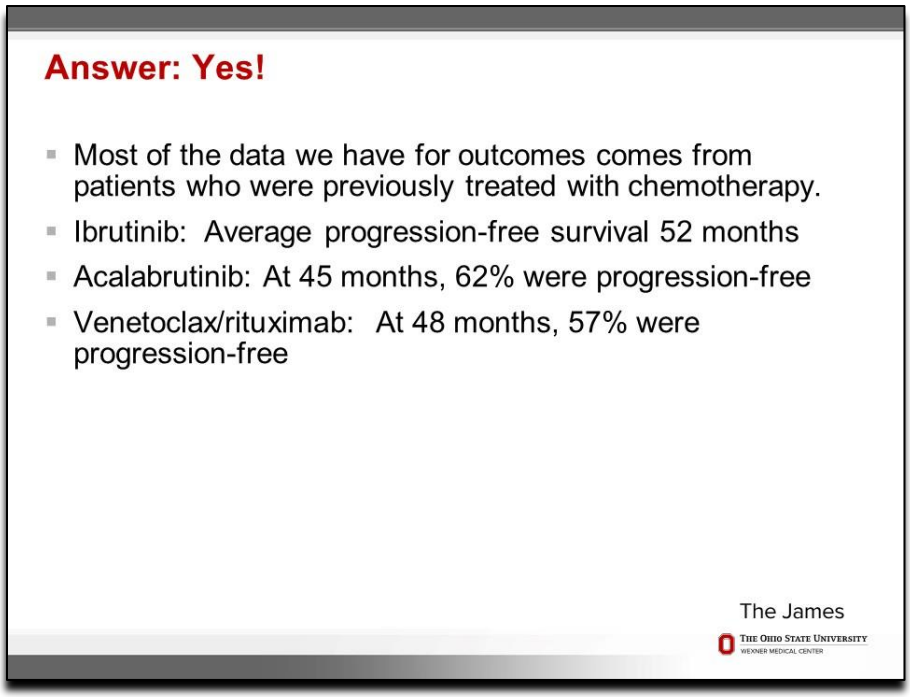
And so, we think about this the initial therapy chemotherapy or was it venetoclax plus obinutuzumab or was it ibrutinib or acalabrutinib?



If Initial Treatment Was Chemotherapy…

And so, if the initial treatment was chemotherapy and the CLL comes back, there are lots of options. We can really do any of our targeted therapies and they're very likely to work. We also could repeat the same chemotherapy regimen. This is not my top choice, and most other physicians don't do this now either since we know that all these targeted therapies are better.

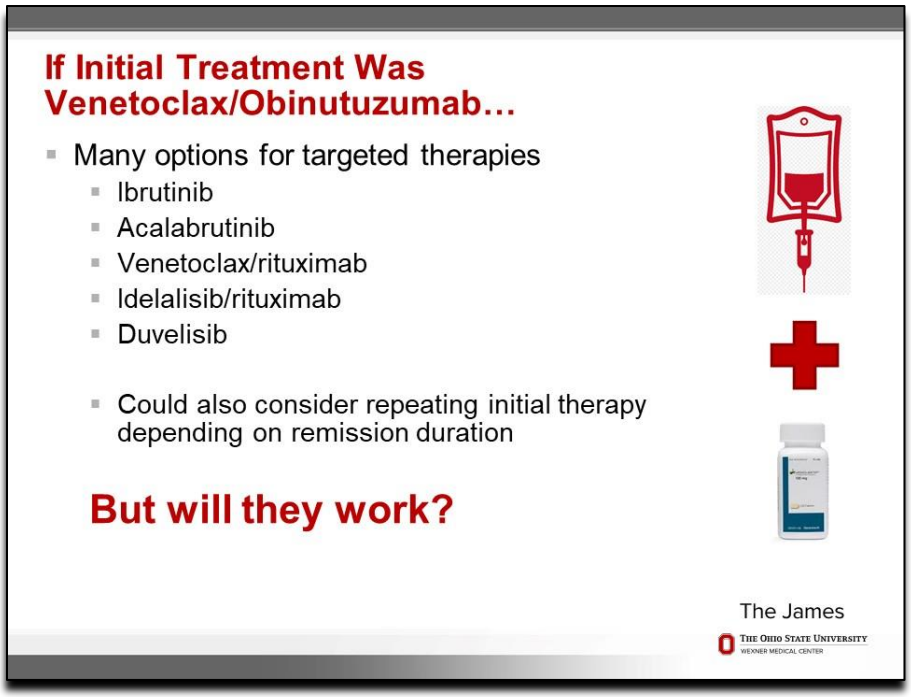
And a big question: Are they going to work?



Answer: Yes!

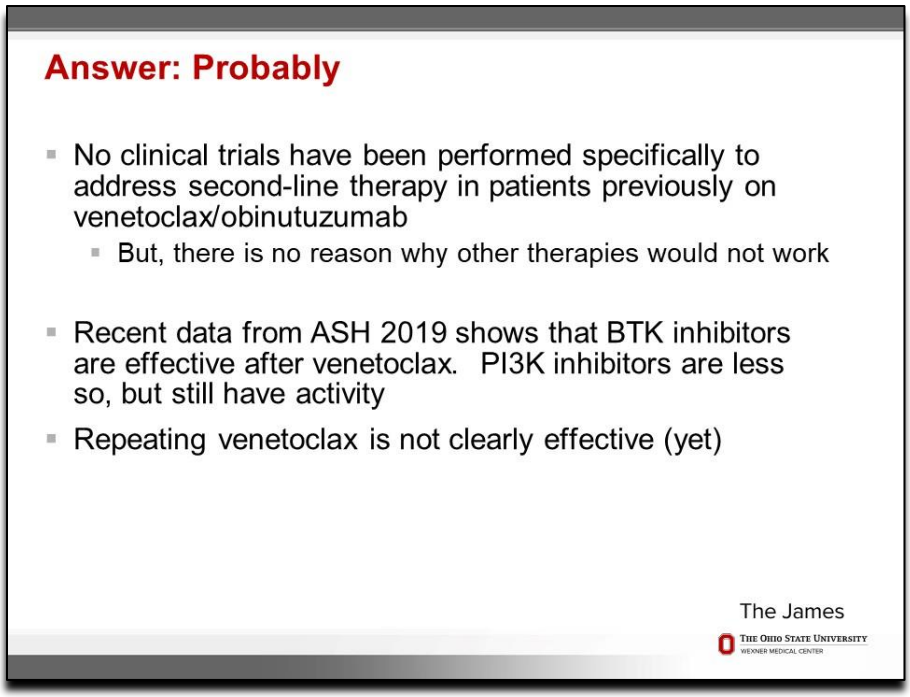
And like I said, the answer there is yes. So, most of the data we have for outcomes with ibrutinib, acalabrutinib, and venetoclax actually are in patients who have had previous therapy. And so, we know that after a person has had chemotherapy, these drugs work very well.

With ibrutinib, the average remission duration is 52 months. With acalabrutinib, at even up to 4 years, most of the patients were progression free. And with venetoclax at 4 years, over half the patients were progression free. So, these drugs are going to work after chemotherapy.



If Initial Treatment Was Venetoclax/Obinutuzumab…

If the initial treatment was venetoclax with obinutuzumab, then we really have a lot of options again because that therapy was probably stopped and the patient is taking nothing at that point. So, we could do a BTK inhibitor: ibrutinib or acalabrutinib. We could do venetoclax with rituximab. We could also do a couple other drugs: idelalisib (Zydelig®) or duvelisib (Copiktra®), which are other targeted therapies with an inhibitor protein called PI3 kinase.



Answer: Probably

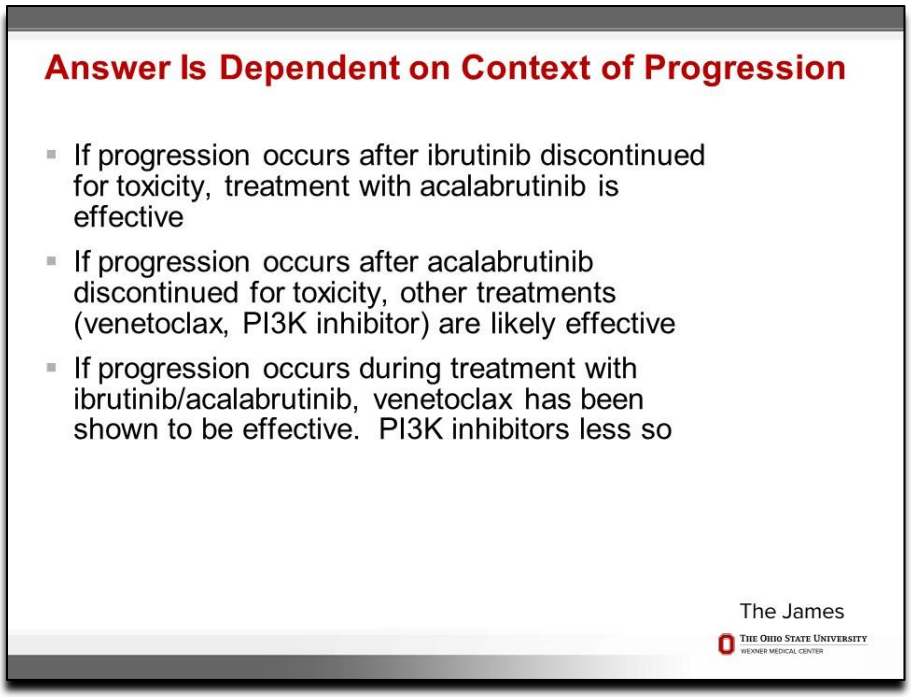
And in this situation—if we want to know if the drugs work—the answer is "probably." And the only reason I don't say "definitely" is because this is a new therapy in the frontline setting and there really have been no clinical trials yet that have looked at patients after venetoclax plus obinutuzumab to see what is the best second-line therapy. But, there really is no reason why these other treatments wouldn't work after venetoclax plus obinutuzumab.

And then, in some kind of small series where different centers are just reporting what they have observed, we've seen that BTK inhibitors seem to be very effective after venetoclax. PI3 kinase inhibitors just are a little less effective than BTK inhibitors in general, but they still have activity.

We don't yet know if you can give venetoclax again after venetoclax was given first, but that's something that's currently under investigation.

If Initial Treatment Was Ibrutinib or Acalabrutinib…

If the initial treatment was ibrutinib or acalabrutinib, we do have other options for therapies.

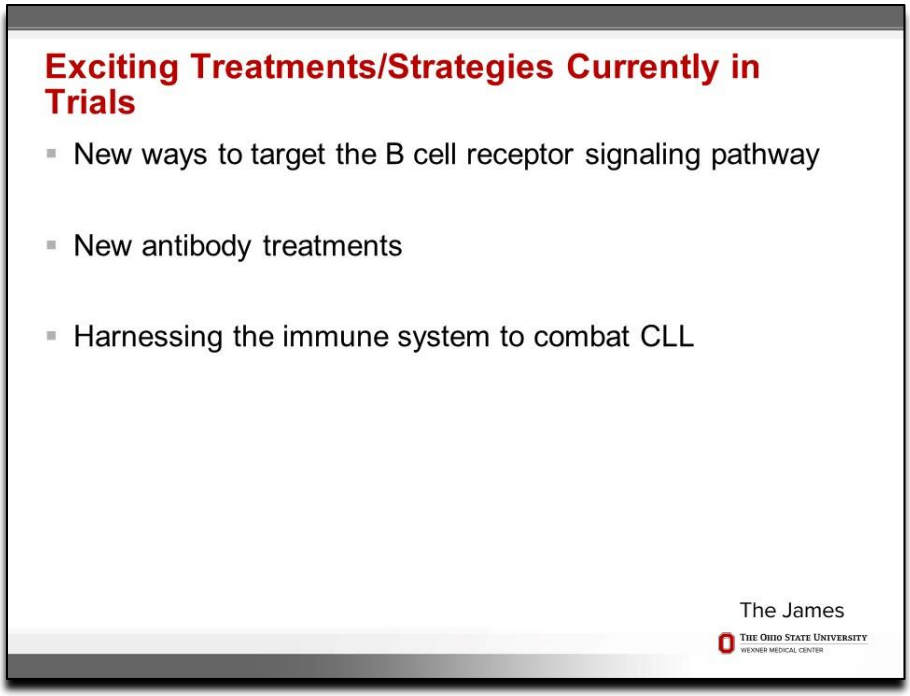


Answer Is Dependent on Context of Progression

So, if somebody came off of the drug because of toxicity, because of side effects to ibrutinib, you could consider acalabrutinib in the future. In any event, you could consider venetoclax, idelalisib, duvelisib. Are these going to work?

And then again, this one is actually dependent on the context of the progression. So, if a patient was on ibrutinib and then came off for a side effect, like I mentioned, you could consider doing acalabrutinib. And that's been shown to be effective. If somebody's on acalabrutinib and comes off because of a side effect, there are other treatments, like venetoclax and PI3 kinase inhibitors that are likely to be very effective.

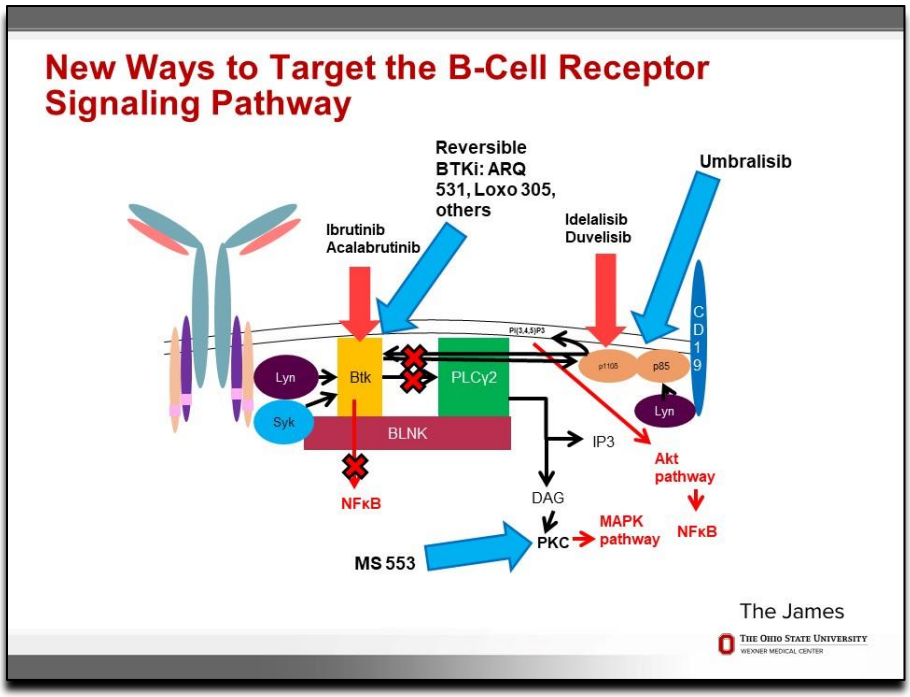
If somebody progresses during their treatment with ibrutinib or acalabrutinib, venetoclax does work. PI3 kinase inhibitors don't work quite as well. But, this is really an area where there's a lot of interest in doing clinical trials.



Exciting Treatments/Strategies Currently in Trials

And so, I'm going to end by just showing you some of what I think are the exciting treatments and strategies that are currently in trials or currently on the horizon. The first of these is new ways to target the B-cell receptor signaling pathway. So, new ways to target BTK and other proteins there. New antibodies. So, we're all very familiar with rituximab and obinutuzumab, which targets CD-20, which is on the surface of CLL cells, but there's other proteins on the surface of the CLL cells, too, that you can consider.

And then, the last one, which is something that is very, very interesting in all of the lay press magazines in addition to the scientific literature, is trying to harness the immune system to combat CLL.



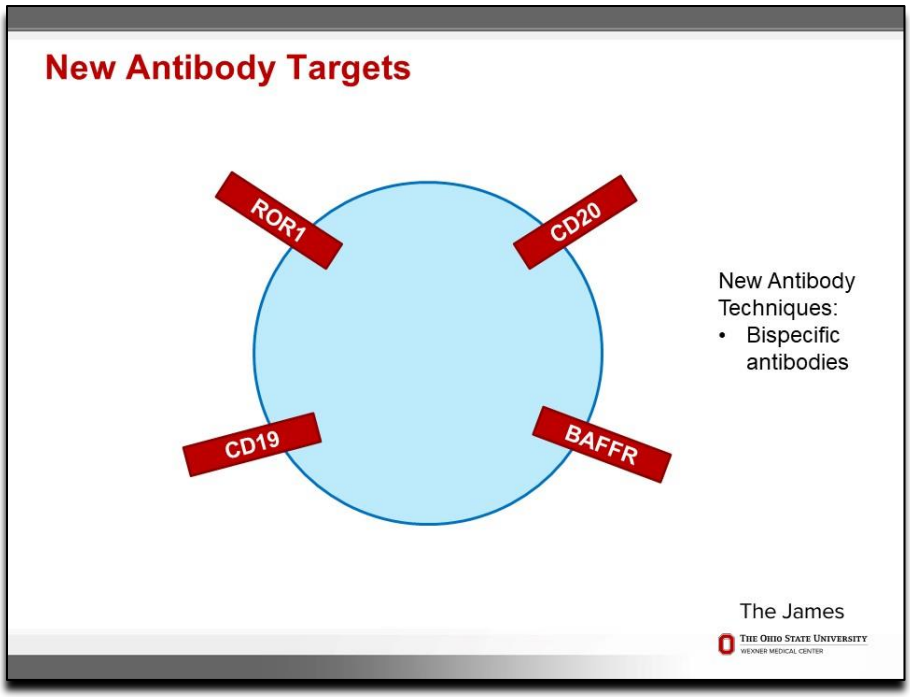
New Ways to Target the B-Cell Receptor Signaling Pathway

So, that's the structure that I showed you initially: the B-cell receptor signaling pathway. So, we have ibrutinib and acalabrutinib pure targeting BTK. I mentioned very briefly these drugs, idelalisib and duvelisib, which targets PI3 kinase.

And then there's this whole new class of medications that are called reversible BTK inhibitors that were actually developed to work when ibrutinib doesn't. And because of that, there are clinical trials looking at these drugs in patients who progress on ibrutinib and acalabrutinib. And so far, these seem to be very active.

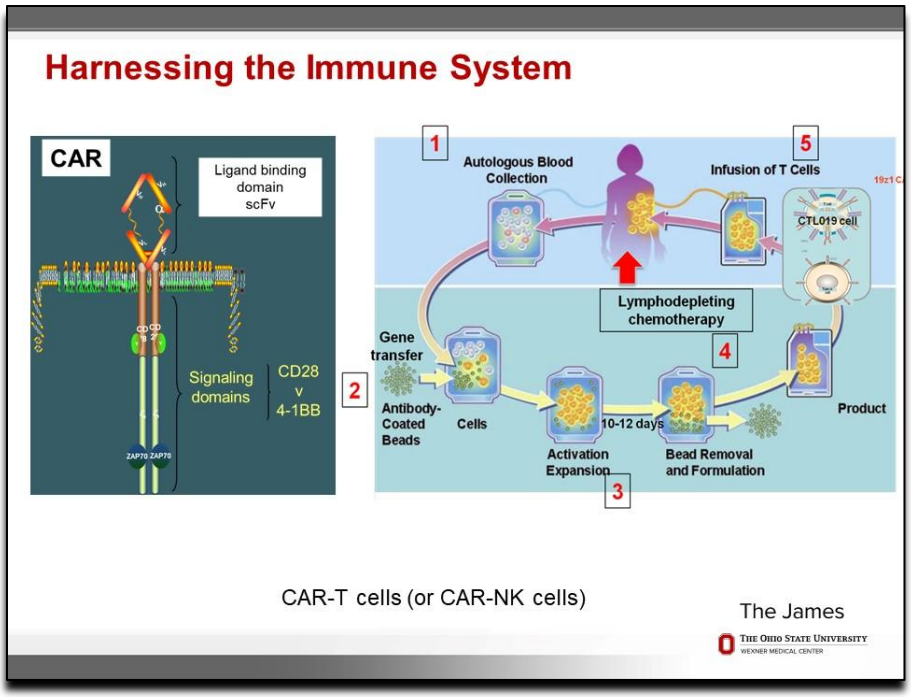
There are also new PI3 kinase inhibitors. One of these that's in clinical trials is called umbralisib and it's having very good data as well. And there's also other targets. So, there's this downstream target called PKC, which is targeted by a drug called MS553, which is in clinical trials right now.

So, this is just a schematic to show you a CLL cell and how there's different proteins that are on the surface. The CD-20 we can target with rituximab, with obinutuzumab. There are other proteins that seem to be really good drug targets. Things like ROR1, CD-19, and the BAFF receptor that all have drugs in development and in clinical trials that are looking to see whether those would be good targets for CLL.



New Antibody Targets

There's also new antibody techniques. One of these is something called a bispecific antibody, where an antibody actually has two targets at the same time. So, it might be targeting both CD-20 and CD-3, which is not on the surface of CLL cells but is on the surface of T cells. And so, what this bispecific antibody can do is actually grab both the CLL cell and a T cell, which is a normal immune cell, and force them into contact with each other so that the T cell can kill the CLL cell.



Harnessing the Immune System

And then, lastly, we can harness the immune system through a process called CAR T cells, which I think a lot of you have probably heard of. And there's also interest in looking at CAR NK cells. And those are natural killer cells.

The way a CAR T-cell process works is we would actually take somebody's T cells, so their normal immune cells from their body, bring them into the laboratory and actually genetically modify them so that all of those T cells are programmed to attack B cells. So, you program them to attack anything that has CD-19 on their surface.

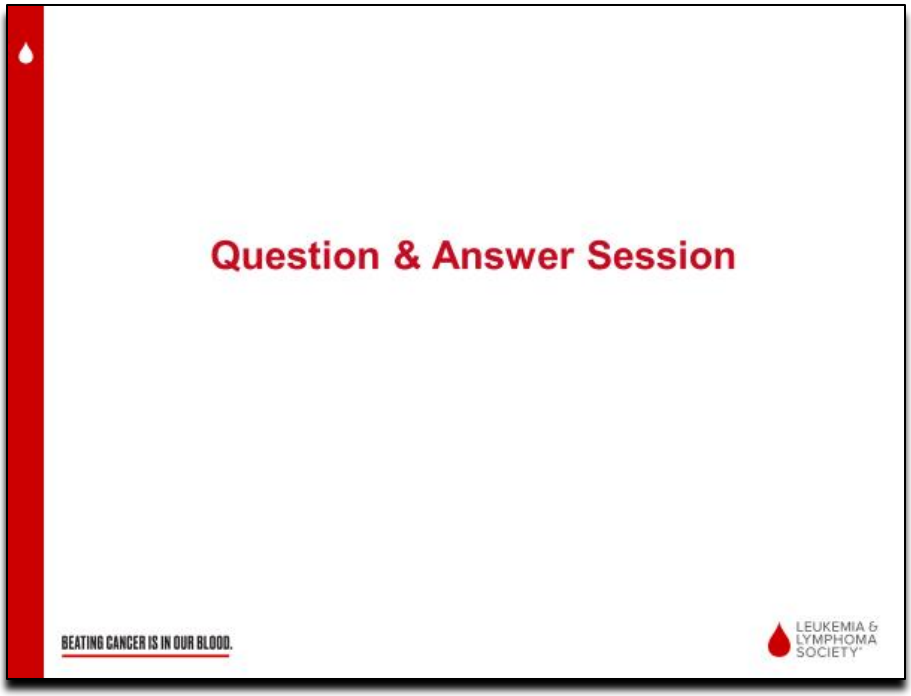
Then, the patient is given some chemotherapy to deplete their own T cells. And the new CAR T cells are infused with a goal then of the new T cells attacking and killing all of the CLL cells that are remaining. So this, again, is something that's in clinical trials right now, is looking very promising, and there's a lot of excitement over.

With that, I would like to just leave you with the thought that there are lots and lots of promising treatments for CLL. Those things that are approved right now that can be prescribed by a doctor right now as well as lots of exciting clinical trials that are investigating what we think might be better therapies for CLL. And for those of you who are in the watch-and-wait status, this is a good time to be watching and waiting. Because the longer you sit on the sidelines, the more these therapies can advance.

For people that are currently receiving treatment, this is also a good time to be getting treatment because our treatments right now are much better than they were even 5 years ago. And we're learning more and more about how to make these therapies continue to work better.

Thank You!

So, with that, I would like to thank you again for being here. And I'd be happy to answer some questions.



Q&A Session

Ms. Lizette Figueroa-Rivera
Thank you, Dr. Woyach, for your very informative presentation. It's now time for our question-and-answer portion of our program.

We'll take the first question from our web audience. Dr. Phillip is asking, "Are treatment options for CLL the same or similar to those for SLL—small lymphocytic lymphoma?"

Jennifer Woyach, MD
That's a great question. Thank you. Right now, SLL—or small lymphocytic lymphoma—is treated exactly the same as CLL. And for those of you who are less familiar with that diagnosis, basically CLL and SLL are the same disease.

If you look at the cancer cells under a microscope, they're exactly the same. They respond the same ways to different medications. However, we call something CLL if there is more disease in the blood. And we call something SLL if there is not as much disease in the blood.

Some clinical trials will either allow or not allow SLL, but we think that anything that we know about CLL is applicable to SLL.

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

Operator
Certainly. Our first question is coming from Trudy from Boca Raton, Florida. Your line is now live.

Trudy
Yes. I have a question. What is the difference between the lymphocytes abs and lymphocytes?

Jennifer Woyach, MD
Yeah. So, I think you're looking at a report of the CDC. And usually, the lymphocyte count, which includes CLL cells but also includes normal lymphocytes. Normal T cells, for example. They're reported as both a percentage of the total white blood cell count, which is usually what they say will lead to saying lymphocytes. And then, "lymphocytes abs" means "lymphocytes absolute." And so, that's going to be how many cells exactly are there per microliter of blood.

Ms. Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our web audience. Dr. Keller is asking, "Is there a danger of watching and waiting too long? Are there any benefits of starting treatment earlier?"

Jennifer Woyach, MD
Yeah. So, that is kind of a difficult question to answer. So, the short answer is no, there's really not a risk in waiting too long. Meaning that somebody with stage IV disease is going to respond just as well to therapy as somebody with stage I disease. The only thing we want to make sure of is that we're not waiting so long that somebody is feeling so sick that they can't tolerate therapy as well.

So really, nothing has shown us yet that it is advantageous to start therapy earlier.

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

Operator
Thank you. Our next question is coming from Louise from Lakewood, Colorado. Your line is now live.

Louise
Hi. I was wondering if a patient has the CLL and also has another cancer, which in order to make it better or get rid of it needs to have chemotherapy for it? How bad is that for the CLL?

Jennifer Woyach, MD
So, most therapies for other cancers—so chemotherapies, for example—for a colon cancer or a lung cancer are not very effective against CLL cells. So, another treatment for another cancer is not likely to do anything to somebody's CLL. It also doesn't really do anything bad. So, it's very unlikely that a chemotherapy that you would get for another cancer is going to hurt your CLL in any way.

And one of the really good things about having so many treatments for CLL is that we can really tailor the treatment for the patient. So, if somebody is needing to be on a chemotherapy, we can pick a medication that can be safely given with the chemotherapy.

So, while of course not ideal to have two cancers at the same time, there is nothing that says that they can't both be treated successfully.

Ms. Lizette Figueroa-Rivera
Thank you. And our next question comes from Martin. Martin says he's a Vietnam veteran diagnosed with CLL attributed to Agent Orange exposure. And what types of treatments, if any, differ for us that is different from other CLL patients?

Jennifer Woyach, MD
So, that's a great question. As we know, patients with Agent Orange exposure are more likely to develop CLL. We don't have any data at this point to say that different treatments would work differently for somebody that has had Agent Orange exposure.

My suspicion is that things like targeted therapies would probably be better than the chemotherapies in that situation because we know that Agent Orange caused a lot of DNA damage, and that's what causes those cancers. So, you would expect that given more chemotherapy might cause more damage and more evolution of different CLL clones, but that's just my thought. But, there really is no data to say that one therapy is better than another.

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

Operator
Thank you. Our next question is coming from Donna from Carmel, Ohio. Your line is now live.

Donna
Yes. What are the dangers of having—I have systemic lupus and CLL, which I have been treated for the last 6 months.

Jennifer Woyach, MD
Yeah. So, that's a good question. So, are there other conditions—like lupus, other autoimmune conditions—that would make CLL worse or make treatment more difficult?
One, actually, interesting thing is that many of the targeted therapies we use, specifically the BTK inhibitors, another place that they're being studied is for rheumatologic diseases. So, things like rheumatoid arthritis and lupus. So, those drugs actually might be beneficial for multiple things like that.

Unless you were taking a medication that is designed to activate the immune system, I don't think that any of our other treatments would really be bad for somebody that has an autoimmune disease.

Ms. Lizette Figueroa-Rivera
Thank you. And the next question. Mike and Robert are both asking about more information about acalabrutinib and obinutuzumab—that combination.

Jennifer Woyach, MD
Yeah. So, acalabrutinib is an FDA-approved treatment for CLL and it can be given either alone or in combination with the CD20 antibody obinutuzumab. This combination is very tolerable. It is very effective.

Unfortunately, the clinical trial that was done was not actually designed to see whether acalabrutinib plus obinutuzumab was better than acalabrutinib alone. So, the data that we've seen so far suggests that there might be a little bit of a remission advantage to doing acalabrutinib with obinutuzumab, but we don't know that for sure.

So, I generally am not doing that combination for most people unless there's some other real reason to do that. And I'm waiting until we get a little bit more long-term data from that study that'll tell us for sure which one of those is better.

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

Operator
Certainly. Our next question is coming from Dana from Sanford, Maine. Your line is now live.

Dana
Thank you. Doctor, I started out on venetoclax in a clinical trial and then went to ibrutinib, but soon I'm going to have to transfer into Medicare. And from the government websites, all I have seen is that ibrutinib is going to cost somewhere between $10,000 and $40,000 a month. Do you know if there's any efforts going on to try to bring the cost of that drug down?

Jennifer Woyach, MD
So, that's a great question. And a huge issue with these drugs is the cost. I honestly don't have a lot of specific information about does one plan cover this and one plan doesn't. Many of my patients, when they do go on to Medicare, will work with the Medicare counselors to try to find a plan that potentially will cover these medicines.

There also are a lot of resources through LLS, through other programs that can provide funding for some patients who have high copays. So, that's something to really talk to your doctor about. And if your facility has case managers and social workers, they're also probably very familiar with what to do to make those drugs affordable.

Most patients—there will be some way to get those copay costs down.

Ms. Lizette Figueroa-Rivera
Sure. And LLS definitely can assist you with your search, as Dr. Woyach said, we do have copay assistance programs, but we can also refer you to other organizations, programs, and other resources.

Doctor, our next question is coming from Leanne. Leanne is asking, "At what point in the progression of CLL does a Richter transformation typically occur?

Jennifer Woyach, MD
Yeah. So, Richter's transformation is a transformation of CLL through a more aggressive type of lymphoma. This is usually something called diffuse large B-cell lymphoma. And Richter's transformation is treated very differently than CLL is.

Richter's transformation can occur at any time during the course of CLL, even in somebody who wasn't already known to have CLL. Generally, we see it now in people who have had multiple therapies, though. And most of the time, it happens in people who have other high-risk genetic features. So, people who have that IGHV-unmutated 17p deletion, TP53 mutation.

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

Operator
Our next question is coming from Anita from Bethlehem, Pennsylvania. Your line is now live.

Anita
Hi. I'm a 73-year-old female and I got diagnosed about 2005 with CLL, and I just had to start on ibrutinib. It's about a year now. And they started me off on—I think it was 240—no. I take 280 now. They started me out on the higher dose, but for the last 6 months I've been on 280. And I'm doing very well with it. But, I really get concerned after reading all the side effects. Like, every time I take the pill I wonder what's this doing to the rest of my body?

So, I was wondering if you know what the long-term effects are and how long it would stay working for me? And then, the other question is, I don't know if I heard you right, but did you say in about 3 years after being on ibrutinib you can get high blood pressure?

Jennifer Woyach, MD
So yeah, those are important questions. One good thing that we've seen with these targeted therapies—ibrutinib and acalabrutinib—is that most of the side effects, if they're going to happen, happen early on. So, people that are out a year or so are very unlikely to develop new side effects.

The exceptions to that are high blood pressure. There's more incidents of it the longer people take the medication. And then the atrial fibrillation, which can happen at any time.

However, these drugs work very, very well. The side effects can be managed. So, I mentioned in a talk that I have patients who have been on ibrutinib for 10 years now and are still doing well. So, I definitely encourage people to stay on it if it's working for them. And certainly, talk to your doctor if you're having side effects that are unmanageable.

In terms of how long it will work, the good answer is we don't know yet because it works so well. So, with ibrutinib, in the frontline setting, the longest follow-up we have is 5 years from a randomized trial. And at 5 years, 70% of people were still in remission. So, this would predict that most people are going to have very long remissions: 7, 10 years, maybe longer than that.

So, it's really hard to say for somebody who is getting ibrutinib as their first therapy how long it will last. For people who have had multiple other therapies and then go on ibrutinib, the average remission is 52 months. So, a little bit more than 4 years.
With acalabrutinib and venetoclax, they're so much newer that we, in the frontline setting, just really don't know how long they're going to last. At about 2 to 3 years, they look similar to ibrutinib. Though we don't know when you get to that 5-year or 7-year mark whether they're going to be different.

Yeah. So, I mentioned that people can develop hypertension, and it's a pretty significant number of people. Probably 30% or so when you look at people over the course of many years.

Ms. Lizette Figueroa-Rivera
Thank you. The next question—and I know that many of our patients are older, maybe possibly 80s, 90s—and Lynn is asking, "Is treatment available regardless of age?"

Jennifer Woyach, MD
That is a great question and the answer is absolutely yes. There should not be a circumstance in my mind where somebody is ever told they're too old for treatment. And really, one of the benefits with having these targeted therapies for CLL is that they actually are much more tolerable for people that are older.

Many of the trials that are currently being designed and are currently ongoing for patients with CLL are designed specifically for older patients for that reason. That it's no good to have a great therapy for a disease, do a trial in people that are 50 years old, and then people who are 80 years old can't tolerate it. So, CLL is not like that. And absolutely, people in their 80s and 90s can be treated with these targeted treatments.

Ms. Lizette Figueroa-Rivera
Great to hear. Thank you. And Mark is asking, "Does CAR T last forever?"

Jennifer Woyach, MD
That is a great question that we don't know the answer to yet. So, CAR T is a newer treatment. And what we tend to see is that if after the person has gotten the T cells, if the T cells expand and remain in the blood stream, people tend to continue to respond.

I don't know whether it's going to be the case that in 5 years down the road they have to still have CAR T cells present for it to work or if at some point some people actually will be cured by this. That's something that there's a lot of people really interested in and hopefully we'll find that out within the next 3 to 5 years.

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

Operator
Our next question is coming from Deborah from Union City, Indiana. Your line is now live.

Deborah
Yes. I am 56, and I have CLL with diabetes and high blood pressure. What is the most treatments that they usually would give for someone in that category? I'm at stage I right now.

Jennifer Woyach, MD
Yeah. So, because CLL is seen most commonly in older patients, there are a lot of people who have diabetes and high blood pressure. While there might be specific medications that would interact with our CLL therapies and so might help us make a decision, there's nothing specific about having those conditions that would make your doctor choose one therapy or the other.

Ms. Lizette Figueroa-Rivera
Thank you. And Marissa is asking, "My dad takes ibrutinib daily. However, the bottle says chemotherapy. So, is this chemo, too? And by targeted therapy, do you mean daily chemo pill versus going to the hospital to get IV?"

Jennifer Woyach, MD
So, people use the word chemotherapy differently. And I think what your pharmacy is saying is this is a cancer treatment, so we're going to call it chemotherapy. We generally use chemotherapy in cancer medicine to mean something that is nonspecific. So, kills all dividing cells. So, things like FCR, fludarabine, cyclophosphamide, bendamustine.

Targeted therapies we tend to use in contrast to that. Meaning, a drug that is only going to hurt the cancer cells while being relatively sparing of normal cells.

So, it just kind of depends on how you're using the terms. Whether you're going to call ibrutinib and acalabrutinib a chemotherapy—I call those targeted therapies. I call rituximab and obinutuzumab targeted therapies too because they're antibodies, they're not going to nonspecifically kill all types of cells that are dividing.

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

Operator
Certainly. Our next question is coming from Joann from Stone Mountain, Georgia. Your line is now live.

Joann
Yes. I've been diagnosed ever since 2010. I've been on ibrutinib for 3 years. The ibrutinib seems to work very well and I've had major surgery also. But, my question is with these clinical trials and if you're doing okay, what's the longest you've heard people living with all this medicine?

Jennifer Woyach, MD
Yeah. So, like I had mentioned, at Ohio State, we've been treating people with ibrutinib on trial since 2010. So, we still have some patients that are on ibrutinib 10 years later. That's really when the clinical trials with ibrutinib started. So, I don't think you're going to find anybody who's had patients on longer than that. But many of those patients are still doing well, and I don't see why they wouldn't continue to do well on the drug for another many years.

Ms. Lizette Figueroa-Rivera
Thank you. And Lauren asks, "With no symptoms, how often is it necessary to have a PET scan?"

Jennifer Woyach, MD
With no symptoms, generally we don't do imaging radiologically for CLL. So, no PET scans, no CT scans. Some doctors will choose to do them in certain circumstances. Like, if they know that somebody has big lymph nodes in their belly that can't be easily assessed on exam or a big spleen and for some reason they can't feel very well, some doctors might choose to do CAT scans or PET scans more frequently because of that.

In general, outside of that, though, I don't get CT scans or PET scans on people routinely.

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

Operator
Certainly. Our next question is coming from Joyce from Indianapolis, Indiana. Your line is now live.

Joyce
Hi. I'm a little bit confused on the last question. So, I'll go through what I have. I've had CLL for 32 years. I had chemotherapy in 1987 and then I had fludarabine in '91 to '92. And the doctor recently told me that I can never have fludarabine again and I wondered why. And currently, they have me on monthly IVIG. And I was diagnosed with stage IV, to give encouragement to people out there when I was diagnosed in '87.

Jennifer Woyach, MD
Thank you for that encouraging comment. That's really nice to hear. So, because our targeted therapies are better than fludarabine and better tolerated, I think that's what your doctor probably meant by not wanting to give you fludarabine again. As well, the chemotherapies, one of the things that they can cause—because they cause that DNA damage is they can cause other cancers, which is something that we don't think we're seeing with the targeted therapies.

So, not to put words in their mouth, but I wonder if what your doctor meant was just that there are better things than fludarabine to treat your CLL with when you need it.

So, the IVIG is an important point, too. So, IVIG is intravenous immunoglobulins. And this is a pool of antibodies, basically, that can be given to people through an IV, usually given once per month and

people with CLL who have low levels of antibodies because of the CLL and are getting frequent infections.

So, IVIG helps prevent some of those infections. It is not a treatment for CLL, though. So, it won't do anything to the disease itself. It just helps people from getting infections.

Ms. Lizette Figueroa-Rivera
Yes. It is nice to hear somebody doing well for a long period of time. Stay well.

And Garrett is asking, "If a person has been on one clinical trial, can they go on another? Does one type of clinical trial negate a person's ability to qualify for others?"

Jennifer Woyach, MD
That's a great question. And absolutely, people can go on multiple clinical trials. The only caveat to that is there are trials designed for first treatment of CLL. And so, if somebody has already had another treatment, they obviously can't go on a treatment for a first therapy for CLL. But, most of the trials in CLL right now are actually for people who have had other treatments.

So certainly, going on one clinical trial would not negate going on a different trial in the future.

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

Operator
Certainly. Our next question is coming from Bruce from Basking Ridge, New Jersey. Your line is now live.

Bruce
Yeah. Hi. This is Bruce. Yeah. I'm still stage 0 from the last 15 years. But aren't some of these people that have gone on FCR and also on the other drug—I've heard that some of them are cancer free for 10 years. Does that mean they're cured?

Jennifer Woyach, MD
Yeah. So, I didn't get into this in the presentation, but with FCR chemotherapy—and this is only limited to FCR chemotherapy—there are a subset of people who are probably cured. The thing is that subset is going to be, first of all, people who can tolerate FCR. So generally, people age 65 or under and those that are IgVH mutated. So, people who are IgVH unmutated will not be cured by FCR.

Those that are mutated have maybe even greater than 50% chance of being cured by FCR. There's a lot that goes into the equation, though, of whether that's the right treatment still. And one of the counterarguments is that FCR in a small percentage of people can cause therapy-related myelodysplasia or acute leukemia. So, it can actually cause a different type of leukemia that occurs down the road.

So usually, when I have somebody who fits that category—IGHV mutated, young, fit—we talk about the risks and benefits of doing FCR compared to the targeted therapies. But you're correct. There probably are people who are being cured by FCR.

Ms. Lizette Figueroa-Rivera
That's encouraging. Usually, we don't hear the word "cure" associated with CLL. So, that's something encouraging, as well as with all these newer treatments.

Now, our next question comes from Margie. Margie's asking is there anything to help with the fatigue? Mine disrupts my whole life. I'm on steroids. I can do more, but I know how hard they are on my overall health."

Jennifer Woyach, MD
Yeah. Fatigue is a very difficult issue in CLL. The first thing that I do is try to make sure that it's the CLL causing the fatigue, which can sometimes be very difficult. But, I like to make sure that I work with somebody's primary care doctor and we rule out things like thyroid abnormalities, diabetes, sleep apnea—other things that can cause fatigue.

As we get to the point where we know that the fatigue is from the CLL if it's disrupting somebody's life—that's an indication to treat the CLL. So, in that case, I would put somebody onto CLL therapy to try to help the fatigue. And usually, if the fatigue is related to CLL, if you treat the CLL the fatigue will get better.

And our next question, doctor. Carolyn asks, "Is there treatment for someone that becomes symptomatic that has the P17 deletion?"

Jennifer Woyach, MD
Yes, absolutely. So, most of our therapies right now don't work quite as well in people with 17p deletion as people who don't have that abnormality, especially the BTK inhibitor. Though ibrutinib and acalabrutinib have considerable efficacy or effectiveness in the frontline setting.

Venetoclax, though, is a little bit less data with. So, I generally will steer my frontline patients who have 17p deletion towards either clinical trials or a BTK inhibitor. But they do definitely work.

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

Operator
Certainly. Our next question is coming from Delvede from New York, New York. Your line is now live.

Delvede
Yes. I had a pericardial effusion on ibrutinib, and I switched to venetoclax and I also had AFib. Is that pericardial effusion associated with ibrutinib?

Jennifer Woyach, MD
Yes. That is actually a very, very rare side effect with ibrutinib. But, when we've looked at large trials, that is something that happens at a higher rate with ibrutinib than we would expect. So, probably yes.

We know that things like edema or swelling in the legs is a lot more common, but some patients can get pericardial effusion, which is fluid around the heart or fluid around the lungs.

Ms. Lizette Figueroa-Rivera
Thank you. And Constance is asking, how often should one see their oncologist? Or could they be followed by an internal medicine physician between oncologist visits if cancer is staying fairly stable?

Jennifer Woyach, MD
So, that's a good question and is probably one that is best discussed with your individual doctor just because there may be reasons for against doing that. In general, when somebody is newly diagnosed, I would see them every 3 months for at least the first year. If there is absolutely no change in a count, no change in symptoms, I would go to 6 months at that point.

And then either a year or two after that if, again, there is no real progression of the CLL, I would go to yearly after that. Assuming that people are seeing their internal medicine doctor or family practitioner at some point other than that.

It's different if you live in the part of a country where you're so far away from your oncologist. Maybe there are situations where it would be appropriate for an internal medicine doctor to follow more closely and an oncologist less closely.

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

Operator
Certainly. Our next question is coming from Alan from Brooklyn, New York. Your line is now live.

Alan
Hi. I've been on Imbruvica® for a year and the only symptom I have is swelling of the ankles, which I understand is a common symptom for that drug. And I take Lasix®. And a cardiologist--I don't have any cardiac problems, but I went for a cardiac checkup and he said, "You shouldn't be on Lasix® for a long period of time." I wonder if there are other drugs to take care of this problem?

Jennifer Woyach, MD
Well, there are other diuretic drugs that you could talk to your doctor about. Things like spironolactone, hydrochlorothiazide. I'm not really aware that there is danger in being on Lasix® for a long period of time. But, certainly, there are other things that could be tried, other medications. Or things just like wearing compression stockings on your legs sometimes, trying to keep them up. Sometimes those things do a lot for getting rid of the swelling associated with ibrutinib.

Ms. Lizette Figueroa-Rivera
Thank you. And Dianne is asking, "Are there certain vitamins, minerals, or herbs that would be beneficial for CLL?"

Jennifer Woyach, MD
So, probably not. There has been some herbs or other supplements that have been tested in CLL. Most notably, green tea extract. And that actually has some effectiveness in bringing the white cell count down a little bit. It can shrink lymph nodes a little bit. You have to take an awful lot of it. And it has never been shown to produce an actual response similar to a drug.

So, in general, I don't think that the supplements and things like that are worth the money that you would spend on them. So, that may change in the future as more of them are studied. But I think right now, there's really not a lot of data for any of them.

Ms. Lizette Figueroa-Rivera
Thanks. And our last question today, Wayne is asking, "By what criteria would you consider a COVID-19 vaccine safe and effective to recommend to CLL patients?"

Jennifer Woyach, MD
Well, I think for any vaccine, if it is not a live vaccine—which a COVID-19 vaccine is not likely to be a live vaccine—it should be safe. Whether it's effective or not is a bigger question because people with CLL don't tend to mount as good of immune responses to vaccines as people without CLL.

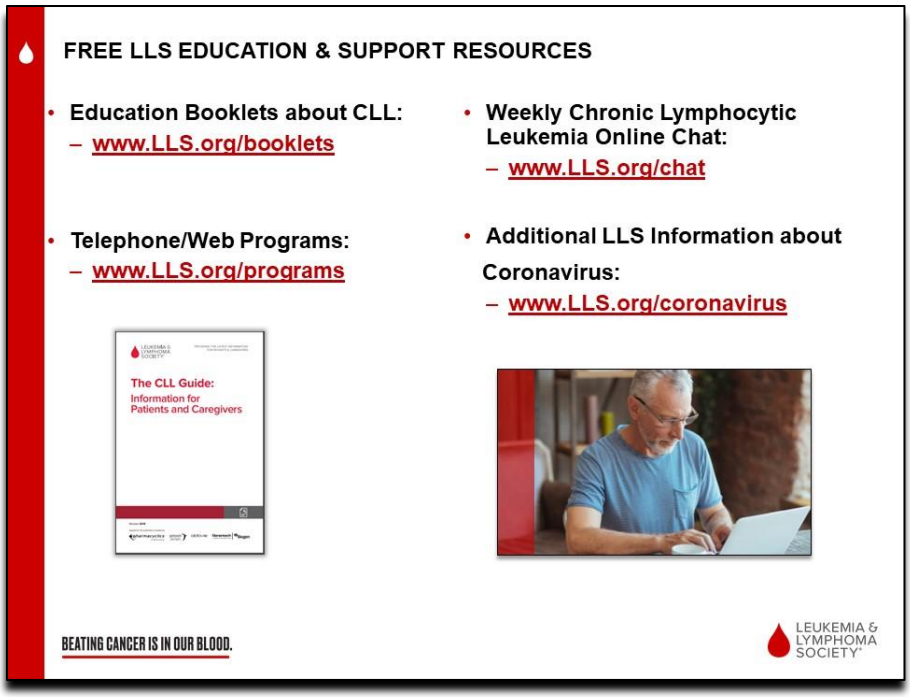
So, certainly, when any new vaccine is developed, after it becomes approved, studies are done in people who are immunocompromised to make sure that it is safe and make sure that it's effective. It may be that people with CLL would need to be vaccinated more often, potentially, or might need higher doses of a vaccine. But, all those things remain to be seen.

But, usually, when a new vaccine comes out—for example, when the Shingrix® vaccine came out—I wanted to see a little bit of data in people with suppressed immune systems before starting to recommend it to everybody with CLL.

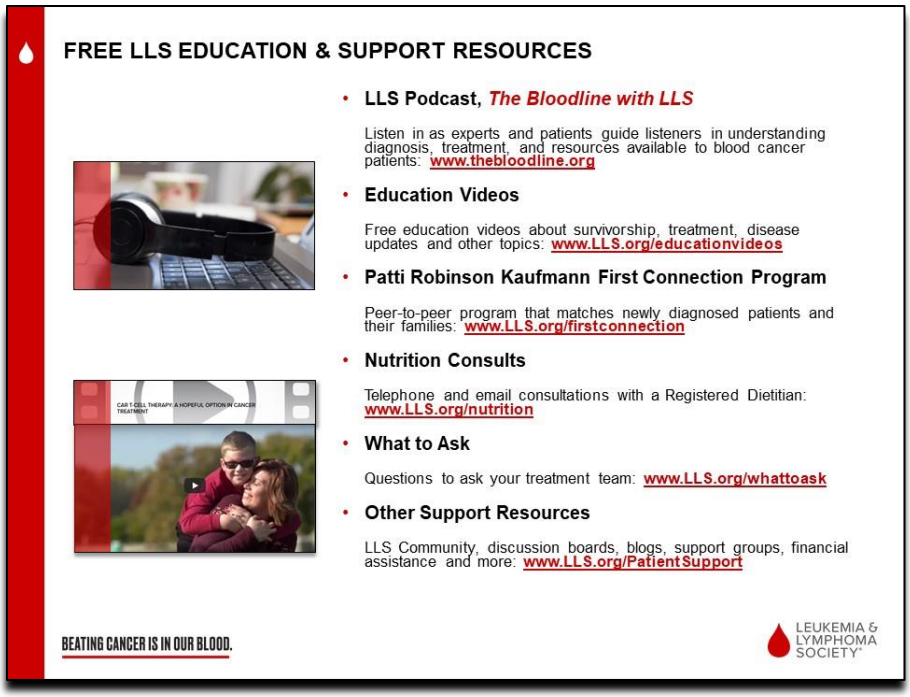
Resources

Ms. Lizette Figueroa-Rivera
Thank you. And thank you all for all of your questions and all of your great participation today. I know that we didn't get to everybody's question.

And if we weren't able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society. I'm going to provide that number to you right now. Their number is 1-800-955-4572. They're available from 9:00 AM to 9:00 PM Eastern Time. Or you can reach us at infocenter@LLS.org. Now, Information Specialists are available to answer your questions about treatment, including clinical trials, or answer the questions you may have about support, including financial assistance programs.



Free LLS Education & Support Resources



Free LLS Education & Support Resources

Thank you so much, Dr. Woyach, for sharing your expertise with us today and for your dedication to our blood cancer patients and their families. And again, we'd like to acknowledge and thank

Genentech & Biogen; Pharmacyclics, an AbbVie Company; & Janssen Biotech; and LLS for support of this program.

Thank You Slide

Dr. Woyach, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Please let us know what you need from us during this time. Take care.