Slide 1: Treatment Advances for Slow-Growing Non-Hodgkin Lymphomas

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society I'd like to welcome all of you. We have over 1000 people participating from across the United States as well as Australia, Canada, and Kuwait today.

Special thanks to Dr. Jonathan Cohen for volunteering his time and expertise with us today.

Before we begin, I'd like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society's President and Chief Executive Officer, who will share a few words.

Dr. Louis DeGennaro:

I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research through advanced lifesaving treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies, that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We're committed to working tirelessly toward our mission every single day.

Today you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers.

Thank you for joining us.

Lizette Figueroa-Rivera:

We would like to acknowledge and thank Celgene, Genentech, and Biogen Pharmacyclics, an AbbVie Company, and Janssen Biotech for support of this program.

I am now pleased to introduce Dr. Jonathan B. Cohen from the Winship Cancer Institute of Emory University in Atlanta, Georgia. You may begin Dr. Cohen, thank you.

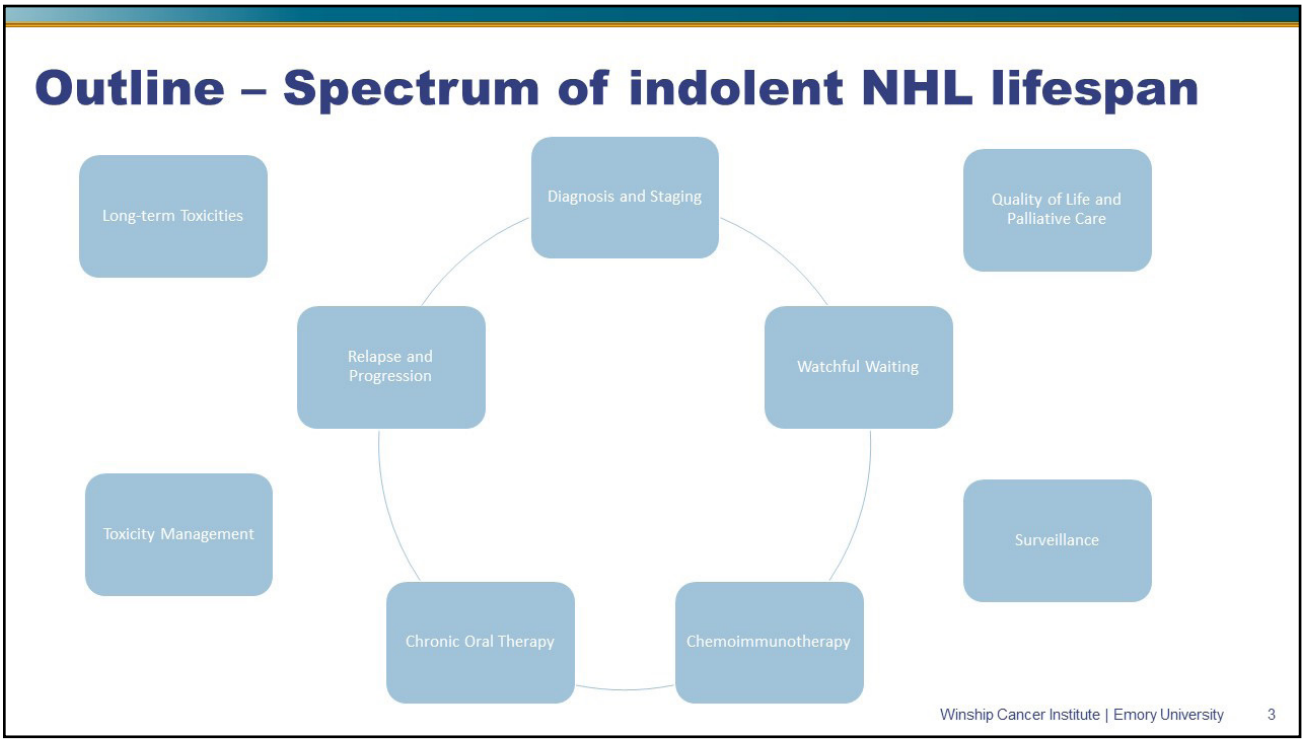
Dr. Jonathan Cohen:

Great, thank you so much, Lizette, and thanks again to The Leukemia & Lymphoma Society for putting together such an important program. And finally, thanks to all of you for joining us today.

I'll be talking this morning about treatment advances for slow-growing, or what we refer to as, indolent non-Hodgkin lymphomas.

Slide 2: Disclosures

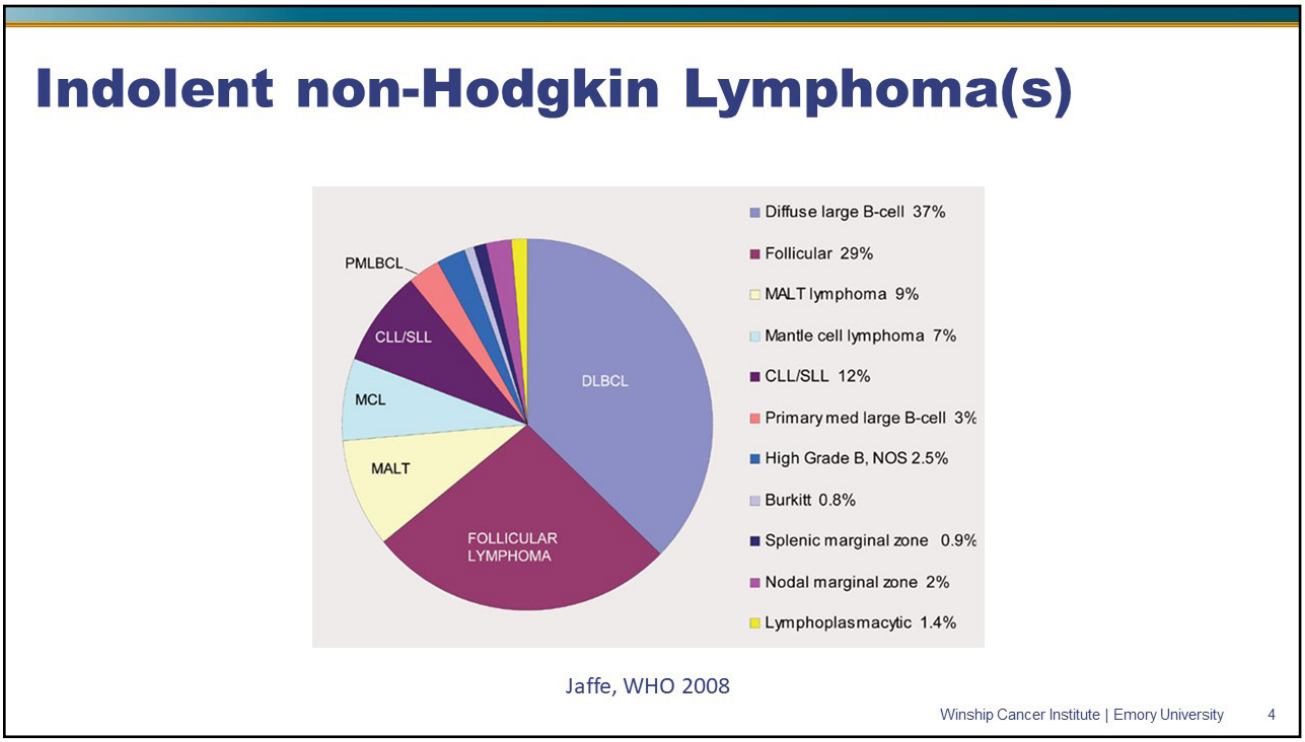
On this slide are some of my disclosures, which primarily relate to the work that I do investigating lymphoma through clinical trials.



Slide 3: Outline – Spectrum of indolent NHL lifespan

So, I think before we begin and get into some of the specifics of the different types of lymphomas and how we manage them, I think it's important to recognize that many of you that are tuned in today are dealing with some portion of the indolent non-Hodgkin lymphoma life span, and that really there is a large range of different experiences that patients have. Some of you may have been recently diagnosed or diagnosed in the recent past and may not even be on therapy right now. Others of you are still going through the diagnosis and staging portion of your evaluation. Some of you may be on treatment with either IV therapies or chronic oral treatments. And, some of you may have been treated in the past and have had your disease come back and have had to think about other options for treatment.

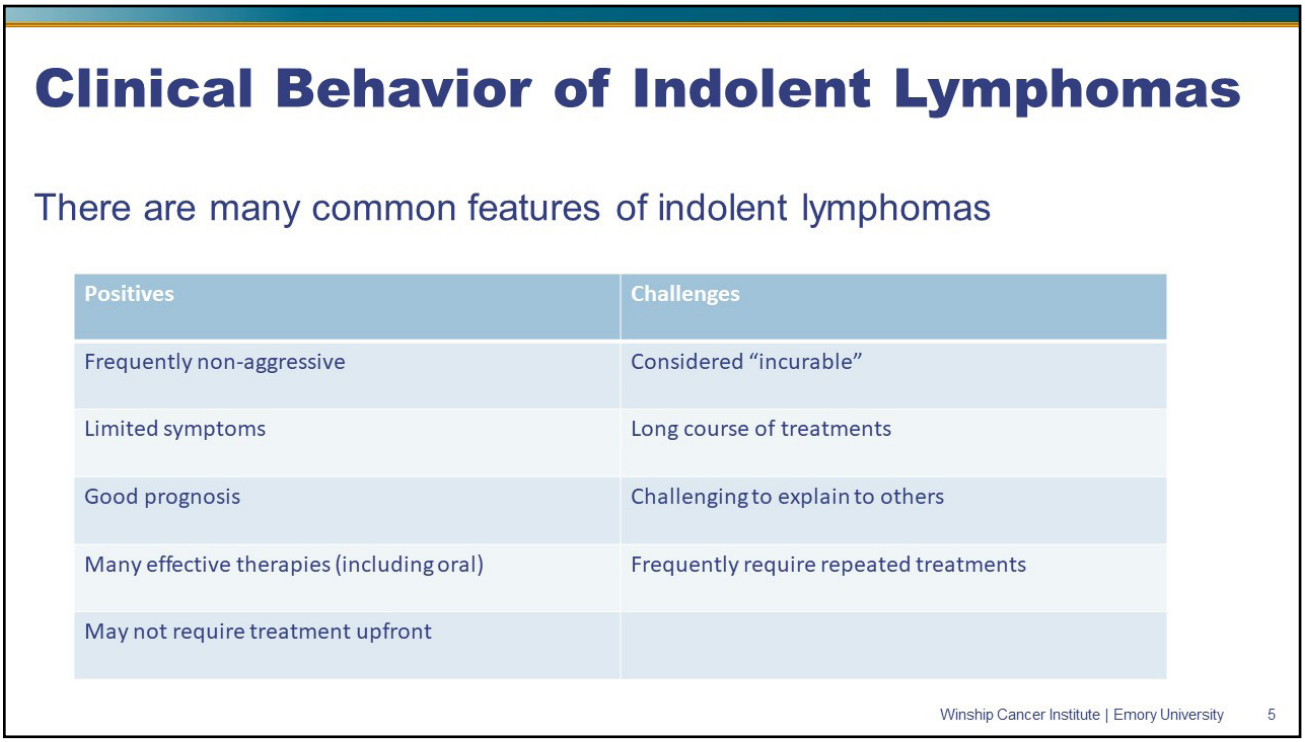
In addition to the treatment options that we'll discuss, there's a number of other aspects of the care of patients with indolent non-Hodgkin lymphoma that are really important to consider. So, there're often a quality of life and symptom management concerns that we have. So, many of our treatments are very effective, but can significantly impact your ability to work or your ability to do the activities that you'd like to do. There are many questions about surveillance as far as how do we evaluate a patient who may be in remission, who's been treated and now we are assessing for relapse of the disease. There are side effects that develop on treatment and then there are long-term side effects. And so, one of the things that as an oncologist who cares for lymphoma patients that I commonly think about when I see a patient is where is this patient on the life span of their disease and what are some of the issues that may be most pertinent to them.



Slide 4: Indolent non-Hodgkin Lymphoma(s)

So, just to talk a little bit about the indolent lymphomas, I think the first question any time I see a new patient is to help them understand, what actually is their diagnosis? Often we think of lymphoma as being 2 different diseases, Hodgkin lymphoma or non-Hodgkin lymphoma. But, the truth is that non-Hodgkin lymphoma is really a collection of a variety of different diseases as you can see from this chart from 2008. And, in fact, in the most recent update of the World Health Organization (WHO) classification there are even more subtypes of non-Hodgkin lymphoma that have been identified.

When we think about indolent non-Hodgkin lymphomas, the most common subtype that we see is follicular lymphoma, which you can see is about 29% of all non-Hodgkin lymphomas. However, there are other subtypes including MALT or marginal zone lymphomas, chronic lymphocytic leukemia or small lymphocytic lymphoma, and then mantle cell lymphoma and Waldenstrom's macroglobulinemia can also behave in a low-grade fashion. And so, whenever I have a patient that is newly diagnosed, one of the most important things that we discuss during their initial visit is do we feel comfortable that we have the right diagnosis and how does this diagnosis fit into the greater landscape of non-Hodgkin lymphomas.



Slide 5: Clinical Behavior of Indolent Lymphomas

Now, for those of you that have been living with these diseases for a long time, you likely recognize that there are many common features of the low-grade lymphomas and many of you have addressed these over time. And, I often like to tell patients that it really is sort of a double-edged sword. On the positive end, these are frequently lymphomas that are not aggressive. Many times, patients have very limited symptoms or no symptoms at all when they're diagnosed. Many people come to see me because of abnormal blood work, or because they were having a scan or a surgery for one reason and, they incidentally identified an enlarged lymph node or some other abnormality that led them to be evaluated and ultimately diagnosed with a lymphoma.

Fortunately, the indolent lymphomas tend to have a very good prognosis. Many of our patients will experience a prolonged life expectancy, often that approximates that of the normal population. There are many effective therapies, including now some oral treatments that we have and many patients don't even require therapy at the time of their diagnosis. And, while this can sometimes be difficult to initially understand, I often will tell patients that I have people that I have seen that we diagnosed with a low-grade lymphoma that have gone 4, 5, or even more years without requiring any treatment. And, other than coming to see me periodically to monitor for the progression of the disease, they're living their life without having to worry about some of the potential side effects or inconveniences of treatment.

However, despite some of these positives, there are some other challenges that patients face dealing with this group of diseases. Unfortunately, in the current era, most of these diseases are felt to not be curable, and I often describe this to patients as if they have a chronic disease. And so, this is something that they often will have to live with for the rest of their life and that they are often unable to be rid of entirely.

Many of the therapies do require a prolonged course of treatment. Sometimes this is because patients are on an oral therapy or sometimes we discuss maintenance approaches, which require treatment for a couple of years.

And then, one of the things that I find for my patients is particularly challenging is how to explain their disease to other people that may not be as familiar with what they're going through. So, when patients are diagnosed with cancer, often there's a lot of people that will come and want to support them and help them but then when the next line is, well, I've been treated with a low-grade lymphoma and don't necessarily need treatment right now, that can sometimes be an awkward conversation or something that's hard to potentially explain to people that are otherwise well-meaning, but may not understand the specifics of the disease. And so, I have a lot of patients that often struggle with deciding how they wish to discuss their disease with other people.

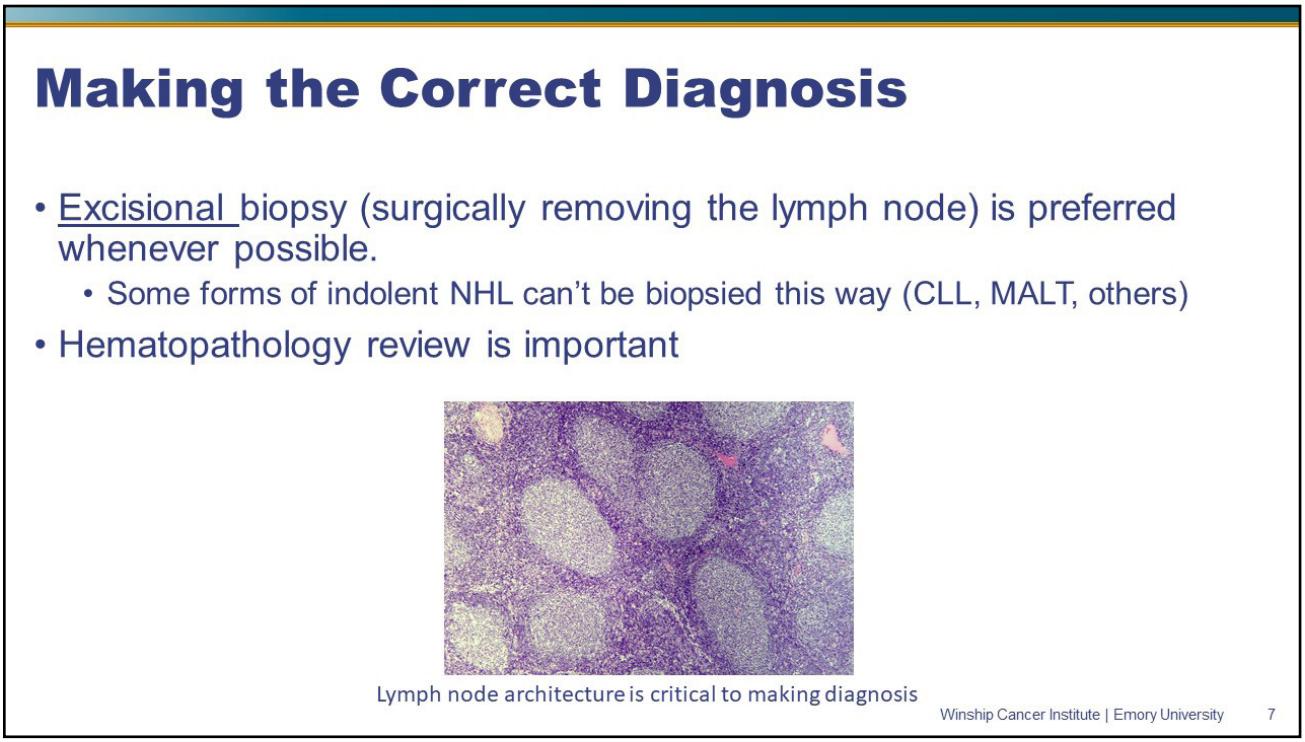
And then, these diseases frequently do require repeated treatment. So, although we can often treat patients and have them go into remission, many patients will ultimately have the disease come back at some point in the future and will have to be treated again.

And so, these are all things that I consider when I'm discussing a new diagnosis with a patient and these are all things that you as patients and caregivers work through every day. But fortunately, again in most cases patients will enjoy a prolonged life expectancy and will respond very well to treatment.

Slide 6: How is it Diagnosed?

So, many of you have already been through this process, but will recognize that at the time of diagnosis a lot of people have no symptoms. So, you know, a lot of men, for example, will come in because they've noticed a lump in their neck or in their jaw while they've been shaving, or they may have an incidental finding where, you know, somebody goes to have their gallbladder evaluated and it turns out that when they get a CT scan their gallbladder looks okay, but maybe there's an enlarged lymph node in their abdomen that needs further evaluation. And, many patients will come to me because they've been on their routine physical, there was an abnormal lab finding or a physical exam finding and where their primary care physician was concerned.

There are, however, other patients that do have symptoms at the time of diagnosis that ultimately lead to their seeking attention. So, many of you may be familiar with what we refer to as the B symptoms and these are a cluster of symptoms that are more frequently associated with more aggressive behaving diseases, but can develop in patients with indolent lymphoma as well. And, these can include unexplained fevers, sort of outside of the setting of an infection. Drenching sweats, especially at nighttime. And, many patients will report that they have night sweats, although typically the sweats that are associated with lymphoma are drenching to the point where you may wake up in the middle of the night and need to change the bed sheets or change your clothes. Patients may have unexplained weight loss. And then, a lot of patients will report fatigue. Now, I'm sure for many of you that are listening, fatigue is a symptom that you're dealing with and one of the challenges that we often face when evaluating new patients is whether the fatigue that someone's experiencing is truly related to their lymphoma or is it potentially related to some other cause, including their thyroid or some other metabolic condition. Or, sometimes patients, you know, that have a very hectic work or home life experience fatigue that may or may not be related to their lymphoma. And then, other people can have different types of symptoms, depending the specific site of disease. So, we really do see a wide range of clinical presentations when we have patients that are newly diagnosed.

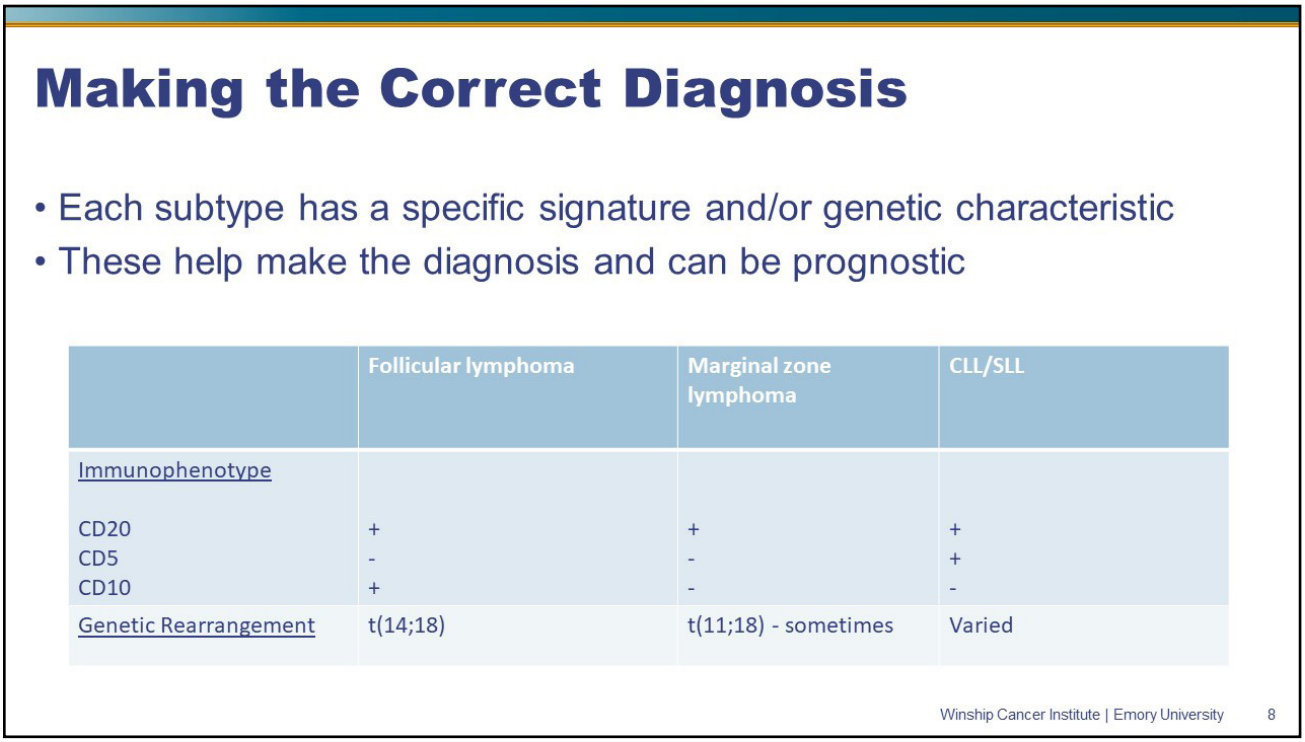


Slide 7: Making the Correct Diagnosis

One of the most important things that as oncologists that we can do when we see a new patient is to be sure that we are making the correct diagnosis. And, I think this is a critical point. When possible, a patient with a suspected diagnosis of a new lymphoma should have what we refer to as an excisional biopsy. And, what we mean by this is that the patient would go to a surgeon and go for an operation where the entire lymph node, or at least a large portion of a lymph node, is removed. In some instances, this is not feasible and a patient may need to have a core needle biopsy instead. But, when possible, we really like to have an excisional biopsy. And, as you can see from this, the pathology slide below, you can see those lightly colored circles that are present. And, one of the things that's particularly important, especially for follicular lymphoma and marginal zone lymphoma, is really getting a look at the lymph node architecture. And, in order to do that you need to be able to see a large portion of the lymph node. And so, often if I have a patient who has come to me with a needle biopsy only, we often have a discussion at that time about whether or not they should go for a surgical biopsy and that is almost always my recommendation unless it's just not possible due to the site of the disease.

Now, there are some forms of indolent lymphoma that can't be biopsied this way. So, CLL frequently exists primarily in the blood and is diagnosed by a blood test. And, some MALT lymphomas, including MALT lymphoma found in the stomach, are not really amenable to a surgical biopsy, and in those cases we work with the material as best as we can. But, when possible, I would always take the time to ask your oncologist about whether or not you would be a candidate for an excisional biopsy.

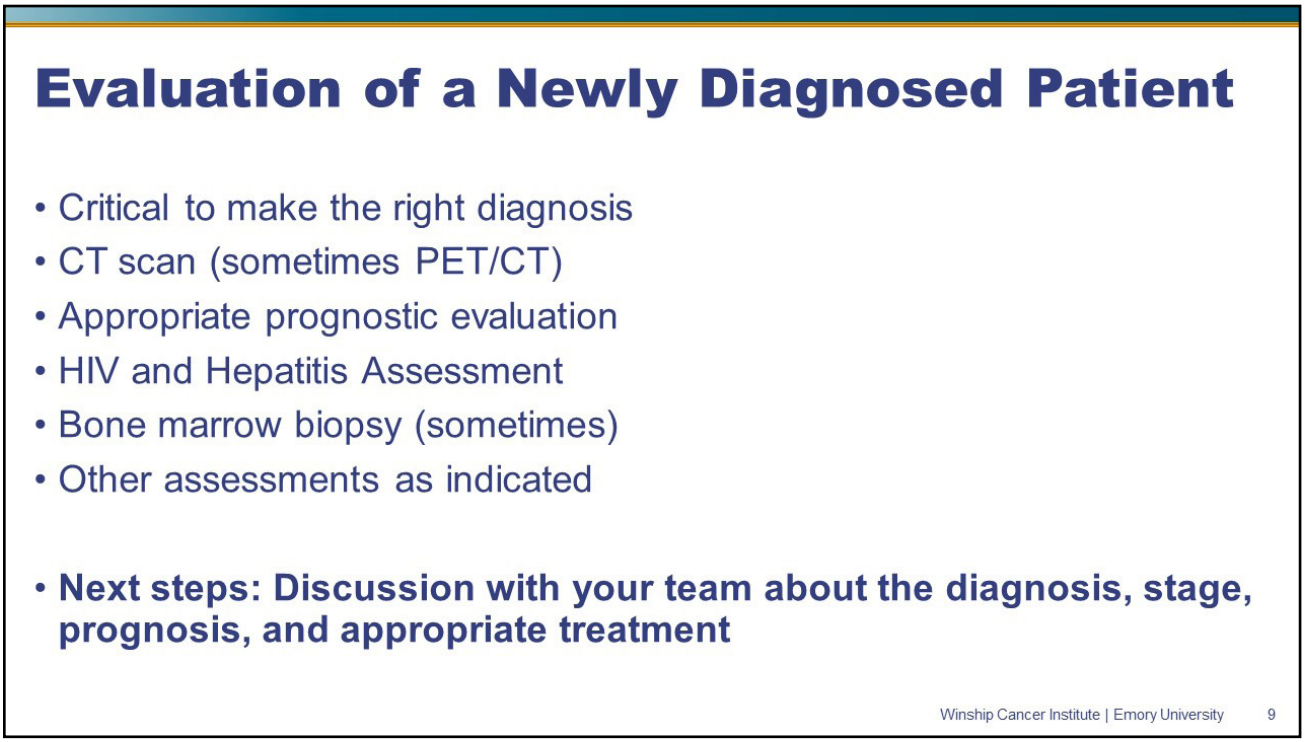
And then, the other point I would make is that having a trained hematopathologist review your pathology is very important. And, this may not be something that's easily apparent to you as the patient, but it's always appropriate to ask your oncologist or the doctor that's discussing your case with you, about whether a hematopathologist has been involved with the review of your case. Many different lymphomas can look the same, and there may be very specific nuanced differences between those 2 lymphomas that may have important implications for your treatment. So, having a pathologist who's trained in the review of blood cancers is very important, especially when making the initial diagnosis.



	Follicular lymphoma	Marginal zone lymphoma	CLL/SLL
Immunophenotype			
CD20	+	+	+
CD5	-	-	+
CD10	+	-	-
Genetic Rearrangement	t(14;18)	t(11;18) - sometimes	Varied

Slide 8: Making the Correct Diagnosis

One of the things that a hematopathologist will do is try to use specific signatures that are for each subtype or genetic characteristic in order to make the right diagnosis. And, these are things that I also review when I'm reviewing a new case, to make sure that the diagnosis rendered by the pathologist makes sense. And, on this table on this slide you can see that among these 3 different subtypes of indolent lymphoma, there are some different markers that help to distinguish those. Sometimes there could be a genetic rearrangement and I always remind patients that these are genetic rearrangements that are not inherited, that you don't have to worry about passing on or worry about other family members, but that exist in the tumor or in the lymphoma. And, these are things that we can test for. And, it's always important that when you're entertaining the possibility of one of these diagnoses, that the specific genetic rearrangements are assessed as well as what we call the immunophenotype or sort of the signature of the cancer cells. And again, you can see from this chart, not that these need to be memorized, but that these are all things that a pathologist will take into account when trying to distinguish among different lymphoma subtypes.



Slide 9: Evaluation of a Newly Diagnosed Patient

So, when I evaluate a newly diagnosed patient, there's a couple of things that I do. And, many of you that have been through this process, likely can recall this from your own experiences. So, as I mentioned, it's critical to make the right diagnosis, and if there's ever a question, that's where we stop and do whatever we can to try to make sure that we have the right diagnosis.

Subsequently, I will typically have patients complete what I call a staging evaluation, where we look to see what parts of the body are involved with the lymphoma. So, for low-grade lymphomas, I will almost always do a CT scan, but in some instances I will also consider a PET-CT scan. And, you can certainly discuss the differences between these scans with your doctor at the time of your evaluation, but I think the most important thing is making sure that you do have some form of imaging done to help identify what stage of lymphoma that you have.

I subsequently will do some additional assessments including a prognostic evaluation and what this means is that I will take a look at some of the different features of the pathology as well as lab values and other potentially medical conditions to help gauge how we expect your disease to behave. And again, in some instances patients have a very low-grade disease that behaves very indolently and may not require treatment right away, and other patients have some higher risk features that do merit treatment more quickly or may merit an adjustment of their therapy in order to address those prognostic features.

I will check HIV and hepatitis for each patient. This is important when deciding about therapies to offer and also may have some impact on the patient's prognosis. I will not always, but sometimes, will do a bone marrow biopsy. In the past, this was a common part of the evaluation for newly diagnosed patients. But we've learned in recent years that for many patients a bone marrow biopsy doesn't add anything to the treatment decision making, and so often I won't do a bone marrow biopsy unless there's a specific reason that I feel like it's needed.

And then, there may be other assessments that are indicated based on your specific presentation. And, these are things that your oncologist can discuss with you.

But, at the end of this evaluation, it's important then to have a discussion with your team, with your treatment team, about what your diagnosis is, what your stage is, what your expected prognosis is, and then what treatment approaches may be available for you. And, these are often extended visits, at least in my clinic, but I think that helping patients and their families understand what's going on at the beginning will really set the table for future decisions because to make sure that everybody's on the same page regarding what we're going to be dealing with over the next period of time.

Slide 10: Things to discuss with your oncologist

So again, these are just some things to discuss with your oncologist and sometimes I know patients may be nervous about asking questions but it's important to remember that especially at the very beginning of your lymphoma journey, or at any time that you're needing to make a decision about treatment, it's important that you have all the information that you need, and it's also important that your oncologist has all the information that they need. So, it's always appropriate to make sure that everyone is in agreement with what the lymphoma subtype is and what your stage is. I often like to have a general discussion about prognosis. Now, one caveat here is that none of us are able to specifically predict the future for any individual patient. And so, I always will tell patients that yes, you have some higher-risk features or fortunately you don't have as many high-risk features and we can talk about what the statistics show, but it's always important to remember that the statistics only do so much and that ultimately we may not always be able to predict what's going to happen to an individual patient.

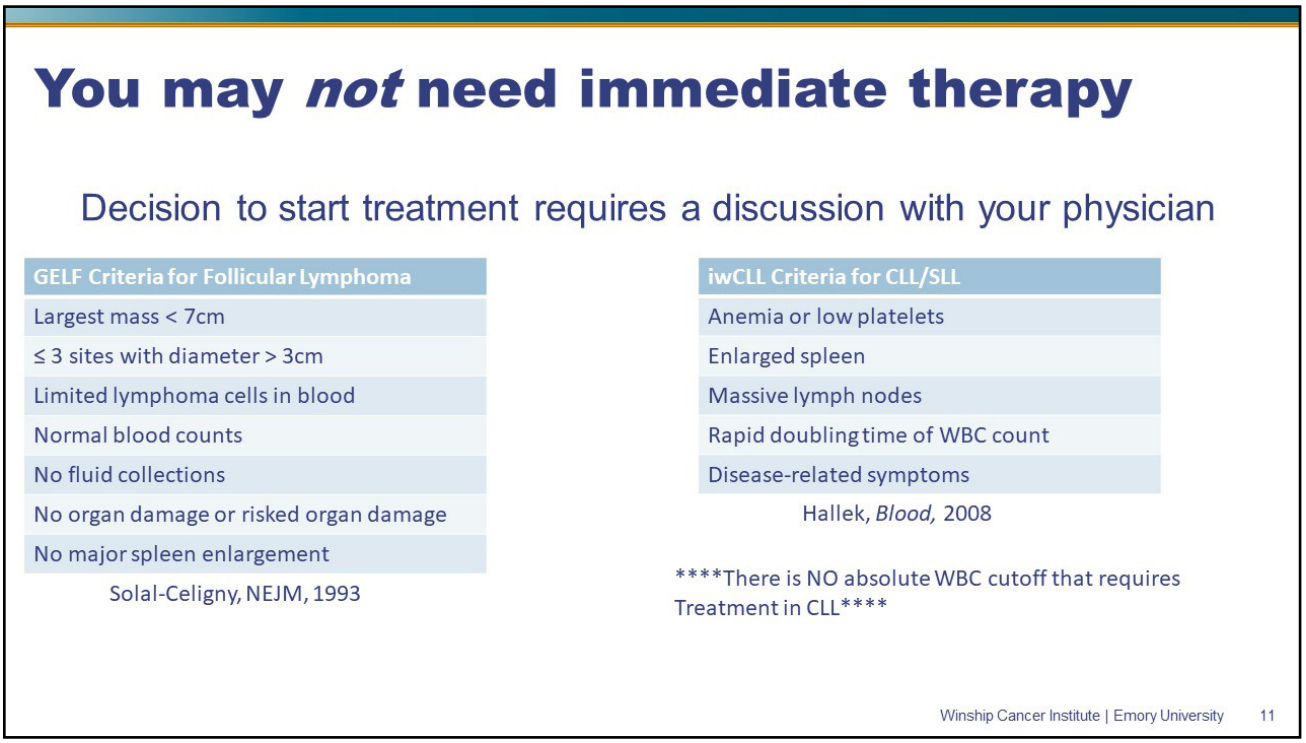
It's important to discuss your symptoms and make sure they're aware of what you're experiencing. And then, especially if there's a question about treatment and whether it's required, it's always appropriate to make sure that you have this discussion openly with your oncologist and work to understand why they are recommending one particular approach.

Make sure that you are discussing your other medical conditions. And so, we often will work very hard to review your medical record before you come for a visit but it's always important to let people know that are going to be taking care of you, that of any heart conditions you may have, diabetes, other medical conditions, as well as, mental health conditions including depression and anxiety. Because all of these comorbidities can potentially cause issues during your treatment and in order for us to be able to manage them appropriately, it's important to know up front, so that we can make sure we do everything we can to keep you safe.

I also think it's important to discuss upcoming life events, as well as priorities for you with regards to your quality of life. So, for some patients continuing to work is critical. Others may be in a position where continuing to work is not as critical and may be able to take on maybe a more intensive but shorter-term treatment. You may have a wedding coming up or some other big life event that you want to make sure that you're able to attend. I've had patients, for example, that have had big reunions coming up and we want to make sure that we do everything we can to allow them to safely attend those events. So, don't be afraid to bring that up. Now, in some instances your oncologist may say, look, I know that this is coming up, but unfortunately given what's going on, I'm concerned about delaying or I'm concerned that we may not be able to plan around it. But, if you at least bring it up we can do everything we can to try to help you attend those events and feel well

while you're doing so.

And then, at the end I think it's always a good idea to discuss whether or not a clinical trial is an option for you and whether it would be appropriate. And, this may or may not be something that always comes up easily, but I think it's always a question worth asking.



Slide 11: You may *not* need immediate therapy

So, as we've discussed previously, you may not need immediate treatment and there are a number of different criteria that we as oncologists use to identify whether a patient with an untreated indolent lymphoma needs to initiate therapy.

So, on the left you can see the GELF Criteria, which you can see are not particularly new. They've been out for 25 or more years now. But, these are still valuable criteria that I often use when evaluating new patients, especially with follicular lymphoma. And, really what they're aimed to do is to try to identify those patients that have a low tumor burden that don't have symptoms, that may be able to delay therapy. And, you can see on the right that for patients with CLL or SLL there are also similar criteria that we use. And again, these are not meant to be absolute. Certainly, it's always important for us to have a discussion about what's going on in your life, what type of symptoms you're having. Certainly, patients with follicular lymphoma that have a lymph node of 6.8 centimeters may be in a position where we feel like treatment is appropriate. And then, I've had other patients who have lymph nodes that are even larger than that where we feel comfortable observing them because maybe they have other medical conditions, or in a position where they really are trying to put off therapy for as long as possible. And so, these are guidelines but I would encourage each of you, if you're considering an approach of watchful waiting to have a good discussion with your oncologist about what they'll be looking for and what might push them to recommend therapy in the future.

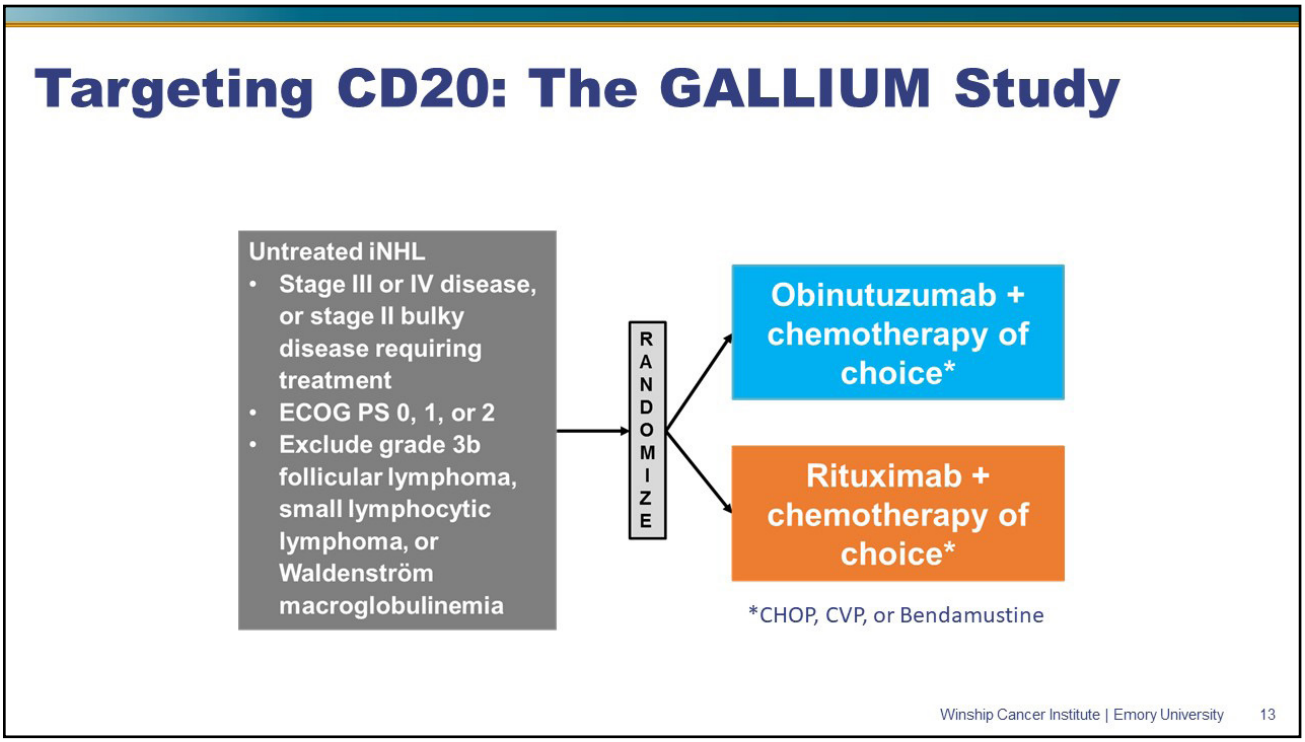
And then, as you can see from the point I've made in the bottom right, for those of you with CLL, one of the things that is often a source of anxiety and concern among patients and families and among physicians is the white blood cell count, and this is often what leads CLL to come to see us in the first place. And, I always like to remind patients that there is no absolute white blood cell cutoff that would require treatment. So, we have some patients that require therapy for other reasons and their white blood cell count is 15. And then, I have other patients that have a white blood cell count of 180 and otherwise are asymptomatic and doing well and don't have any other indications for therapy and I continue to observe those patients. And so, the most important point from this slide is that we do have guidelines that we use, but that at the end of the day it really comes down to an interaction with a patient to discuss their concerns and their symptoms.

Slide 12: Treating Follicular Lymphoma

So, let's talk a little bit more specifically about follicular lymphoma. For those of you with untreated follicular lymphoma, there are fortunately many options that can be very effective. So, some things that your oncologist would likely be thinking about and that you would discuss with them is, is chemotherapy required and so again some patients can be observed. Other patients might be able to be treated without getting traditional chemotherapy. If you are going to use chemotherapy, which chemotherapy is most appropriate for you? Which antibody is most appropriate for you? So, we frequently use antibodies that target CD20, which is a marker of the B cells that make up your lymphoma. But, as some of you may know, there are a couple of antibodies that are currently available. And, these are all things that we consider when we're making a treatment decision.

Some of you may be candidates for radiation and then also there's a question about maintenance therapy. So, maintenance therapy refers to that treatment that we administer, usually every couple of months, after somebody has completed their initial, more in-depth course of treatment. And, it's something that's designed to try to prolong your remission.

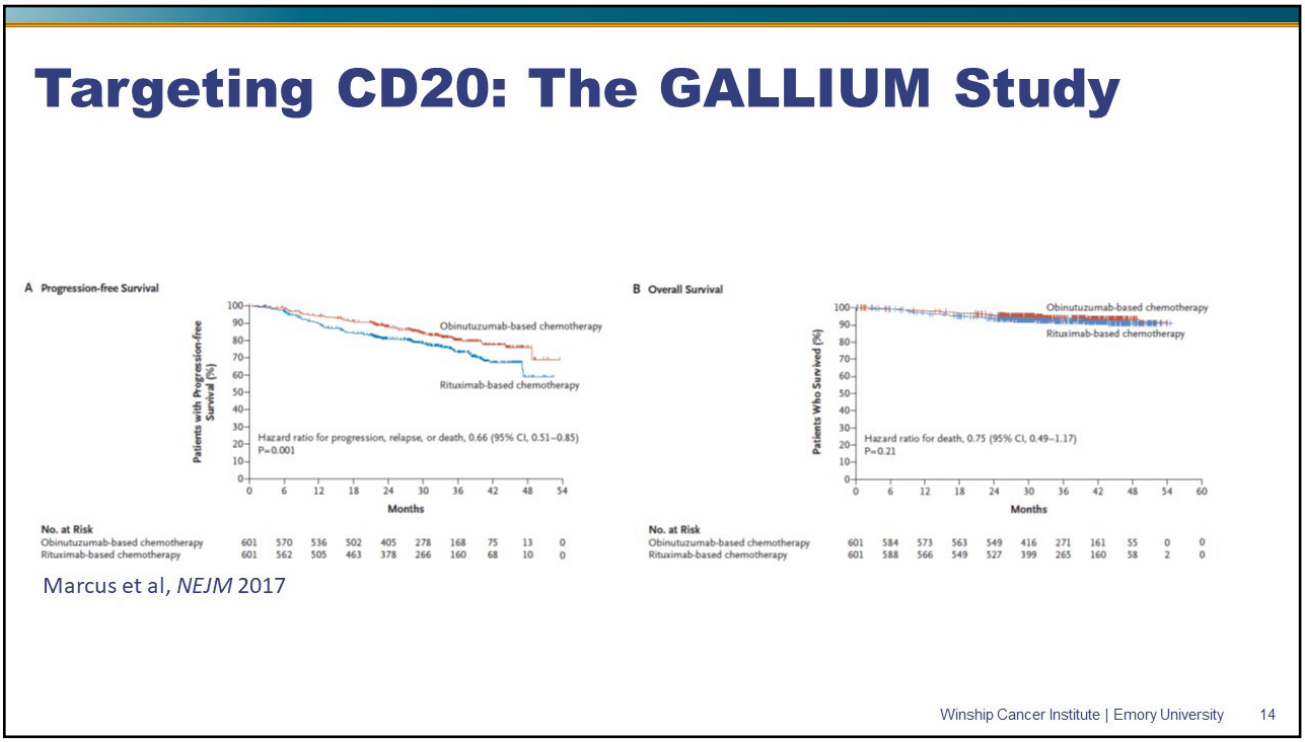
So again, as I've already discussed, it's essential to consider your personal goals, the prognosis of your particular type of lymphoma, other medical conditions, your lifestyle, and overall the disease-related expectations when you choose a treatment. And, it is certainly not a one-size-fits-all discussion.



Slide 13: Targeting CD20: The GALLIUM Study

So, let's talk about some of the key studies that have helped to inform our treatment of patients with indolent non-Hodgkin lymphoma. So, the first study that we'll discuss is one called the GALLIUM Study. And, this was a study that compared rituximab, which has traditionally been the CD20 antibody of choice, with obinutuzumab, which is a newer form of monoclonal antibody. And, in this particular study patients were able to receive the chemotherapy of choice. So, they could either receive CHOP, which is a more traditional chemotherapy regimen, they could potentially receive CVP, or bendamustine. And, these are 3 chemotherapy backbones that are frequently utilized for indolent lymphoma.

And, patients were randomized between these 2 antibodies, so otherwise it was felt to be a controlled study, so that the groups were generally similar, aside from whether or not they received the antibody.

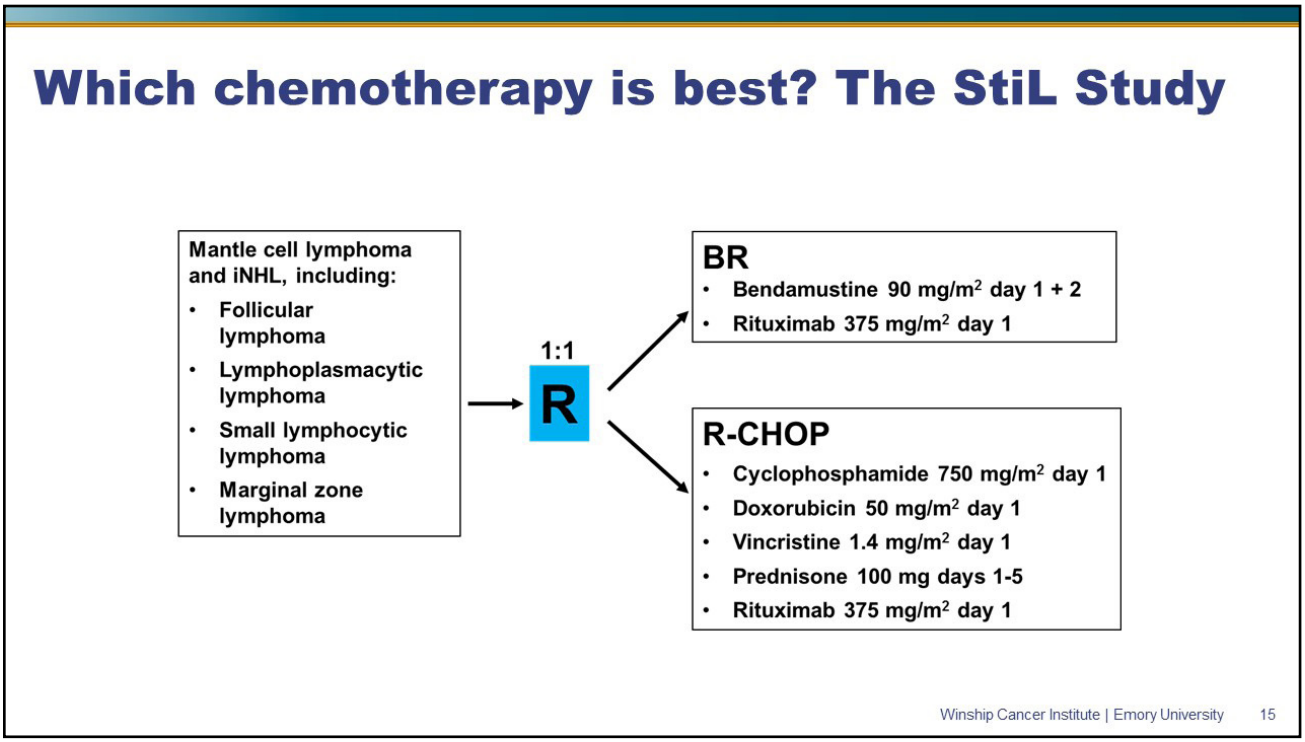


Slide 14: Targeting CD20: The GALLIUM Study

And on this slide I included 2 Kaplan-Meier curves from the publication of this study. And, for those of you that may not be as familiar with a Kaplan-Meier curve, this is a curve that we use often to estimate outcomes after treatment. And so, if we start with the curve on the left you can see that it's labeled progression-free survival. And, what that means is that we are estimating the number of patients that are alive and free of progression of their disease. Okay, and this is where, this – meaning that you have been treated, have gone into remission and are still alive and in remission. And, everybody starts, if you look at the bottom, the X axis, everybody starts at month zero. And, at month zero, when people initiate treatment, they are alive and free of progression by definition. And, as time goes on, you can see it goes out in 6 month increments, a certain number of patients may ultimately progress. And, what you're trying to see is if there's any separation of these curves. And, what we saw in the study is that there was a modest improvement by using obinutuzumab instead of rituximab, meaning that you are statistically more likely to stay progression-free if you received obinutuzumab as opposed to rituximab as your antibody.

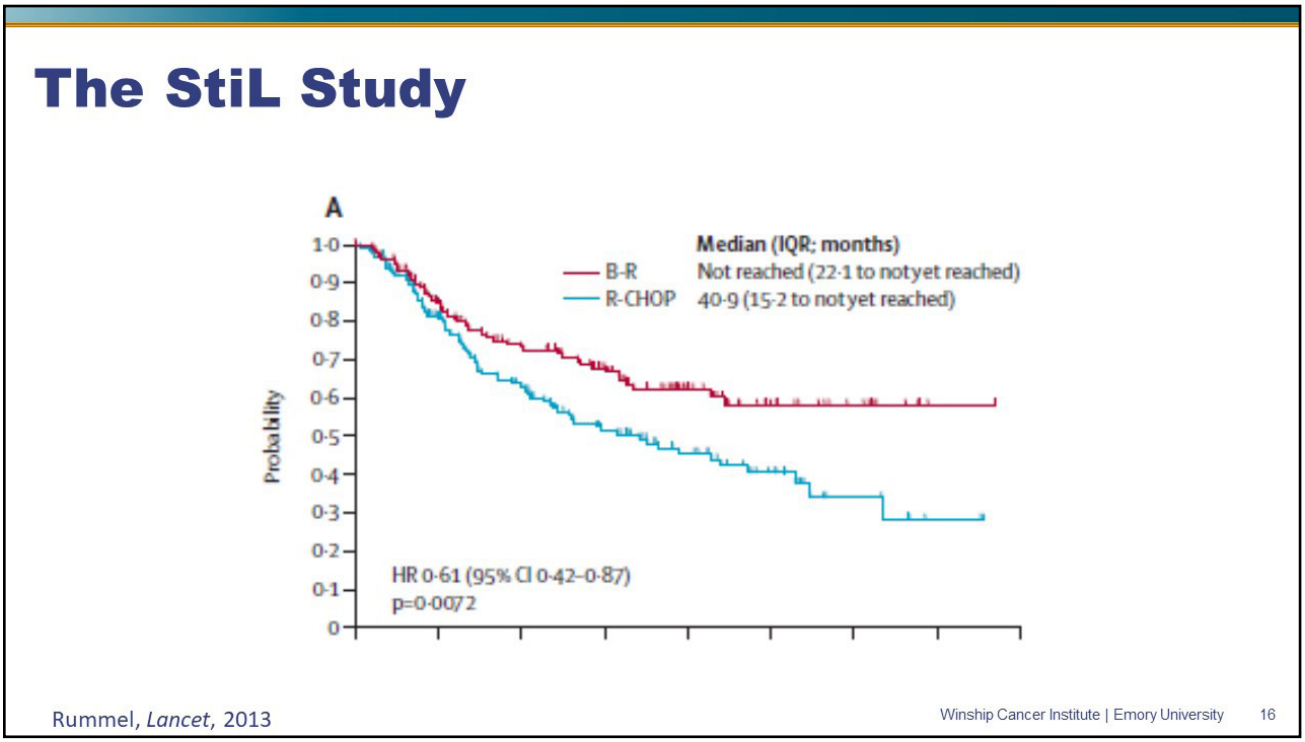
Now, you can look over on the right and you can see that when they looked at overall survival, and so this just means patients that are alive, and they may have relapsed and gone on to another therapy, but they are alive, that there was no difference, that the curves overlap. And so, what this means to me is that you might be able to have patients stay in remission a little bit longer if you administer obinutuzumab instead of rituximab with the data that we currently have available, that it does not appear that a patient would necessarily live longer by using this newer antibody.

And so, based on that, I think it still is very much an open question about which antibody is best. Because one of the other things that we did find is that there were some increased side effects for patients that used obinutuzumab as opposed to rituximab. So, this is a discussion that I have with each individual patient, but right now I would say it still is an area of open debate. Fortunately, though, as you saw from those curves, the majority of patients will stay in remission for a very long time.



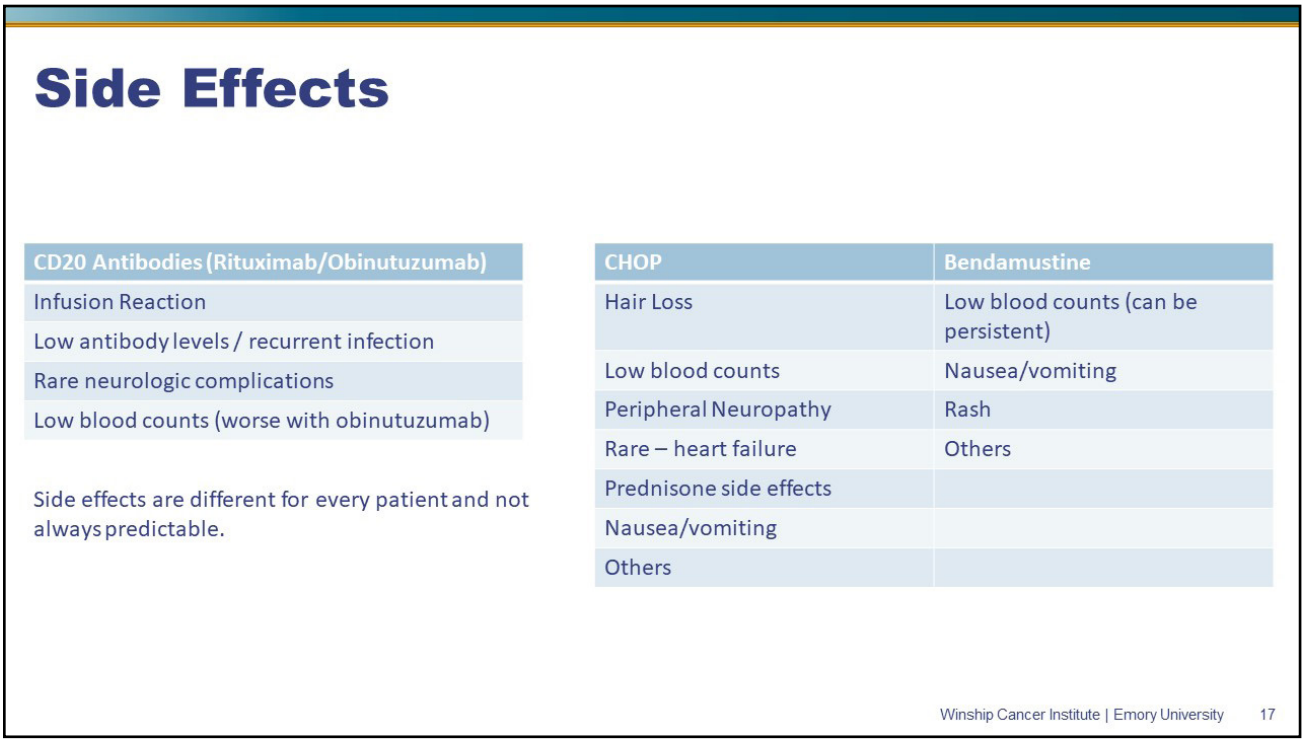
Slide 15: Which chemotherapy is best? The StiL Study

Now, the GALLIUM Study evaluated which antibody was best but it still has been unclear over the years which chemotherapy is best. And so, this was a study that was published several years ago from Europe that compared bendamustine with CHOP. And again, CHOP has been around for a long time. Many of you that have been treated in the past may have received it. Bendamustine has also now been around for quite some time, but not quite as long as CHOP. And, this was a study that randomized patients between bendamustine-rituximab and R-CHOP, and you can see on the left that there were a number of different indolent lymphoma subtypes that were utilized in the study.



Slide 16: The StiL Study

And, this is the Kaplan-Meier curve from this study which was looking at progression-free survival. And, you can see that these curves do separate more than the last study that I demonstrated. And, this again suggests that bendamustine-rituximab is probably superior to R-CHOP for patients with low-grade lymphomas. Having said that, you can see that if you look under where it says Median, next to R-CHOP it says 40.9 and that means that the patients who received R-CHOP still had almost 3½ years of remission on average but the bendamustine patients, they hadn't even reached the median, meaning half of the patients still hadn't progressed. And so, based on this finding, although patients can still do well with R-CHOP, most patients in the current era will receive bendamustine as their chemotherapy if they're going to receive chemo for indolent lymphomas.

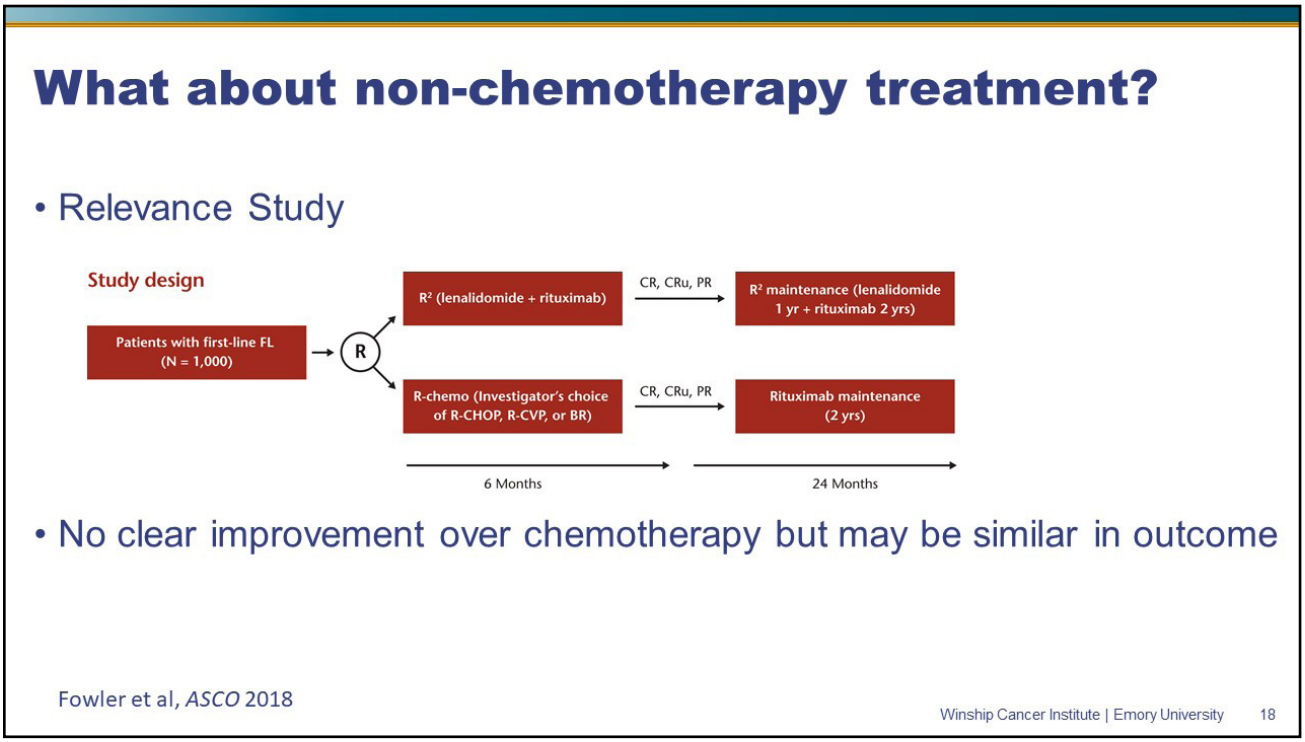


Slide 17: Side Effects

Now, it's important to recognize that any of these therapies can have side effects. So, both rituximab and obinutuzumab can be associated with an infusion reaction, and so this is something that occurs typically in the infusion center where you can have shakes or chills or hives, or rarely it can be even more serious than that and you can have blood pressure or breathing issues and have to be in the hospital. Fortunately, hospitalization is very, very rare and most patients will tolerate this just fine. There can be some infectious complications, as well as some complications with low blood counts, especially with obinutuzumab. But most patients will tolerate the CD20 antibodies quite well.

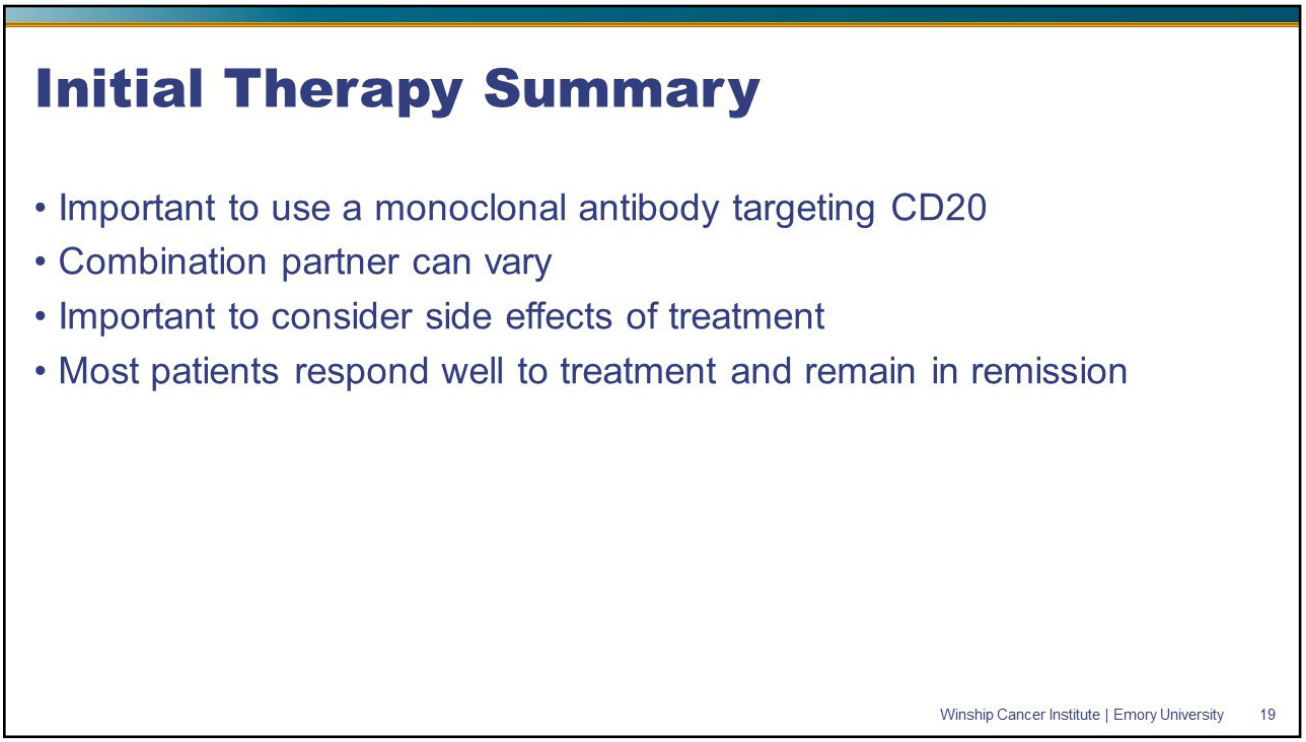
Now, when looking at chemotherapy, though, there are some significant differences. So, CHOP, for example, typically is associated with hair loss, whereas bendamustine is not. Bendamustine, however, can be associated with low blood counts that can persist for a long time, whereas the low blood counts with CHOP tend to not persist for quite as long. And, you can see I've listed some additional side effects that we see and that we monitor for over the course of treatment.

For any individual patient, it's hard to predict which specific side effects they will have. Some patients will have very limited side effects and others may be more affected. And, it's important that we monitor patients throughout the course of their treatment, so that we can try to adjust these side effects and maximize the amount of treatment that they're able to receive.



Slide 18: What about non-chemotherapy treatment?

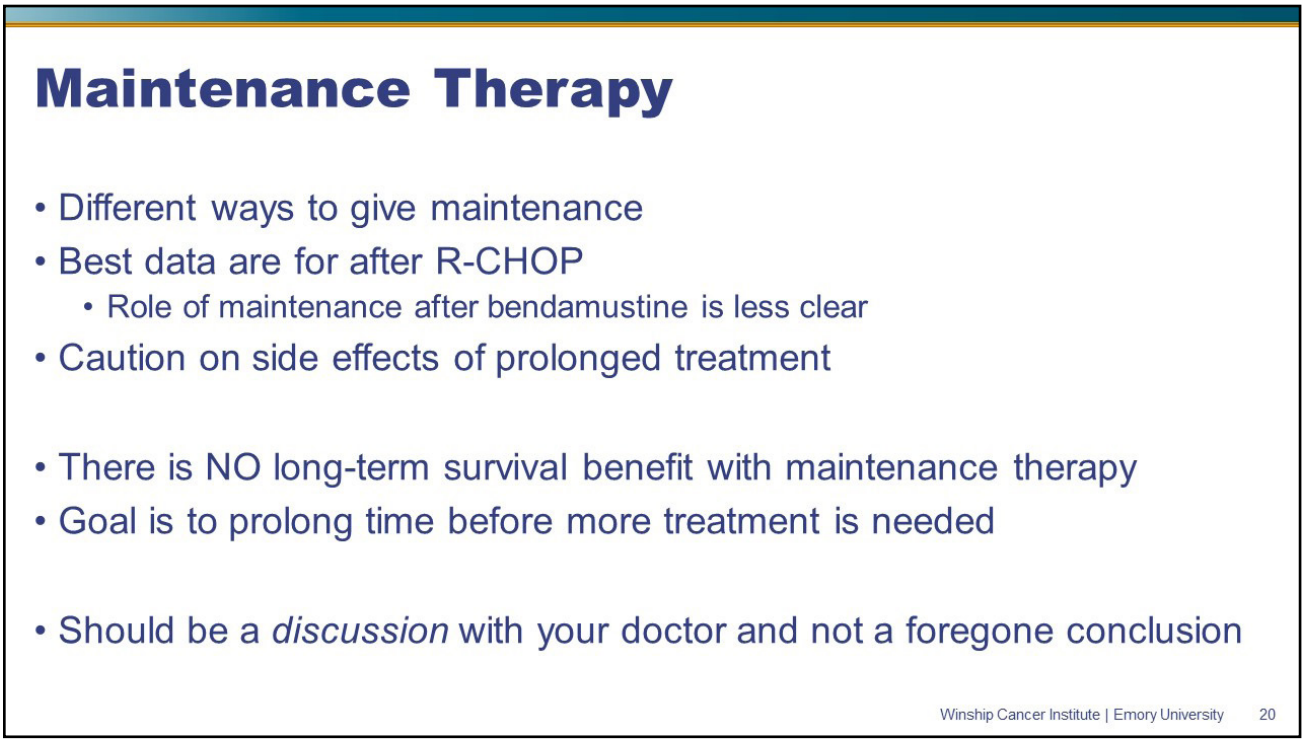
Now, what about non-chemotherapy treatment? So, right now in the United States, most patients will receive bendamustine or some sort of chemotherapy backbone if they're receiving treatment for indolent lymphoma. But, there have been other studies looking at non-chemotherapy approaches. This is the Relevance Study that was initially presented about a year ago, that used rituximab plus lenalidomide, which is an oral therapy which is felt to increase your immune system, and it was compared to R-chemo. And again, you can see patients could receive CHOP, CVP, or bendamustine. And then, these patients also went on to receive maintenance. And, interestingly there were no clear improvements over chemotherapy, but the outcomes were similar. And so, if there were to be a patient that potentially couldn't tolerate chemotherapy, this would suggest that you could potentially use a non-chemotherapy approach. However, it does not appear to improve on what we've been using previously. And so, this is something just to keep in mind moving forward and I wanted to bring it up just to highlight that there are non-chemotherapy treatments that are currently being investigated.



Slide 19: Initial Therapy Summary

So, just to summarize, for the initial therapy for follicular lymphoma most would agree that using a monoclonal antibody targeting CD20 is important. I think it is still up for debate whether or not rituximab or obinutuzumab is better, but I think that one of them is important. And, the combination partner can vary. And so again, most people receive bendamustine, but many patients can do just fine using CHOP or CVP or some of the other options.

It's always important to consider the side effects of treatment, and fortunately most patients will respond very well to treatment and will remain in remission for many years.



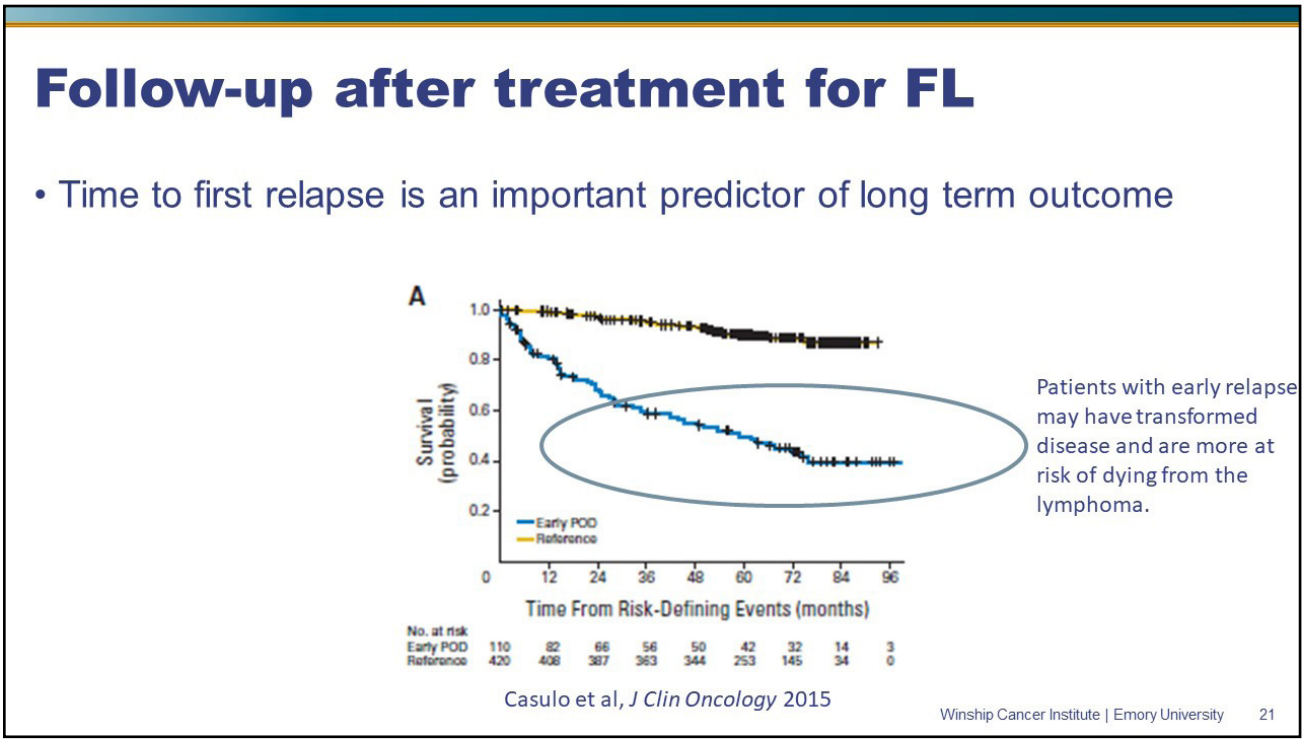
Slide 20: Maintenance Therapy

So, now let's talk for a few minutes about maintenance therapy and this is often one of the next big points where we have a real sit down with our patients to have a discussion about moving forward. So, often patients have completed therapy, they're in remission and then we're talking about what can we do to try to maintain that remission.

So, maintenance in follicular lymphoma especially almost always refers to rituximab or a CD20 antibody by itself. There are other investigations looking at other approaches, but in general, outside of setting of a study, we're talking about giving rituximab or obinutuzumab.

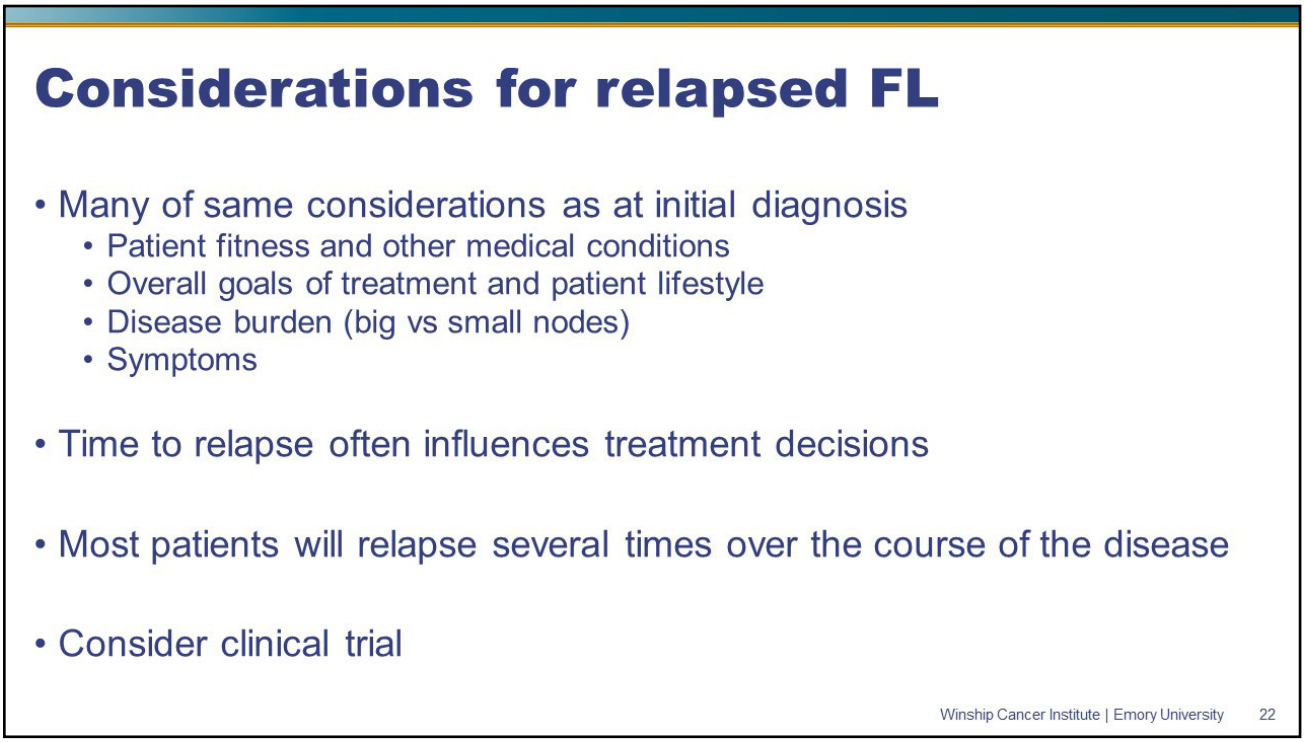
And, the best data to support maintenance are for patients who have received R-CHOP. For patients that have received bendamustine it's less clear how important maintenance is, and that type of study hasn't been done in the same fashion that it has after R-CHOP.

I think it's important to recognize that there can be some side effects of prolonged treatment with maintenance therapy and I always like to remind patients that at least right now there is no long-term survival benefit by giving maintenance. And so, the way that I typically give maintenance is to give a dose of rituximab every 2 months and the goal is to try to prolong the amount of time before treatment is needed, but I always caution patients that I can't necessarily make them live longer just by doing the maintenance therapy. And so, at the end of the day I feel like this is an important discussion to have with your doctor but I would not accept it as a foregone conclusion that you need it. I think at this stage of your treatment it's a good time to sit down, see how you've done with your treatment so far, talk about what your goals are, talk about what your lifestyle is, and then make a decision about whether maintenance is something that you're interested in pursuing.



Slide 21: Follow-up after treatment for FL

So, for the majority of patients, they will receive therapy when it's time for treatment and will have a good response. But, one of the things that's most important after patients have completed therapy is to see how long that response lasts. And, this is a fairly famous study that was published now a couple of years ago, which divided patients into those who progress early after completing therapy for follicular lymphoma, so within 2 years, or those patients who don't. And on this curve you can see that the yellow line, which are those patients who did not relapse early, tended to have an excellent survival and this survival really is not much different than the general population that doesn't have lymphoma. However, those patients that were on the blue curve or those that had an early relapse tended to be an increased risk of potentially even dying from their lymphoma. And so, this is a group of patients where there's a lot of intense research going on to try to improve these outcomes, because these patients tend to have not done as well as most patients do with indolent lymphoma.

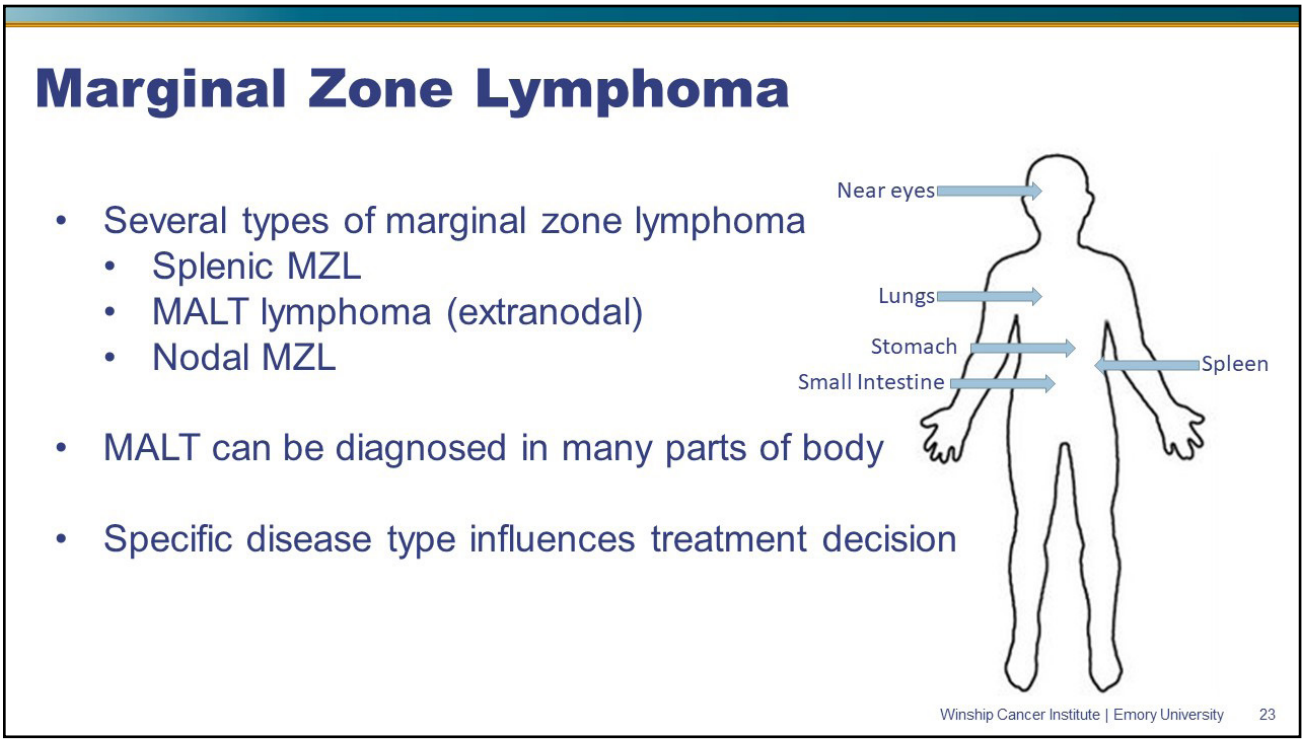


Slide 22: Considerations for relapsed FL

So, there are a number of very effective options for patients with relapsed lymphoma and in the short time we have today it would be hard to go through all of them. But, I think it's important to highlight some of the things that I think about when making a decision about patients who have relapsed lymphoma and need therapy.

First of all, I consider many of the same things I did at the time of the initial diagnosis. So, if somebody is fit and has limited medical conditions, they may be eligible for some therapies, whereas somebody who is maybe not in as good a shape or has other medical conditions, may have more limited options for treatment. Discuss overall goals of therapy as well as the patient's lifestyle and what's important to them at this time in their life. We'll look at their disease burden and symptoms. And again, the time to relapse often influences these treatment decisions. And, I like to counsel patients when the disease does come back that most patients will relapse several times over the course of the disease, and so this is something that's an expected part of treating patients with follicular lymphoma and of living with the disease. And, my goal is to really think about sort of where they are in their disease and try not to introduce therapy that's going to be too toxic, keeping in mind that they may require additional therapy down the road.

And then, as I mentioned at the beginning, it's always important to consider a clinical trial for patients with relapsed disease, because this is often where we are evaluating some of the newer therapies that may show the most promise.

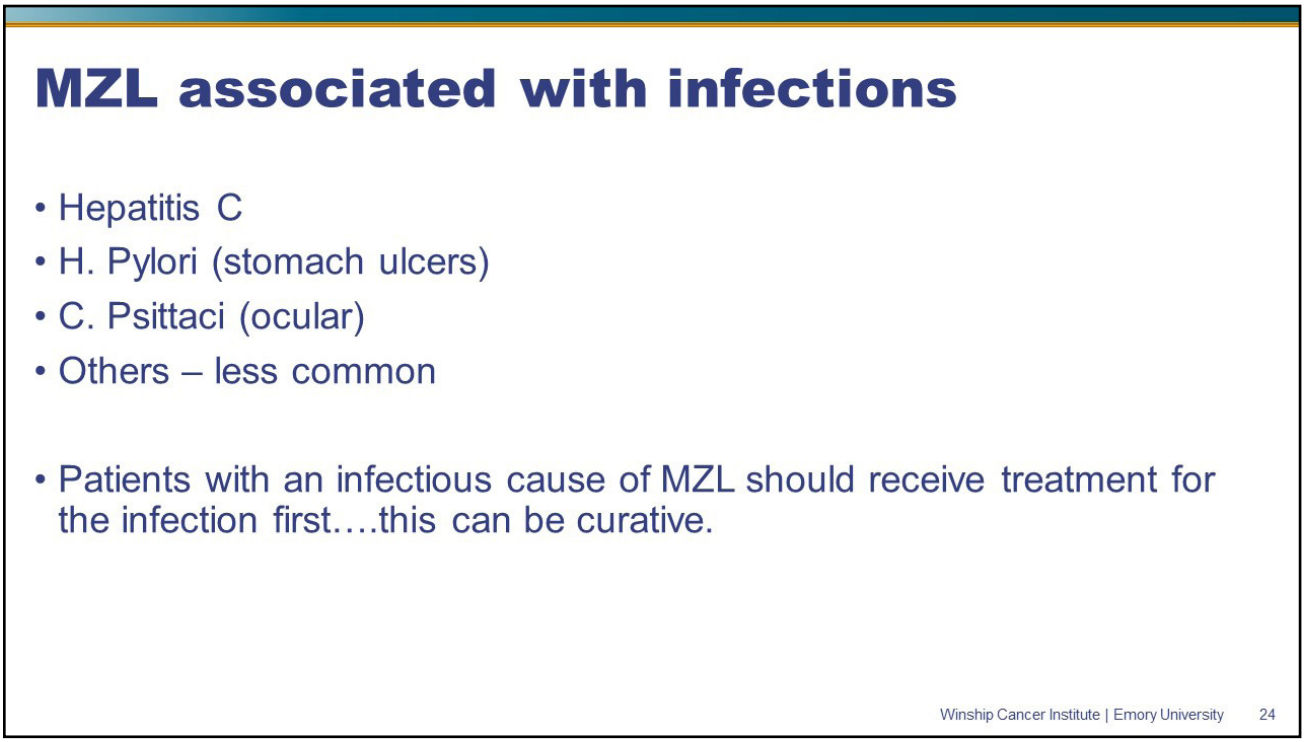


Slide 23: Marginal Zone Lymphoma

So, next we'll talk a little bit about marginal zone lymphoma. Now, this is a less common lymphoma than follicular lymphoma, but it's still I think an important one to discuss and one that can affect a large number of parts of the body.

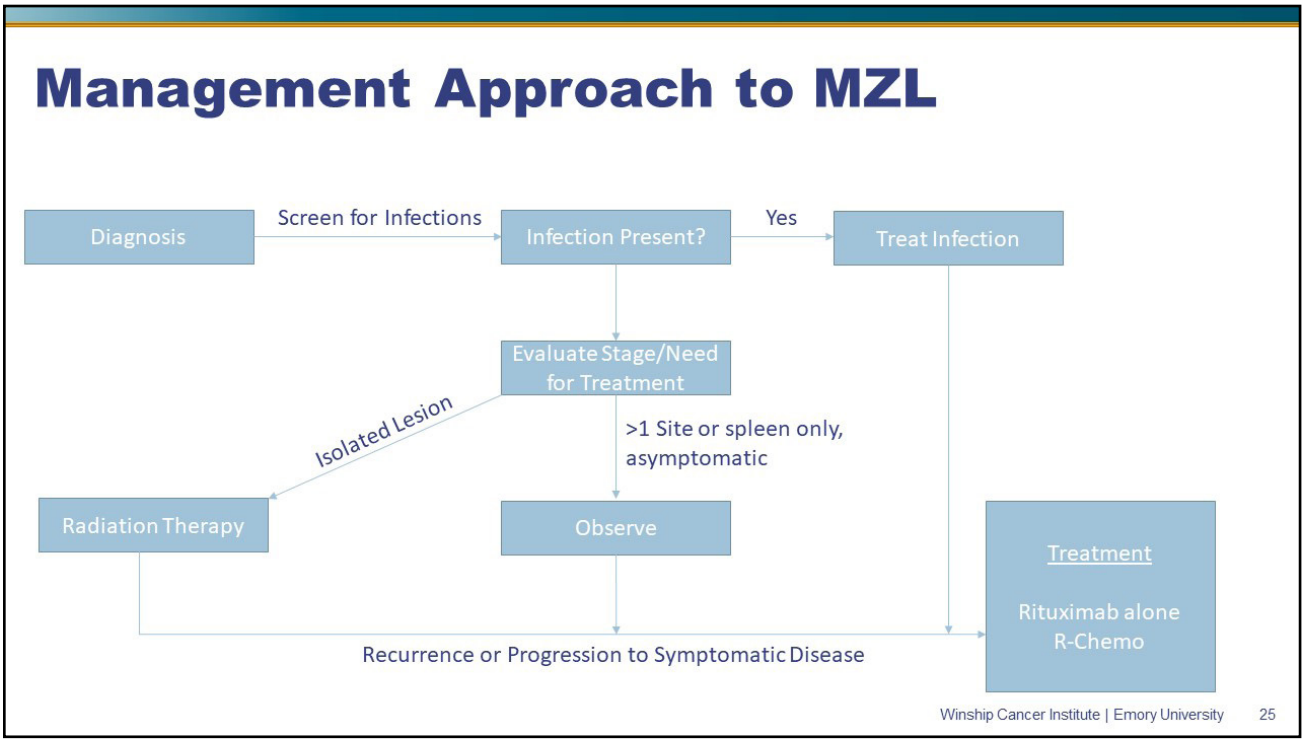
The first thing that I would say is that even though this in and of itself is a rare lymphoma, it's actually divided into 3 different subcategories which can behave differently and can be treated differently. So, there's splenic marginal zone lymphoma, which typically involves the spleen as well as potentially other parts of the body. There's MALT lymphoma, which typically involves areas outside of the lymph nodes. And so, as you can see from the mannequin here, I've highlighted some potential areas that can go, including the lungs, the stomach, the small intestine, and sometimes near the eyes. And, then there's nodal marginal zone lymphoma, which is the least common subtype of marginal zone lymphoma and which involves primarily the lymph nodes.

MALT can be diagnosed in many parts of the body and I've had patients come to me from their gastroenterologist, from their ophthalmologist, or a pulmonologist, or really from any specialist because the disease has been found there. And, the specific disease type that you have really does influence the treatment decision.



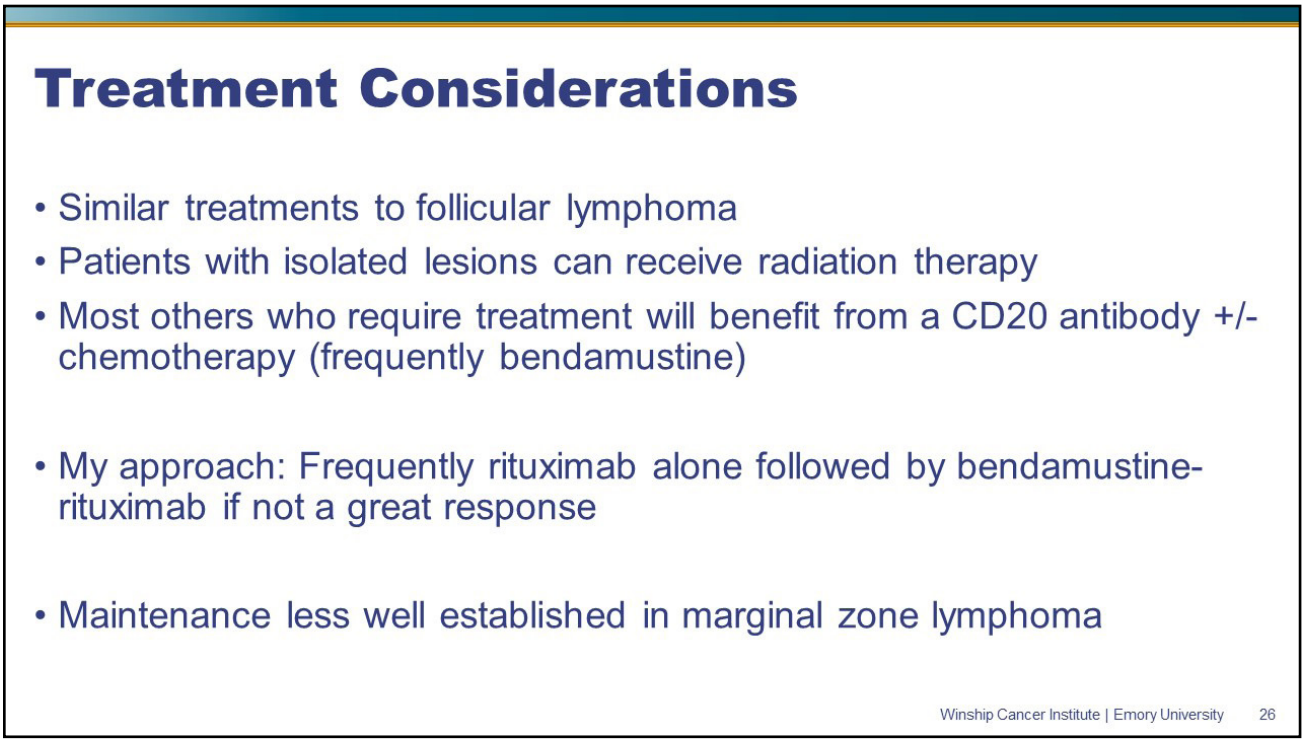
Slide 24: MZL associated with infections

One of the things that's particularly interesting about marginal zone lymphoma is that it's often associated with infections. And so, often people will ask me in general, well, why did I develop lymphoma, and in many cases we don't have a great answer for them, but marginal zone is one that is frequently associated with different infections. So, we know hepatitis C, for example, is frequently associated with the development of marginal zone lymphoma. And, for patients that have marginal zone in their stomach, it often is associated with *H. pylori*, which is a bacteria that can cause ulcers. And then, there are others that are less common. And, this is one of the few forms of lymphoma that can be treated just by treating the underlying infection and this can be curative. And so, I've had patients who have *H. pylori*, that resulted in stomach ulcers, they have this marginal zone lymphoma in their stomach, and we treat them for the *H. pylori* infection and the disease goes away. And so, this is always an important part of the evaluation of patients with marginal zone lymphoma.



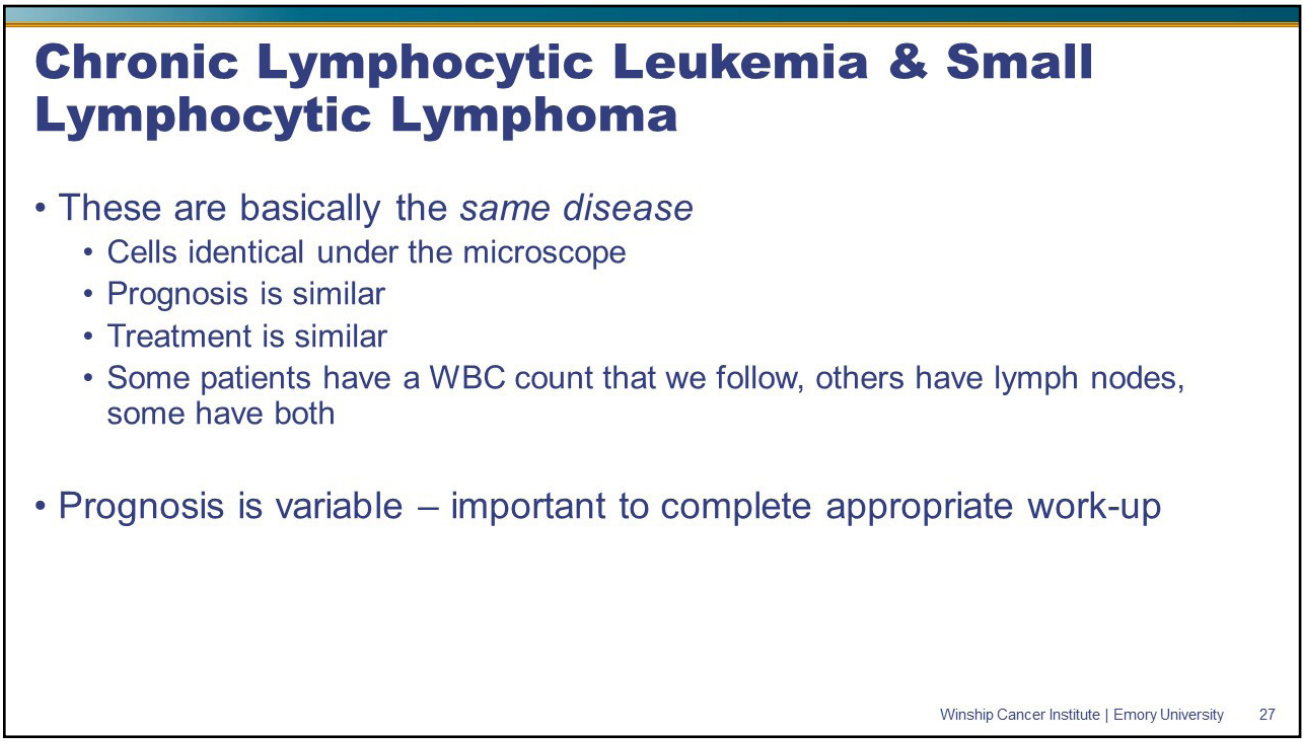
Slide 25: Management Approach to MZL

So, on this slide I've highlighted my general management approach to marginal zone lymphoma, although again I would highlight the fact that there are a number of different subtypes and it's not a one-size-fits-all approach. Normally, though, at the time of diagnosis we'll screen for infections, as I just mentioned, and if an infection is present and is treatable, then the first order of business is to treat the infection. And, in many cases that will result in resolution of the lymphoma. If there's no infection present, however, then patients should be staged and evaluated the same way we do for follicular lymphoma, so really trying to determine whether or not they need therapy and what their stage is. And, patients with marginal zone lymphoma that have an isolated lesion, so only in the stomach, only in the eye, or the area by the eye, only in one particular area, often can be managed with radiation therapy and don't require chemo or more systemic treatment and can do quite well. If patients, however, have more than one site, but they don't have symptoms, then I often will observe those patients the same way I will for follicular lymphoma patients that are asymptomatic. Ultimately, however, if a patient progresses, either after treating the infection or after radiation or after observation, we typically then would look at treatment options and sometimes that could include rituximab by itself, sometimes that includes rituximab with chemotherapy. And so, these are all again discussions that I'll have with patients. And, I think it's important to highlight for marginal zone as well as for follicular, that even when we engage in a watchful waiting approach, that doesn't mean that we don't see patients or don't evaluate them. I typically will see patients once every 3 months at least for the first year or 2 and then potentially start to spread things out. So, this is not a scenario where we just say call us if you need us. Typically, this is an ongoing observation process.



Slide 26: Treatment Considerations

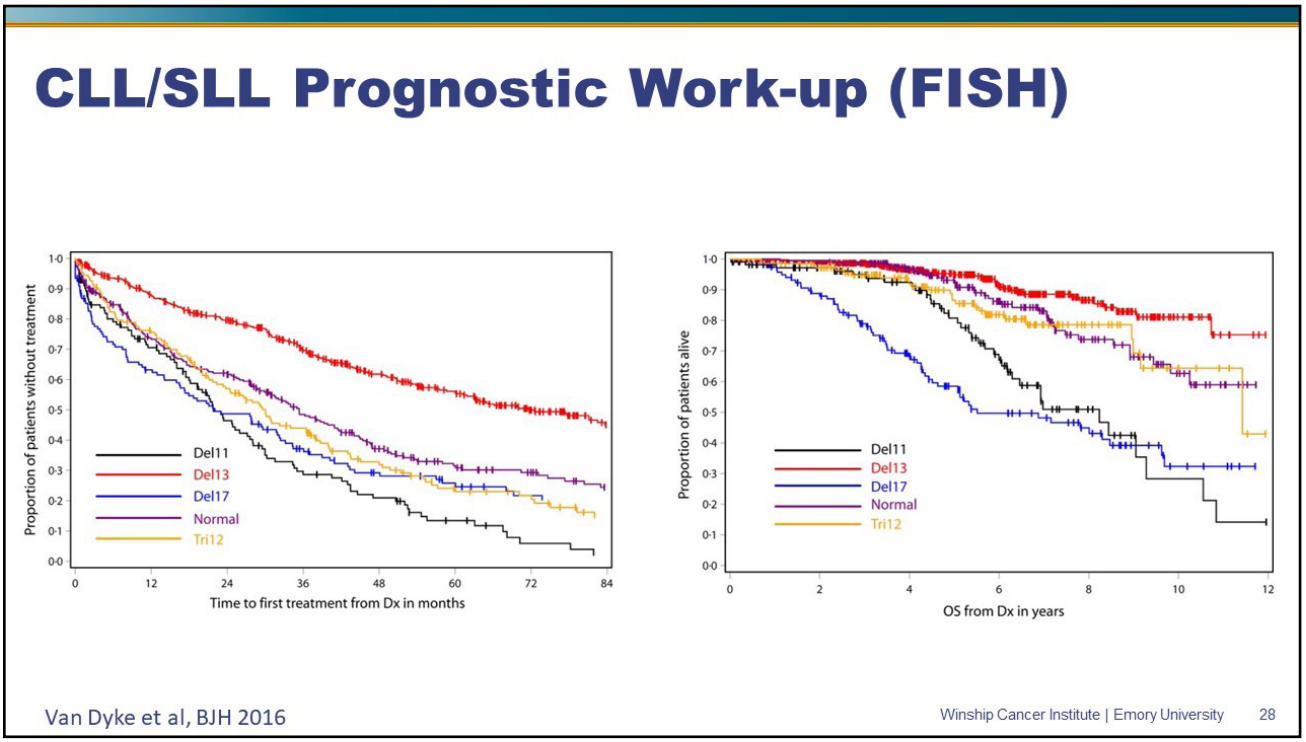
So, just some general treatment considerations for marginal zone lymphoma. There're often are similar treatments to follicular lymphoma and patients with isolated lesions can receive radiation therapy. And, this can be a curative approach for patients with limited stage disease. Most patients, though, who ultimately require systemic treatment will benefit from a CD20 antibody like rituximab and they may need chemotherapy as well. And, I often will use bendamustine in this setting as well. So, my typical approach is to use rituximab alone if I have somebody with limited symptoms and that's not particularly ill. And then, if they don't have a great response we may proceed to something like bendamustine. I would also point out that maintenance therapy is less well established in marginal zone lymphoma and so I have used it before, but it is not part of my standard approach.



Slide 27: Chronic Lymphocytic Leukemia & Small Lymphocytic Lymphoma

So, next we'll talk about CLL and SLL. And, one of the first things I want to highlight is that these basically are the same disease. So, I often try to help patients understand that they don't have 2 different cancers. These are the same disease, they look the same under the microscope, they have the same prognosis and treatment. Some patients that have more of a CLL, a chronic lymphocytic leukemia variety, we follow their blood work primarily. Other patients have more lymph node disease and not as much in the blood and on those patients we follow their lymph nodes. Some patients have both, an elevated white blood cell count and enlarged lymph nodes. But, it's very important to recognize that these are truly just, I think of them as a spectrum of the same disease and not as 2 separate diseases.

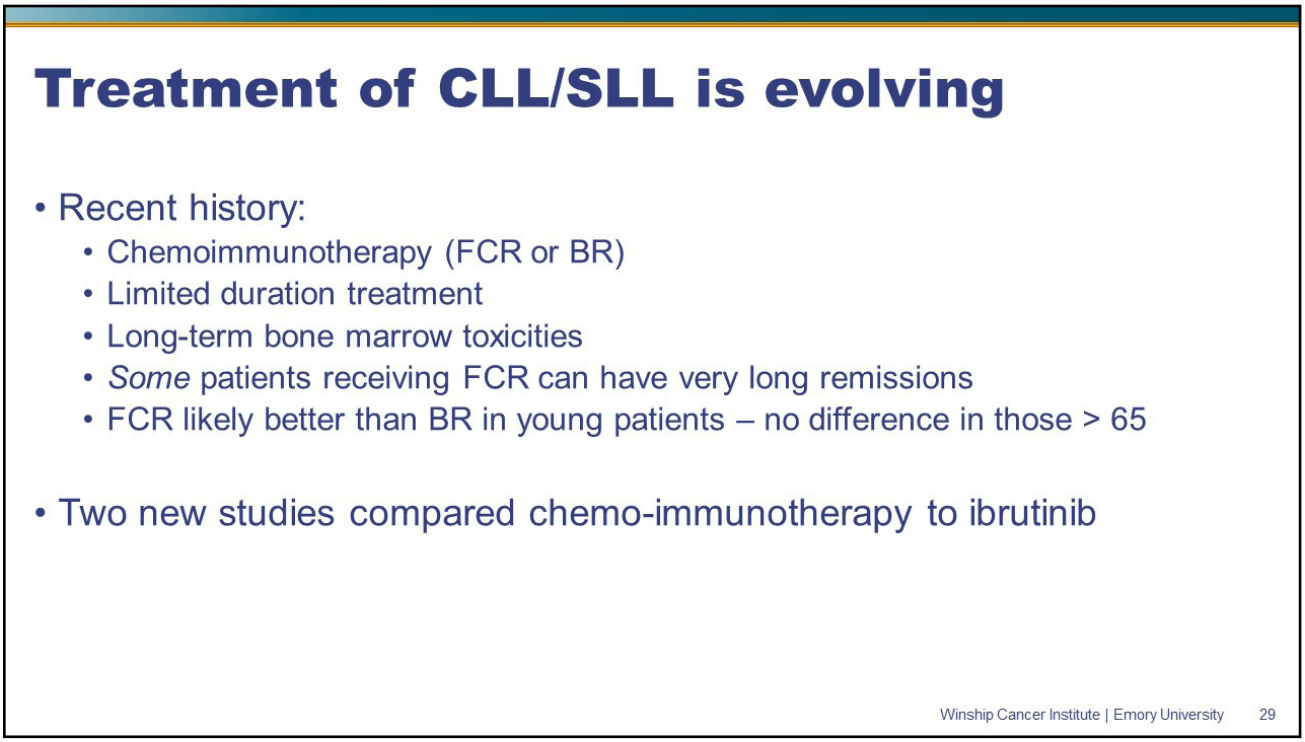
The prognosis is variable and so in this disease in particular it's critically important to complete the appropriate work-up. So, it's not enough just to say you have CLL, but there are several different variables that we look at to help us determine how a patient's disease may behave.



Slide 28: CLL/SLL Prognostic Work-up (FISH)

One such important variable is an assessment called FISH. And, what FISH is, is a test to look for specific genetic changes in the CLL or SLL cells. And, like I mentioned before, these are not changes that you have to worry about as far as passing them or that you've inherited, but these are things that happen in the cells themselves, in the cancer cells. And, you can see that depending on what FISH abnormalities you may have, it can impact your prognosis. And so, patients that have a deletion 13q, those on the red line at the top, tend to have the best prognosis, whereas those patients that have either a deletion 11q, or a deletion 17p, tend to have a more aggressive behaving disease. And, those patients at least historically have not responded as well to our standard approaches like chemotherapy.

So, this is an important discussion to have with your oncologist at the time of your diagnosis to see what your prognosis may be and it will likely inform how you may require therapy in the future.



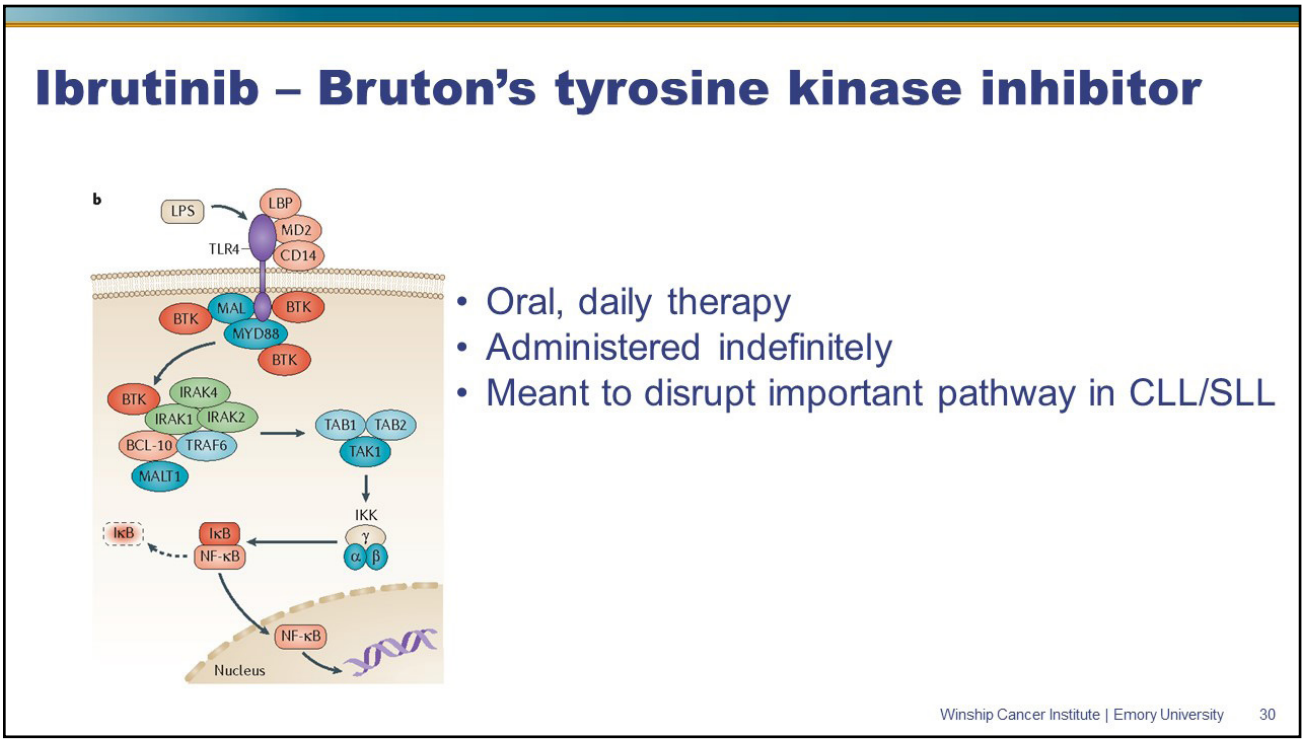
Slide 29: Treatment of CLL/SLL is evolving

I think it's also important to recognize that the treatment of CLL and SLL is evolving. And so, if you were diagnosed currently, you may be treated very differently than somebody that was diagnosed even 2 or 3 years ago. And so, if you happen to have an acquaintance or somebody that has this disease, they may say, oh, well, why are you doing this, when I was treated we did this. And, that's because historically we used chemoimmunotherapy. So, bendamustine-rituximab. Or, sometimes we would use, a fludarabine-based regimen called FCR. These were therapies that were given over about 6 months and were very effective, but could be associated with pretty significant bone marrow toxicities, including the development of acute leukemia in the future.

Now, we've used these for a long time because some patients, especially those receiving FCR can have very long remissions, and there are a small subset of patients that are potentially even cured with such an approach. But, most patients are not. And, we also found that FCR is better than BR in younger patients, but in those over the age of 65, there's not much of a difference, and in fact FCR can be overly toxic for people, especially over the age of 65.

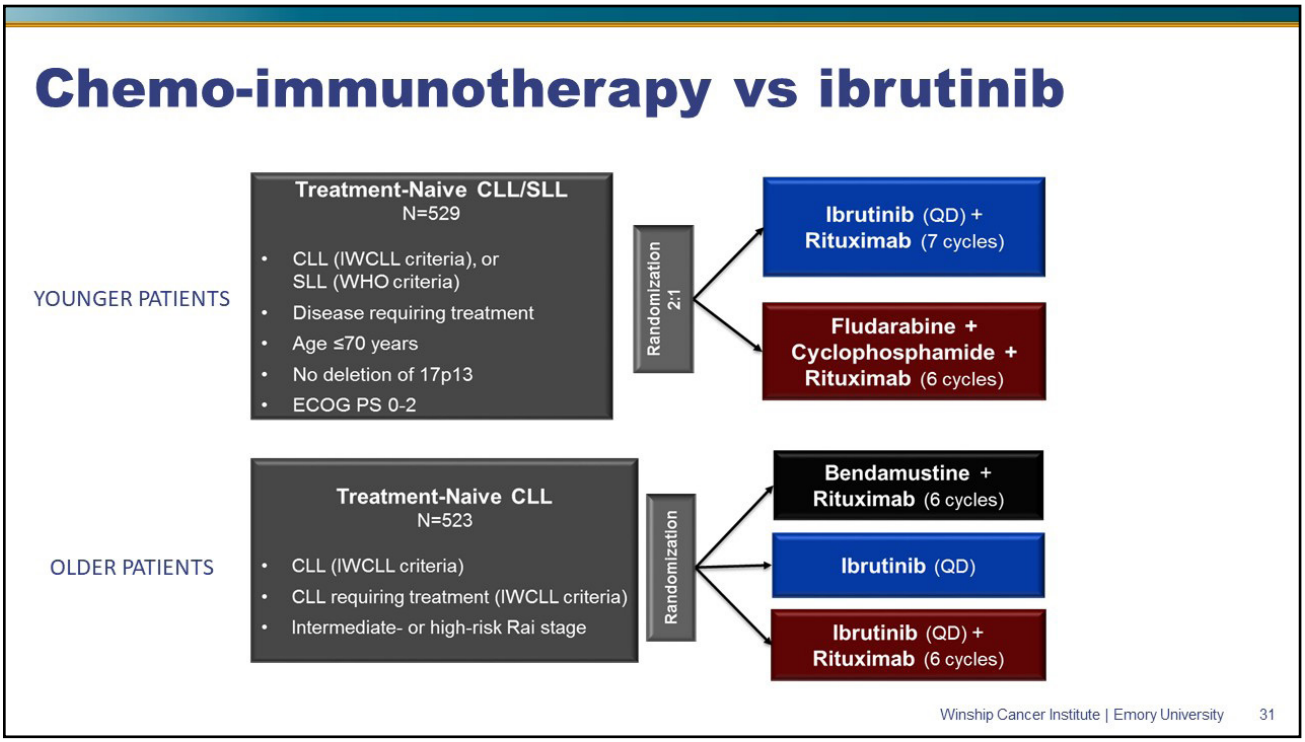
But, for a long time, this was what we had and this was how we would manage most patients with CLL.

In the recent year, however, there's been 2 new studies that were conducted in the United States, which compared this more standard approach of chemotherapy plus rituximab to an oral therapy called ibrutinib. And, many of you may be on this therapy or may be familiar with it.



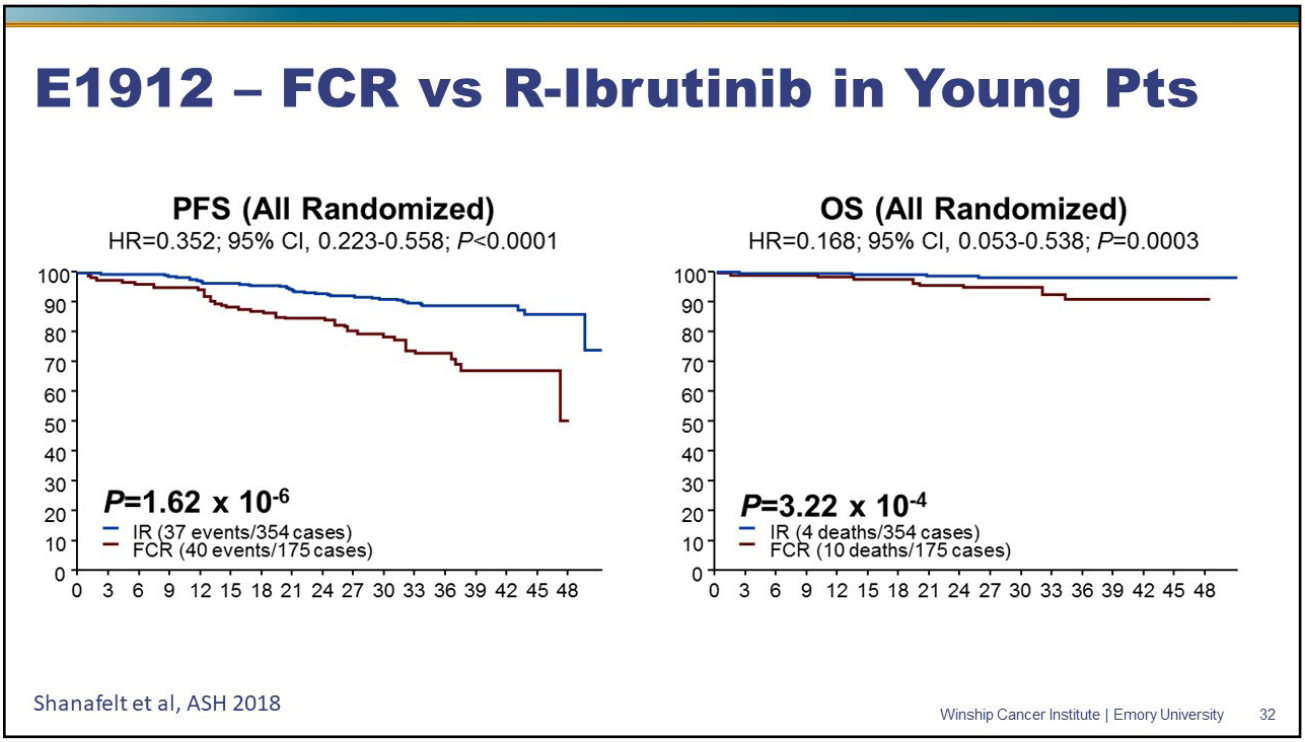
Slide 30: Ibrutinib – Bruton's tyrosine kinase inhibitor

What ibrutinib is, it's a Bruton's tyrosine kinase inhibitor. So, now what does that mean? And so, on this slide you can see that there is a bunch of ovals that are highlighting a pathway in the cancer cells. So, this is called the B cell receptor signaling pathway, and it's a pathway that stimulates B cells to grow, and in some diseases, including CLL, we feel that it is likely abnormally stimulated and causing the disease to progress. And, if you look at the top left of the figure you can see BTK, which is a little red oval, and that's an important part of this pathway. And, what ibrutinib does is it inhibits BTK and arrests the growth of the cells and the division of the cells. And so, it's an exceedingly effective therapy for CLL and SLL. The challenge with it, though, is that it's administered indefinitely. And so, on the one hand it's an oral therapy, you take one pill a day. But on the other hand, it is a therapy that you're committed to taking over a long period of time.



Slide 31: Chemo-immunotherapy vs ibrutinib

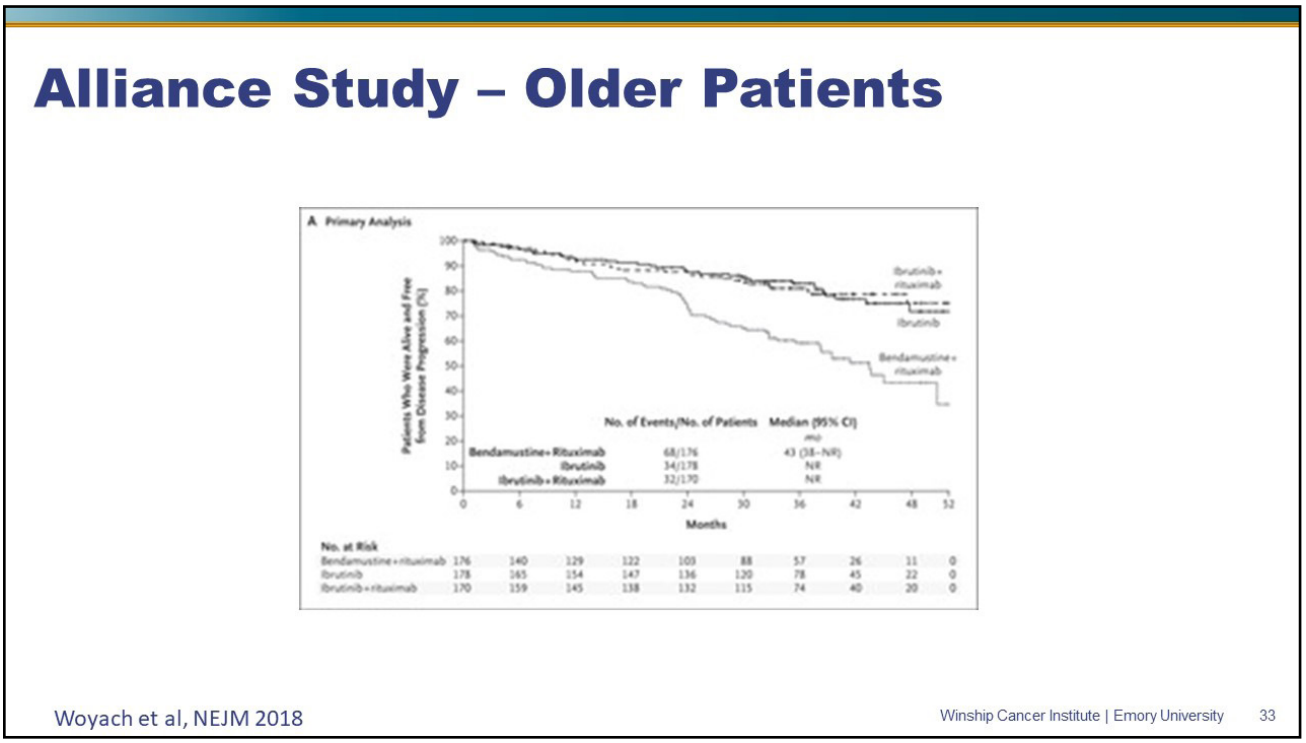
These are the 2 studies that were done which compared ibrutinib-containing therapy versus chemotherapy, versus more traditional therapy. The top one was in younger patients, it went up to the age of 70, and the bottom one was in older patients that went down as young as 65. And, the goal again was to try to compare more standard therapy to the newer oral treatment.



Slide 32: E1912 – FCR vs R-Ibrutinib in Young Pts

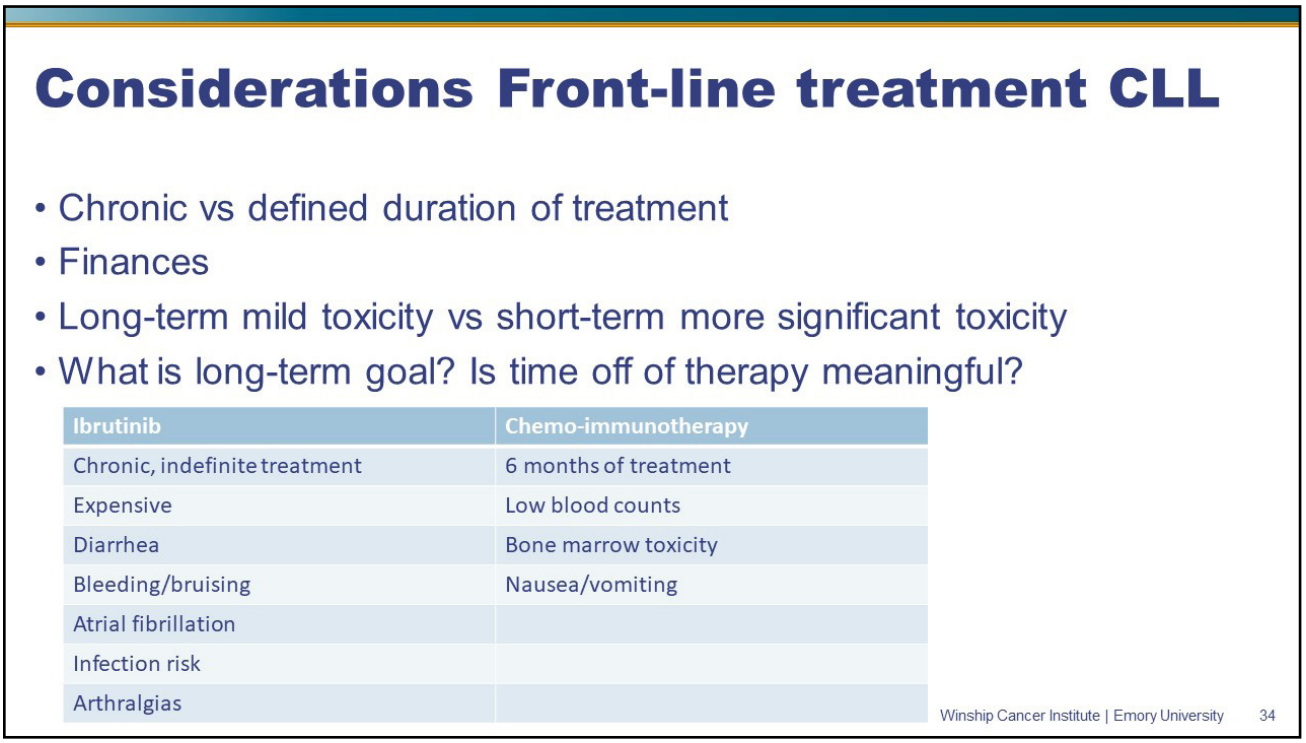
And, in the study for the younger patients, which was this E1912 study, you could see that patients who received ibrutinib-containing therapy, those in the blue line, had an improved progression-free survival, whereas those patients who received FCR had still a good progression-free survival, but not quite as good as ibrutinib. And so, what this would suggest is that if you received ibrutinib as part of your initial therapy, you were more likely to stay in remission longer than if you received FCR.

Although the curves don't seem to be separated by very much on the right, the overall survival actually did appear to be improved for patients using ibrutinib as opposed to FCR. And so again, this would suggest that not only do you stay in remission longer, but you may actually live longer by using ibrutinib as opposed to chemotherapy.



Slide 33: Alliance Study – Older Patients

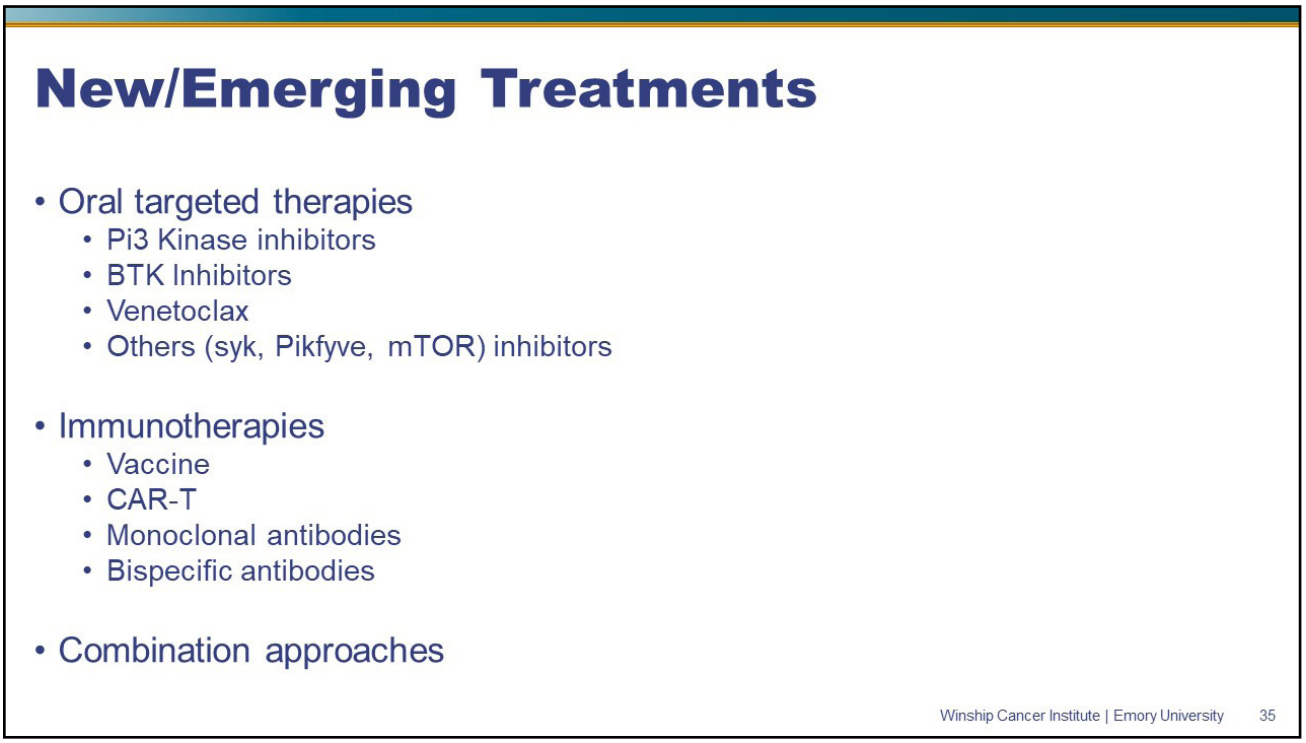
A very similar analysis was done for patients that were older in the Alliance study. And, you can see on this curve, that may not broadcast too well, but that the patients who received ibrutinib, so the top 2 lines, did better than those patients who received rituximab-bendamustine. And so, this would suggest that for older patients as well, that using a newer therapy like ibrutinib is better than using chemotherapy.



Slide 34: Considerations Front-line treatment CLL

And, so for many of my patients this ends up being a discussion that we have when it's time for treatment. There's a number of things to consider. So, although the ibrutinib may be associated with longer-term remission and potentially longer-term survival, it's not necessarily a free lunch, so to speak. And, there are drawbacks to using ibrutinib. The first is, is that you're typically committed to a chronic therapy, whereas chemo is administered over several months and then you're done hopefully for a long time. There can be financial considerations. And then, one of the biggest things that I think is probably under-appreciated is that ibrutinib, although it may not be as toxic as chemotherapy, there can be some mild toxicities that last for a long time, that last for as long as you're on the therapy. And so, if you're having some mild toxicity like diarrhea, for example, that lasts for 2 years while you're on the therapy, that can be problematic over time. And so, these are all things that we like to consider when talking with patients.

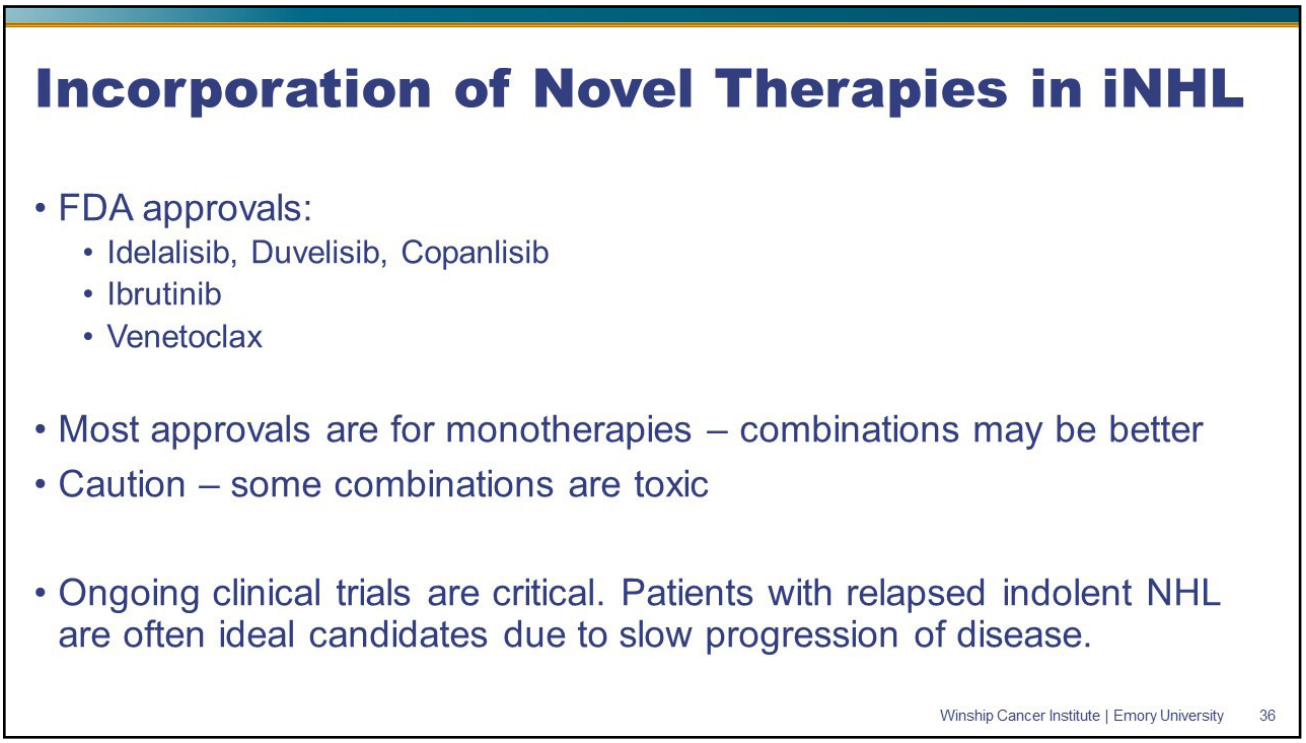
And, you can see here that I've highlighted some of the differences between these different approaches, so with the chemoimmunotherapy like BR or FCR, it's a shorter course of therapy but can be more toxic. Whereas those patients that are on ibrutinib, it's chronic indefinite treatment and it can be expensive, depending on your prescription drug coverage and assistance programs. And, there can be some serious side effects, but most patients will actually feel well while they're on it. And so, these are often discussions that I'll have with patients at the time when they're discussing, or when they're having to make a determination about therapy.



Slide 35: New/Emerging Treatments

Now, there are a number of new and emerging treatments that are coming along for indolent lymphomas as well as CLL. Some of which are currently approved and others are still under investigation. So, there are Pi3 kinase inhibitors like idelalisib or copanlisib or now duvelisib, some of which are oral and others which are IV, which work in a way that is similar to ibrutinib. There are newer BTK inhibitors that are coming along. There is a drug called venetoclax, which is currently used for CLL and is also being evaluated in a number of different settings. And then, there are a number of other targets that are still now just being evaluated that may actually provide additional options. In addition, as many of you are aware, there are a number of immunotherapies that are currently under investigation. At my institution, at Emory at Atlanta, we had a study using vaccines for patients with untreated follicular lymphoma. There are CAR-T cell therapies. And then, there are other antibodies that are being evaluated. And so, I urge you at any time when you're having to consider therapy to at least inquire about the availability of clinical trials because that's often the best way to have access to some of these newer exciting therapies.

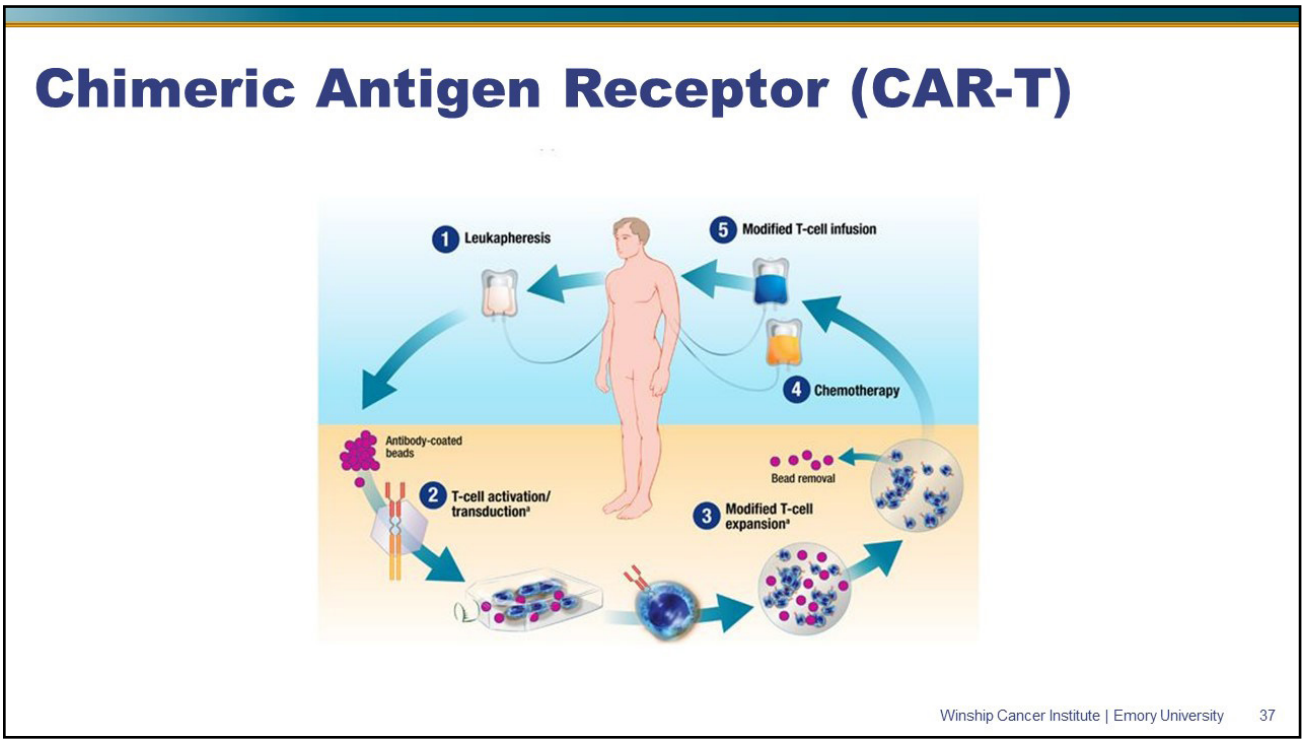
And then, the other thing I would point out is that many of these therapies have been evaluated primarily by themselves but are now being evaluated in combination, either with other novel treatments or other immunotherapies and so forth. And so, these are all important questions that are being asked to try to identify which is the most appropriate combination and most appropriate therapy for individual patients.



Slide 36: Incorporation of Novel Therapies in iNHL

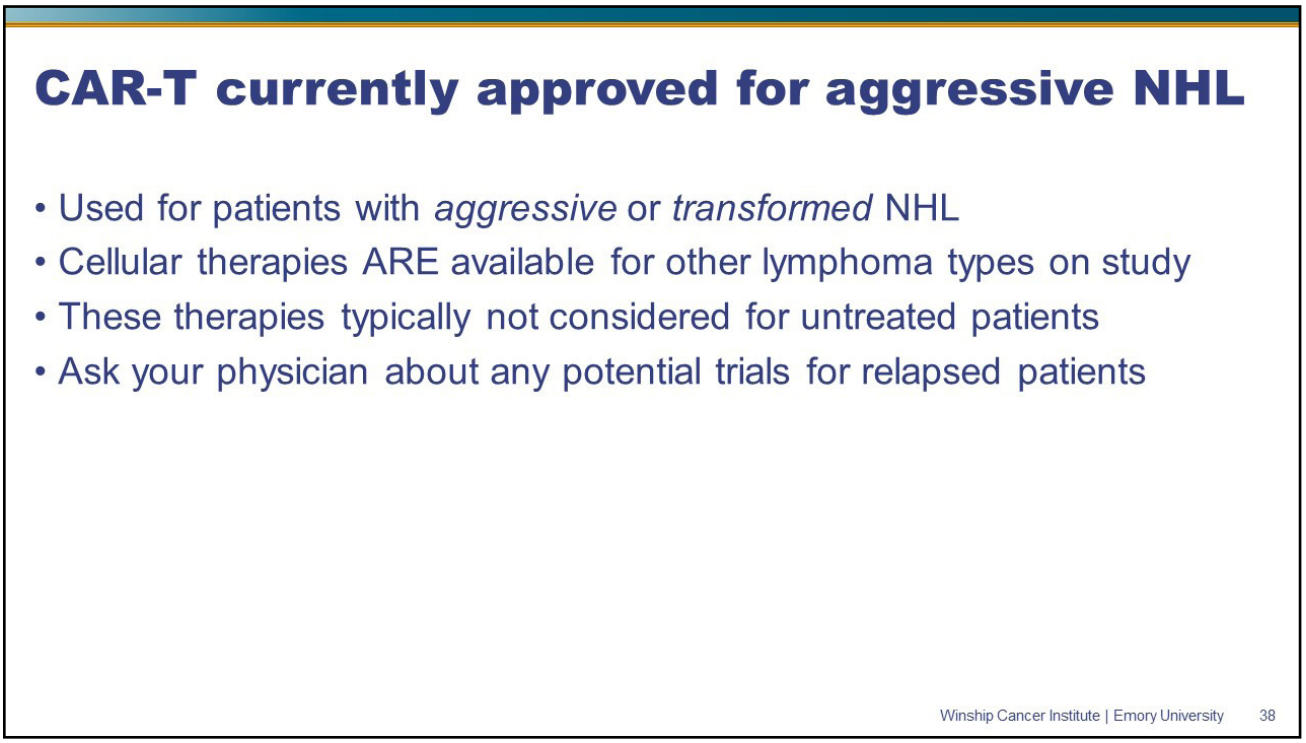
So, I do want to take a minute to highlight some of the specific FDA approvals and so idelalisib, duvelisib, and copanlisib have all been approved for a variety of indications. Ibrutinib, as I mentioned, has been approved, especially for CLL and SLL, but also for marginal zone lymphoma and Waldenstrom's macroglobulinemia. And, venetoclax is currently available for CLL as well as for some other hematologic or blood cancers.

Right now, many of these approvals are for monotherapy. Not all of them, but most are for monotherapy, meaning you take the drug by itself. And, combinations may ultimately be better, but some of these combinations are toxic and the way we find this out is through treating patients and learning more about the mechanisms of a disease. And, this is why clinical trials are so critical because it helps us identify the most appropriate combinations and identify the most promising therapies to bring them forward to the most patients.



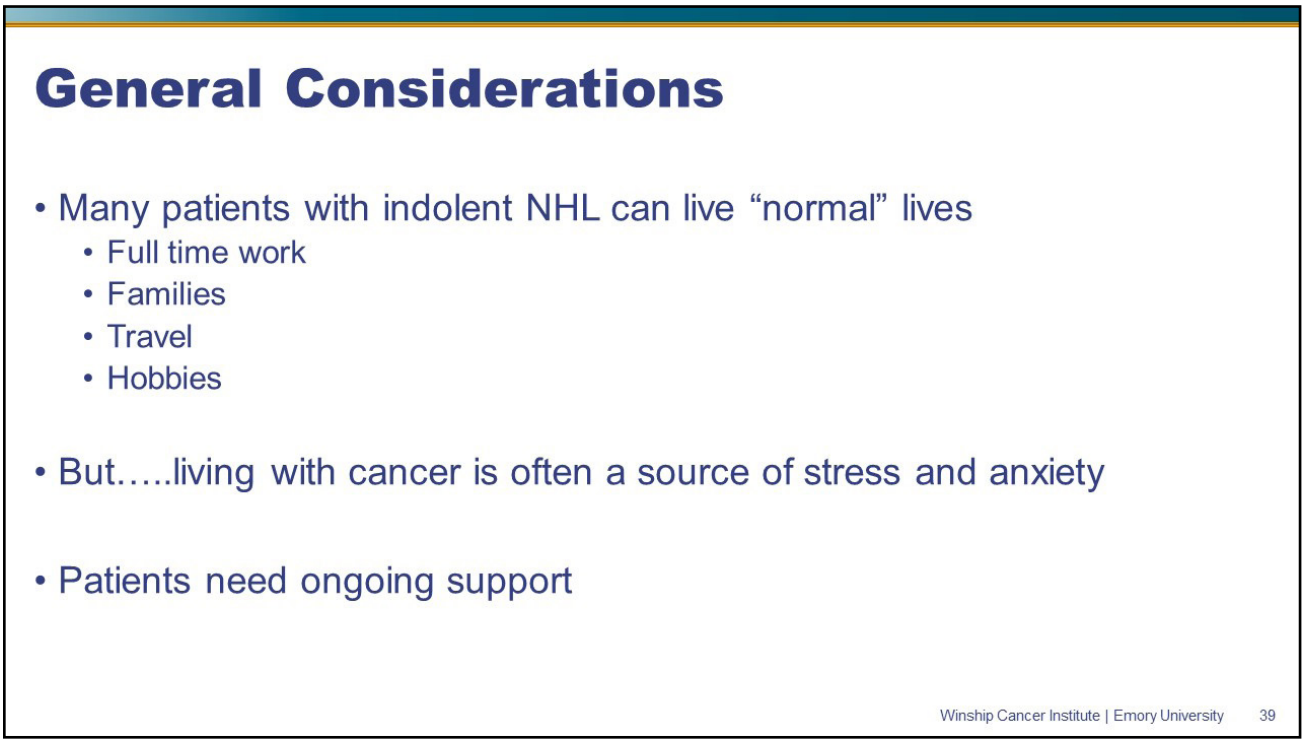
Slide 37: Chimeric Antigen Receptor (CAR-T)

So, many of you may be familiar with CAR-T or chimeric antigen receptors. For those that are not, this is a new immunotherapy approach. Right now, it is only approved for aggressive lymphomas as well as acute lymphoblastic leukemia. But, it's currently under investigation for other lymphoma subtypes. This is an illustration of the way the process works. And so, you start with the patient and, we remove blood from the patient, just through a regular IV. And, that blood is then sent off to a manufacturing facility, where they take your T cells from your blood and engineer them in a way that they then recognize the target. So, for B cell lymphoma we typically have them recognize CD19, which is one of the known targets in B cell lymphoma. And so, these T cells are engineered and then they are grown and then they send back a cell product that we then infuse into the patient. And so, this process takes a couple of weeks, but it's an exciting new therapy because we really are using your own immune system that's just been stimulated in a specific way to target your cancer.



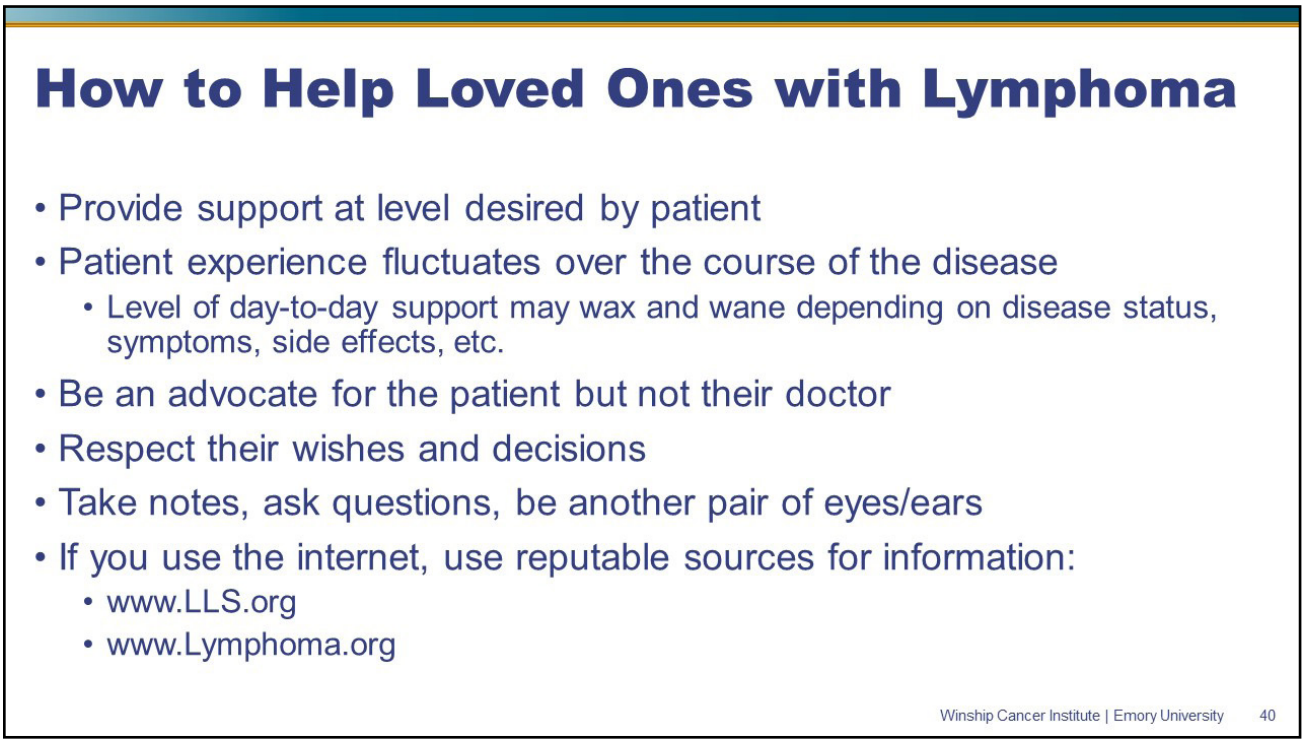
Slide 38: CAR-T currently approved for aggressive NHL

And so, as I mentioned, CAR-T is currently approved only for aggressive lymphoma or for those patients who started with an indolent lymphoma, but for whom it has now transformed. But there are a number of studies that are currently available using cellular therapies like CAR-T or even next generation therapies that are worth considering. And, these are especially of interest for patients with relapsed disease. Right now, they're not typically considered for patients that are untreated, although in the future that may change. But, I would certainly recommend that you ask your physician about any potential trials using immunotherapies or cellular therapies, especially if you're in a position where your disease has come back.



Slide 39: General Considerations

So, just to finish up, there are some general considerations that I've highlighted throughout the talk, but that I want to make sure that we come back to. Many patients with non-Hodgkin lymphoma can live normal lives. And, what I mean by normal is not just meaning that you live a normal life span, but that you can actually live a normal life. So, many of my patients will work full time, they are fully engaged with their families, they travel, they pursue hobbies, they are basically living the way they were before their diagnosis. And, my goal when I'm treating patients is to try to minimize the impact on your life as best I can. Now, in some instances we need to think about more aggressive treatment or we have to make some short-term adjustments, but from the very beginning my goal is to try to preserve the lifestyle of my patient as much as possible. But, having said that, living with cancer is still often a source of stress and anxiety. And, for patients with indolent lymphoma it can be difficult because although you may be living a normal life, this isn't necessarily something that goes away and it's something that you live with over a very long period of time and is something that other people that aren't directly involved may not always fully understand. And so, I do work with my patients quite a bit to help them cope with some of these stresses, and I have a very low threshold to get some of my mental health colleagues involved to help patients that are struggling. I also would highly recommend that you reach out to support groups or other communities, especially that are, you know, involved with patients that are going through a process similar to you because those are people that really do understand what you're going through and what it's like to live with this disease. And so, patients often will come back and be upset that they're so anxious or so stressed, even though they have a, quote, low-grade disease, and I try to help them understand that still living with a cancer like this can be very difficult and can be very anxiety-provoking.



Slide 40: How to Help Loved Ones with Lymphoma

And so, in summary, for those of you that may not be the patient yourself, but may be a caregiver, I think it's important to provide support at the level that's desired by the patient. So, I have some patients that bring their spouse and ask their spouse to sort of take the lead with taking notes and helping to make treatment decisions. Other patients like to take the lead themselves and really just want somebody to be there just to sort of be there for support, but not necessarily to be quite as directly involved with the discussions. And, I think it's important to, you know, as you're working with your own loved ones to help them understand what it is that they need for you, and this can sometimes change depending on what's going on with their disease. So, somebody that may require more limited day-to-day support when they're under observation may require more while they're on treatment. And again, that's because experience can fluctuate over the course of the disease, and so I think it's important to be aware of that.

I think it's also important to be an advocate for the patient, but not necessarily their doctor. And so, many times well-meaning family members can bring things up that they may have seen online or that they may have heard about that may or may not pertain to the patient. And, this is certainly not meant to say that you shouldn't educate yourself and ask good questions, but often what the patient really needs is for somebody to be there, to help engage in conversations with their healthcare team and to support them. And so, I think that's important and I've seen in some instances where almost an adversarial relationship can develop among, you know, again, well-meaning loved ones. And, I think it's just important again to maintain that open communication with the patient. And, it's important to respect their wishes. And so, fortunately for low-grade lymphomas patients often do quite well, but a patient may, for example, decide that they wish to pursue a clinical trial that someone else may not feel as optimistic about. And, ultimately it's important to remember that while the patient needs the support of their family and certainly benefits from having other people thinking about their case, but at the end of the day that the patient is the one that ultimately can make those decisions.

Take notes, ask questions, and be another pair of eyes and ears, as this can often be very overwhelming for patients, especially at some of the initial visits. And, having another person there that is able to ask questions and just sort of be another sponge to absorb all this information can be important.

And then, I would just say that if you're going to use the internet, which is an incredibly valuable tool, make sure that you are using reputable sources for information, anybody can write anything on the internet. And, I usually will refer patients to the LLS website and then also the Lymphoma Research Foundation at lymphoma.org. Those are the 2 places that I will always refer patients because we know that that information is good information and these are 2 incredible organizations that are really devoted to improving outcomes for patients.

Slide 41: Summary

So, in summary, indolent lymphoma is a variety of diseases with a number of different treatments that are available. These are not very quick conversations and decisions. These are discussions that take place often over a series of visits. Many patients can be observed for years before their first therapy is initiated. And, patients I often, again, counsel them to expect to be treated on several occasions over the course of their disease. So, I always tell people when I first meet them that we're going to get to know each other very well over the long haul, and that my goal is to do as little to them as necessary, but that we'll be ready to come in with therapy when needed.

There are newer therapies that are currently approved or in development, including a number of exciting combinations. And again, I would strongly encourage you to consider clinical trial enrollment as this is how we develop our future treatments.

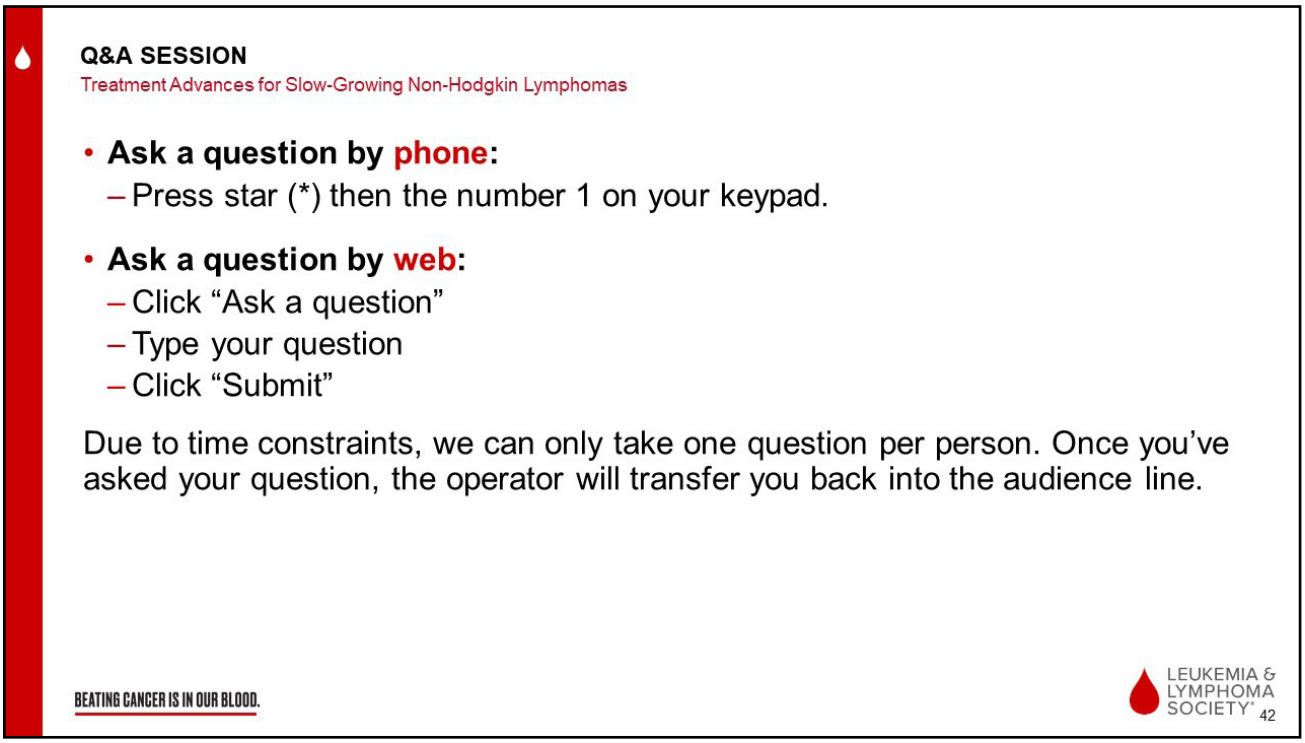
And then finally, ask questions and be informed. Programs like this I think are important. It helps patients understand a little bit more about their disease, and also gives you the opportunity to hear from somebody else that may not be your physician, so that you can have some questions to ask when you go back.

So, thank you very much again to LLS and to you for your attention.

Lizette Figueroa-Rivera:

Thank you so much, Dr. Cohen, for all of this information and for volunteering your time with us today.

It's now time for the question and answer portion of our program.



Slide 42: Q&A SESSION

Lizette Figueroa-Rivera:

And we'll take the first question from our web audience. Doctor, Gail and Terry are both asking if the number of recurrences influences the treatment protocol.

Dr. Jonathan Cohen:

So, this is an excellent question. There are a couple of things that I'll think about when I am treating a patient who has relapsed disease. As I mentioned during the talk, one of the things we'll look at is the time to relapse, so how long it's been since their most recent therapy. But, as you bring up, the number of prior relapses is also important. There are some therapies right now that are only available for people that may have had 2 or 3 relapses as opposed to at the time of your first relapse. And, depending on how many times your disease has come back and how quickly it's come back, we may discuss potentially some more aggressive approaches like a stem cell transplant or other cell therapy approaches. So, the short answer to your question is yes, I think that's an important consideration, when deciding what therapies a patient may be eligible for.

Lizette Figueroa-Rivera

Thank you, Doctor. And, we'll take the next question from the telephone audience, please.

Operator:

We'll take a live question from Nancy in Virginia. Please go ahead, your line is open.

Nancy:

Thank you. what about Waldenstrom's, how does that fit into the pattern that you've spoken about?

Dr. Jonathan Cohen:

So, thanks Nancy for bringing that up. So, as you know, we didn't have a chance to get into Waldenstrom's as much today. I think of Waldenstrom's as being like many of my other indolent lymphomas, but as you may know, if you or a loved one

are a patient yourself, there can be some very specific differences. So, the first is, is that Waldenstrom's macroglobulinemia tends to be associated with the production of an abnormal protein called IgM. And, this introduces some different features of this disease that we don't always see with some of the other indolent lymphomas. Sometimes if IgM accumulates too much in the bloodstream it can cause some neurologic conditions or other cardiac conditions. Sometimes it can cause neuropathy or other symptoms related to that as well. And so, although a lot of the therapies are very similar, the monitoring and the assessment of a patient with Waldenstrom's can be different than indolent lymphomas.

There are a number of very effective therapies for Waldenstrom's. We often do consider ibrutinib in that setting. Other times we'll use rituximab with chemotherapy or an additional medication called bortezomib. So, there are a number of therapy options there. But, although it is an indolent lymphoma, it does tend to behave a little bit differently in some instances.

Lizette Figueroa-Rivera

Thank you, Doctor. And, our next question comes from Rick. Rick asks, does Emory always use a hematopathologist to diagnose?

Dr. Jonathan Cohen:

So yes, at our center we're very fortunate. We have a number of excellent hematopathologists. I speak on the phone with them frequently, especially when we're discussing potentially a challenging case. We have routine meetings with them. Most big centers do have a hematopathology team that's involved with the evaluation of blood cancers. And so, depending on where your diagnosis was made and your doctor, that's something you could ask your doctor about, is whether or not it's needed or appropriate to have a hematopathologist review your case. And, in some instances, if there's not one available in your community, the case can be sent out as a consultation to one of the big centers. So, Mayo Clinic frequently will take cases as a consultation. The NIH (National Institutes of Health) will and Emory will as well as a number of other sites. And, this typically does not require you to go to that site. Sometimes just your pathology specimen can go and they can render a diagnosis.

In some instances this is not critical, but in most cases I do like to have had a hematopathologist review cases, especially at the beginning when we're trying to zero in on the diagnosis.

Lizette Figueroa-Rivera:

Thank you. And, our next question comes from the phone line, please.

Operator:

We'll take a live question from David in Maryland. Please go ahead, Sir.

David:

Thank you. Does maintenance treatment actually provide greater survival because it is prolonging the relapse?

Dr. Jonathan Cohen:

So, excellent question. So, I think I'll try to address primarily the follicular lymphoma scenario, because that's where most of the data exists for maintenance treatment. Right now, at least from the randomized clinical trials that have been conducted in follicular lymphoma, there is not a clear benefit in overall survival with maintenance therapy, meaning that if you take 2 patients that are in remission at the conclusion of their initial therapy, and you give one maintenance and you don't give the other one maintenance, it's not clear that the patient that receives maintenance will live longer. And, part of that is because when they do relapse there are a number of very effective therapies available. What we do know, though, is that most of those patients that get maintenance will go longer before they need to get another treatment and will stay in remission longer. And, for many patients this is a very meaningful, it is worth it to do, you know, a treatment once every 2 or 3 months for a couple of years if it means that they'll go that much longer before they need a subsequent therapy.

Lizette Figueroa-Rivera:

Thank you. And, we'll take the next question from the web audience. Rochelle asks since pregnancy suppresses the body's immune system, is there a higher likelihood of relapse for women who are in remission and become pregnant?

Dr. Jonathan Cohen:

Rochelle, that's a really interesting question. I would say that at least to my knowledge that's not something that's been shown systematically. One of the things actually that we have found with lymphoma treatment is that most patients who are treated for lymphoma at a young age can still become pregnant. And fortunately, we don't see patients who are in remission from their lymphoma that ultimately do become pregnant, we have not seen a large amount of relapses. So, it's definitely an interesting thought but fortunately it's not something that we've encountered routinely in practice. And, I certainly do not recommend against pregnancy for my lymph patients who have completed therapy for lymphoma. So, if you're in remission and you've recovered from your treatment and you're interested in becoming pregnant, we do everything we can to help support that.

Lizette Figueroa-Rivera:

That's great to hear, Doctor, thank you. And we'll take the next question from our telephone audience, please.

Operator:

We'll go next to Charlie in Oklahoma.

Charlie:

Yes, my question is regarding what is the average years of remission with the maintenance rituximab? You mentioned many, many years, which is a subjective term. So, I'm wondering if there's actually any metrics that show the average years of remission, particularly in individuals with no comorbidities?

Dr. Jonathan Cohen:

Sure. So, probably the best information we have for that is from a study that was done in Europe that compared maintenance versus no maintenance for patients who received R-CHOP. And, what we found or what they found at the most recent update was that at about the 10-year mark, about half of the patients that received maintenance were still in remission. So again, that doesn't necessarily speak to what will happen to an individual patient and we don't know, you know, where it will be when they have 15 years of follow-up, we'll see how many of those patients are still in remission. But right now, the longest follow-up we have is at roughly the 10-year mark and again half of patients who received maintenance are still in remission after R-CHOP from that study.

Lizette Figueroa-Rivera:

Thank you, Doctor. And, the next question comes from Kristin, and Kristin is asking about transplant. She recently spoke to a patient with Stage 3-A follicular lymphoma, who thought she understood that transplant will not affect overall survival, but does help keep the lymphoma from progressing. Is this true and does it make sense for a 55-year-old woman with follicular lymphoma to receive a transplant?

Dr. Jonathan Cohen:

So, Kristin, I guess normally for patients that have follicular lymphoma or large cell lymphoma for that matter, who are going through their initial therapy, we typically do not recommend stem cell transplant. So, I'm wondering if maybe in your particular case you're describing somebody who may have relapsed. So, when we look at patients at the use of stem cell transplant for patients with relapsed follicular lymphoma, there's 2 potential options. One is to use an autologous transplant and the other is to use a donor or an allogeneic transplant. The autologous transplant tends to be much better tolerated and is associated with prolonged remission but unfortunately is unlikely to be curable. And so, as you mentioned it likely prolongs the amount of time before the disease would come back. Where I at least myself have been using autologous transplant most frequently is in patients who have an early relapse. So, as I mentioned, those are patients that are at particularly high risk and so if somebody has an early relapse and they're otherwise a candidate for aggressive therapy, I often will at least have a discussion with them about the use of autologous transplant.

Allogeneic transplant does have the potential of being curative in follicular lymphoma, but can be associated with a number of long-term side effects. And, given the fact that most patients will still enjoy a very long life expectancy, I typically don't go down the path of allogeneic transplant unless I have somebody who's relapsed on multiple occasions and where we really

feel like we need to do something a little bit more definitive.

Lizette Figueroa-Rivera:

Thank you. I know we were getting a lot of questions in regards to transplant for indolent non-Hodgkin lymphoma. And, we'll take the next question from the telephone audience, please.

Operator:

Next, we'll go to New Jersey and to Barbara.

Barbara:

Hello. Actually, I have a question about nodal marginal zone lymphoma. As you mentioned during your presentation that the cause of nodal marginal zone is most likely due to some sort of an infection. Could it also be some sort of a toxicity or a toxic substance, too? And, do you have any sort of information about that?

Dr. Jonathan Cohen:

So, it's possible, so for nodal marginal zone lymphoma we typically will screen for infections, but that's one where, as opposed to some of the other marginal zone subtypes, we don't have quite as much, it's not quite as frequently associated with infections. The question of toxic exposures is certainly one that's been in the news a lot lately and where we feel like there probably is something there. So, for example, in the state of Georgia we've done work, or one of my colleagues has done a study which identified that levels of benzene in the soil may be associated with the development of aggressive lymphomas. So, for nodal marginal zone lymphoma it's a fairly rare subtype of lymphoma and I'm not aware of any definitive information, but I think there's no question that there're probably environmental exposures that we don't fully understand yet, that are, that at least put patients at increased risk for development of a number of different lymphoma subtypes.

Lizette Figueroa-Rivera:

Thank you. And, I'm going to stay on the topic of marginal zone lymphoma. Debbie is asking, is Imbruvica® also a treatment for marginal zone?

Dr. Jonathan Cohen:

It is. It is currently FDA approved for marginal zone lymphoma. Compared to CLL/SLL, the response rate with Imbruvica® after, or ibrutinib after for marginal zone lymphoma is not quite as high, so it's about 50%. But, it is a very effective therapy. I frequently will use it in patients who have received rituximab or rituximab with bendamustine and then the disease has come back or for whom chemotherapy is not an option. As I mentioned before, one of the potential downsides of such an approach is that it requires indefinite therapy and so for most patients with marginal zone lymphoma I try to see how long of a remission they can have with other approaches before moving to ibrutinib. But, it is approved therapy and can be very effective.

Lizette Figueroa-Rivera:

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

Operator:

Next, we'll go to Janet in Florida. Please pose your question.

Janet:

Yes, hi, Dr. Cohen. I have Waldenstrom's, which is a low-grade lymphoma. I'd like to know more about is there a support group in the Ft. Lauderdale area. I go to my oncologist who, because I'm 11-year survivor of breast cancer, then they found the Waldenstrom's, so I'd like to, I'm not taking no medication or chemo and I'm wondering if there's a hospital that has support group, used to be at Holy Cross, which is in Ft. Lauderdale. Could you tell me if there's any group or where I could go?

Dr. Jonathan Cohen:

Sure. So, Janet, I'm sorry, I don't know of any specifically down in the South Florida area. I do know, though, that there are several really outstanding lymphoma physicians affiliated with the University of Miami. And, I know that obviously is a little bit of a hike from Ft. Lauderdale, but that group there may be the best to connect you with a group. I also know that organizations like LLS and the Lymphoma Research Foundation have ways to connect with people where you may be able to reach out to those organizations and they could help connect you with a local chapter that could point you in the right direction.

Lizette Figueroa-Rivera:

Sure. Janet, The Leukemia & Lymphoma Society can certainly point you in the right direction and we can provide you with either in person or telephone support, as well as other organizations that cover Waldenstrom's macroglobulinemia, we can give you their information also. Thank you.

And, the next question actually comes from Ellen. Doctor, Ellen asks, have there been any studies to determine if there's a genetic link with NHL? My oncologist told me no, but my mom, oldest brother, and myself have all had it.

Dr. Jonathan Cohen:

So, the truth is at least right now, we do not have a gene that we can test for that specifically predisposes patients to the development of lymphoma. So, many of you may be familiar that for breast cancer, for example, there's a gene that we can test for or for colon cancer but for lymphoma we have not found that. And, traditionally it was not felt to be an inherited condition. But, as you point out, Ellen, there are a number of families out there where multiple members of the family have had lymphoma, and so it suggests to me that there clearly is a link but at least at this stage we don't know enough about it yet to be able to identify, you know, what that gene is and potentially be able to screen for it.

Lizette Figueroa-Rivera:

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

Operator:

We'll take a question from Persia dialing from Florida. Please go ahead, your line is open.

Persia:

Thank you. I was diagnosed in 2004. I had chemo twice in 2010 and 2015. My lab work is for a Waldenstrom's patient, it's good. And, what I suffer from mostly is fatigue, physical fatigue, and I can't seem to get that under control. And, I'm just feeling very tired. I have to take a siesta, a nap in the afternoon. My level of endurance is severely limited. I'm 81 years old and I am fighting this because I used to be a very physically active person, who taught aerobics, tai chi, yoga, for many years. What can you suggest?

Dr. Jonathan Cohen:

Persia, I'm sorry to hear that you're been struggling here lately. I think what you highlight with Waldenstrom's is that it can be a particularly challenging disease because sometimes patients can have symptoms that, as you point out, don't always correspond to what we're seeing in their lab work. So, any time I have a patient with Waldenstrom's or with any indolent lymphoma that's experiencing progressive fatigue, you know, the main question that I'm trying to determine is, is this because of the disease or is there something else going on. And so, I always will recommend that patients have a good evaluation with their primary care doctor, if you haven't already, just to make sure that there's not some other process going on like your thyroid or other hormonal imbalance or something like that. If it turns out that the sense is that this is related to your Waldenstrom's, I think then it really comes down to a discussion with your oncologist about what treatment options are available, what you've already had. You mentioned having had chemotherapy on 2 prior occasions, so you may be a patient, for example, that would want to think about something like ibrutinib, if that's a therapy that's an option for you based on maybe some of your other potential medical conditions. I think that it is often challenging to determine whether or not fatigue is related to the cancer, but in somebody like you who's previously been so active and the absence of an

alternative explanation, it may be worth having a discussion with your doctor about ibrutinib or what – or other therapies that may be available for Waldenstrom's.

Lizette Figueroa-Rivera:

Thank you. And, Trisha's asking what is the most effective integrated therapy that can be done in conjunction with or after treatment for indolent non-Hodgkin lymphoma, for example, exercise, diet, keto diet, stress reduction, etc.?

Dr. Jonathan Cohen:

So, this is a very common question. And so, the first thing I always like to tell people is that if your disease comes back it is not because of something that you did or didn't do. And so, sometimes patients have disease that behaves in a particular way and it comes back and despite their best efforts. And then, we have other patients who we make some recommendations to and they don't really, you know, they don't necessarily follow the recommendations and they do just fine. So, I think that there's a lot to the story here, and so I never want anybody to feel that they're responsible for their disease coming back. Now, having said that, there are certain things that we feel can improve outcomes and can lower your susceptibility to relapse. One of the things that we think is actually important is trying to reduce chronic stress. And so, things like exercise are very important. And, making sure that you're doing activities that try to help lower stress. Now, that doesn't mean we want you to quit working or quit leading an active life because obviously stress is a part of life, but I think the more you can do activities that help keep you calm, the better. The other thing that we recommend is eating a good balanced diet. I tend to not like patients to take on a real intensive different diet than normal. We do think that maybe fish-based products are good or plant-based proteins could be good, but like I tell folks, if you really like a steak and you're going out for your birthday and you want to have a steak, then you should have a steak, and that's not going to be the reason that your disease comes back.

So, most important things in my mind are keeping active, eating a healthy diet, and doing activities that help to lower your stress level.

Lizette Figueroa-Rivera:

Thank you, Trisha, for the question. Wendy asks, what is the appropriate screening after the patient has been in remission for 10 years?

Dr. Jonathan Cohen:

So, that is one of our favorite visits, is when we have patients that are multiple years out and doing well. I think some of that depends on your disease and what was going on with your disease. Typically, if I have a patient that has good primary care follow-up and so forth, I will typically see them on a yearly basis, once they get that far out. And, most of what we're doing at that point is just making sure that nothing new has come up, that there hasn't been some sort of a new long-term complication that may have developed. I usually will not have people do scanning especially when they're that far out from their treatment. Most of it is a yearly visit with blood work and a good physical exam and just really catching up and making sure that nothing new has popped up that makes us concerned.

Lizette Figueroa-Rivera:

Thank you, Wendy, for that question. And, our last question today, Sheila asks, can you please explain if taking probiotics as nutritional supplements might increase white blood cells in NHL patients and interfere with test results, and if so, what's your recommendation?

Dr. Jonathan Cohen:

So, that is not something that I have encountered. We do have patients that either take probiotics or that use yogurt that's not something that I've found has had a significant impact on their blood work. And, if it were to have a mild impact on their blood work it wouldn't necessarily likely impact – it wouldn't make necessarily a clinical impact, meaning I wouldn't necessarily do something differently. I do think probiotics can be helpful. Not necessarily for the management of the disease, but certainly while people are on treatment or if they need antibiotics or something along those lines, it can help prevent some of the GI complications of antibiotic use especially. And so, I don't make my patients go on them, but if I have somebody that's on it or if they like yogurt or something along those lines, I think that's very reasonable.

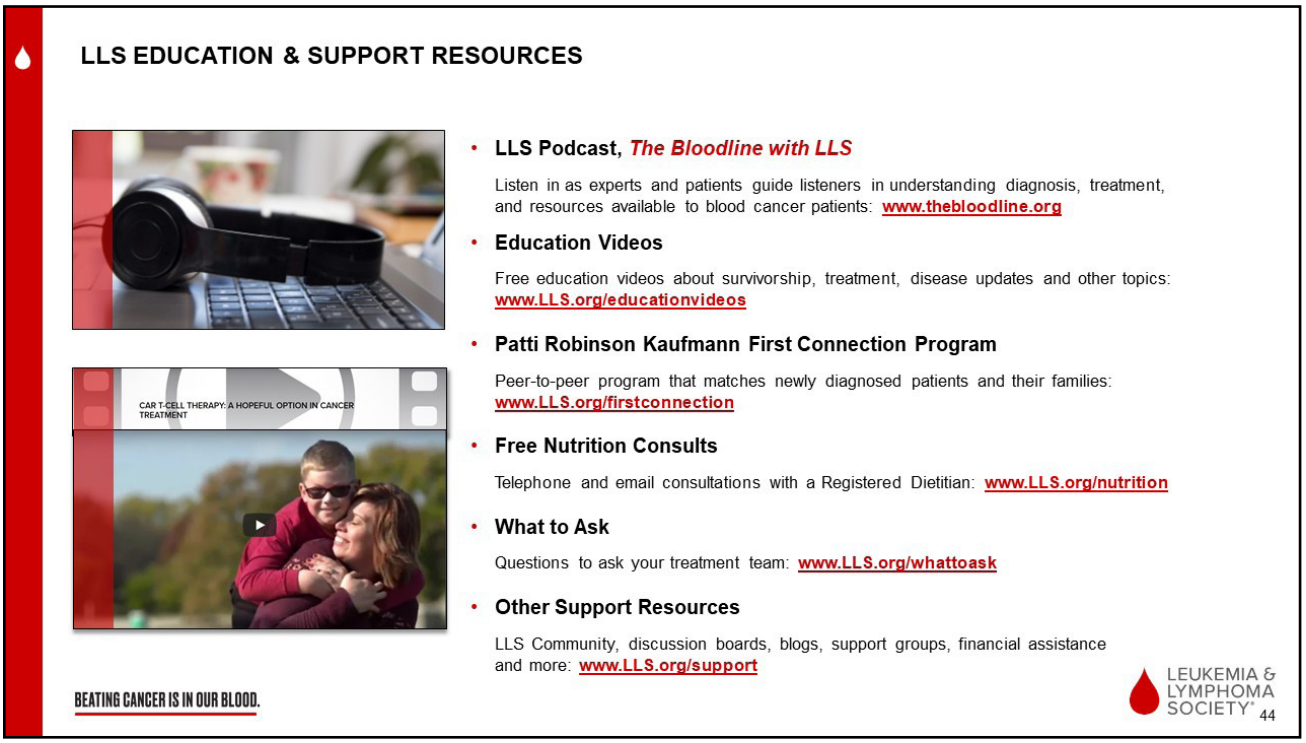
Lizette Figueroa-Rivera:

Thank you so much, Dr. Cohen, for your continued dedication to patients and for all of the great information that you gave us today.

And for those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

Slide 43: LLS EDUCATION & SUPPORT RESOURCES

If we were not able to get to your question today, I know that we've had a lot of questions still on the phone and a lot of questions still on the web, you can definitely speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org.



Slide 44: LLS EDUCATION & SUPPORT RESOURCES

Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, finding a support group near you, as well as financial assistance for treatment.

Again, we'd like to acknowledge and thank Celgene, Genentech and Biogen, Pharmacyclics, an AbbVie Company, and Janssen Biotech for support of this program.

Slide 45: THANK YOU

Dr. Cohen, again, thank you for volunteering your time with us today. And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

END