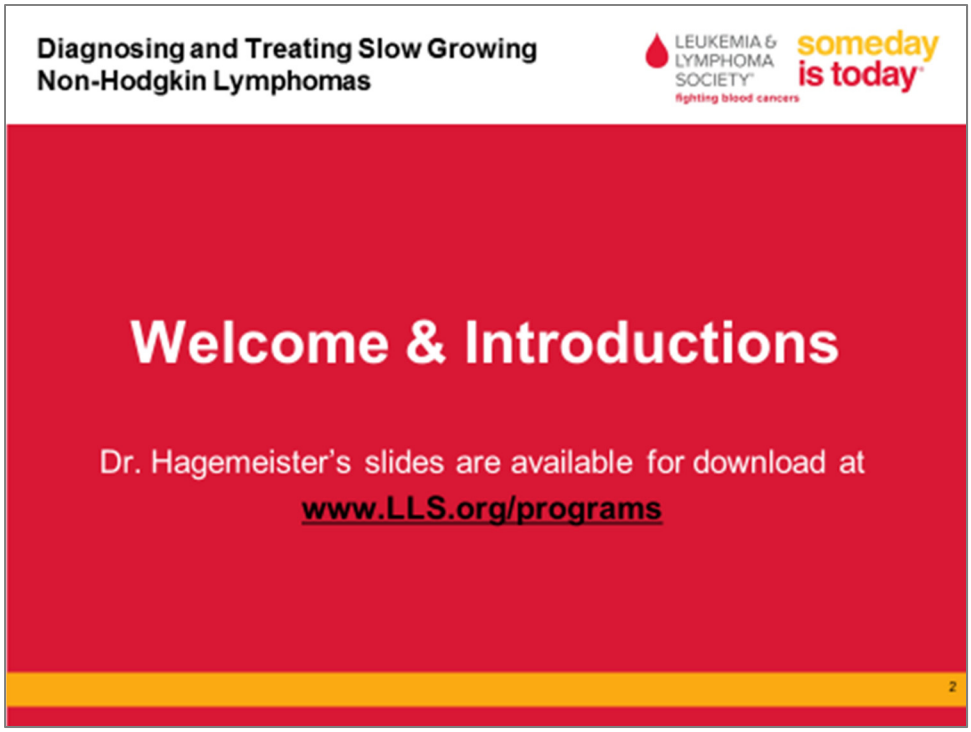
WELCOME AND INTRODUCTION



Lizette Figueroa-Rivera, MA

Hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Fredrick Hagemeister for sharing his time and expertise with us today. We have over 1,400 people participating in today's program from across the United States and Canada. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's President and Chief Executive Officer, Dr. Louis DeGennaro, who will share a few words. Dr. Lou, please go ahead.

Dr. Louis DeGennaro, PhD

Thank you, Lizette, I'd like to add my welcome to patients, caregivers and healthcare professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and to ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and the quality of life for many blood cancer patients. To date, we have invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from the bench to the bedside.

As today's program demonstrates, we are also the leading source of free blood cancer information, education and support; and we touch patients in their communities through our 56 chapters across the US and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for

patients and survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

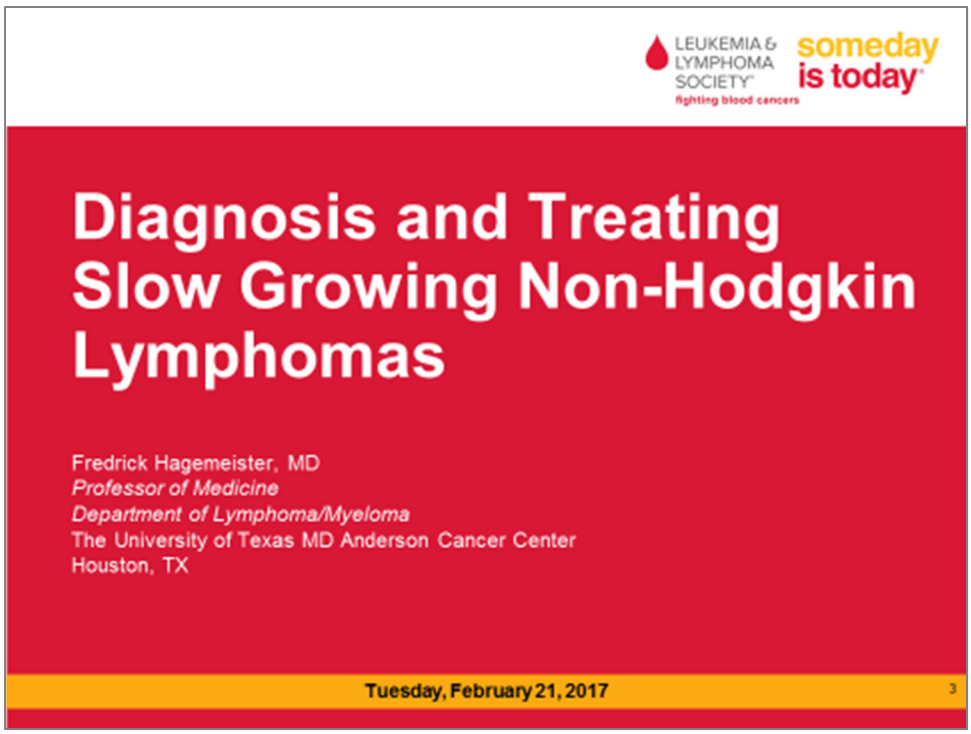
Today, we're extremely fortunate to have as our presenter Dr. Fredrick Hagemeister, one of the nation's leading experts in non-Hodgkin's lymphoma. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. On behalf of LLS and those we serve, I'd like to thank him for providing us with important information on the diagnosis and treatment options for non-Hodgkin's lymphoma patients.

And now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera, MA

Thank you, Dr. Lou. We would like to acknowledge and thank Bristol-Myers Squibb, Genentech and Biogen, and Pharmacyclics and Janssen for their support of this program.

PRESENTATION



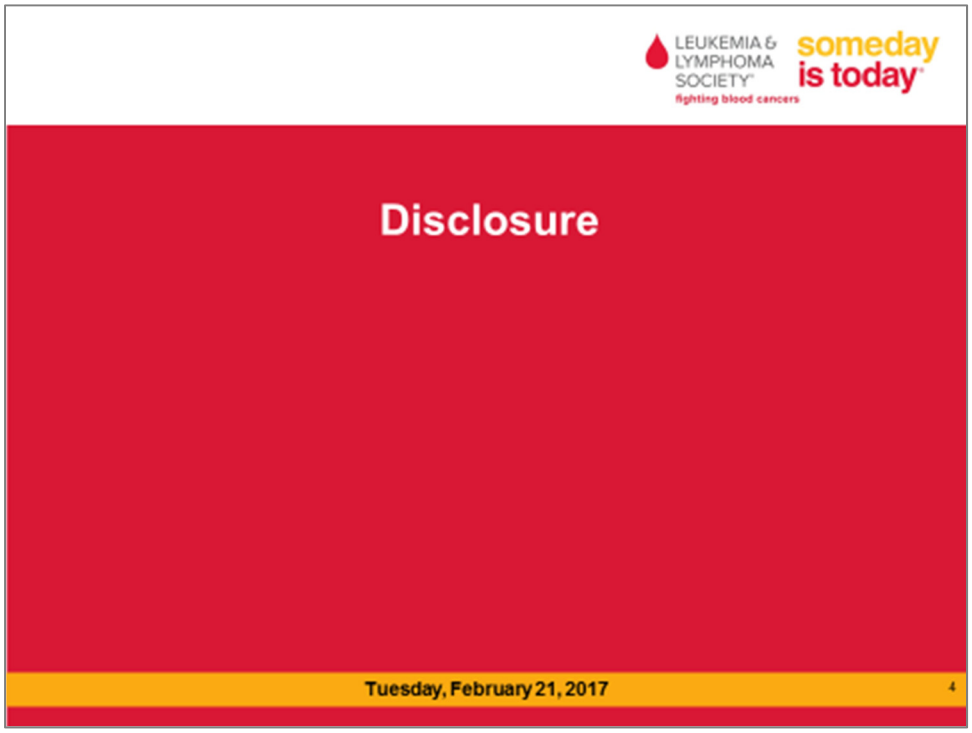
Lizette Figueroa-Rivera, MA

I am now pleased to introduce Dr. Fredrick Hagemeister, Professor of Medicine, Department of Lymphoma/Myeloma, at the University of Texas, MD Anderson Cancer Center in Houston, TX. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us.

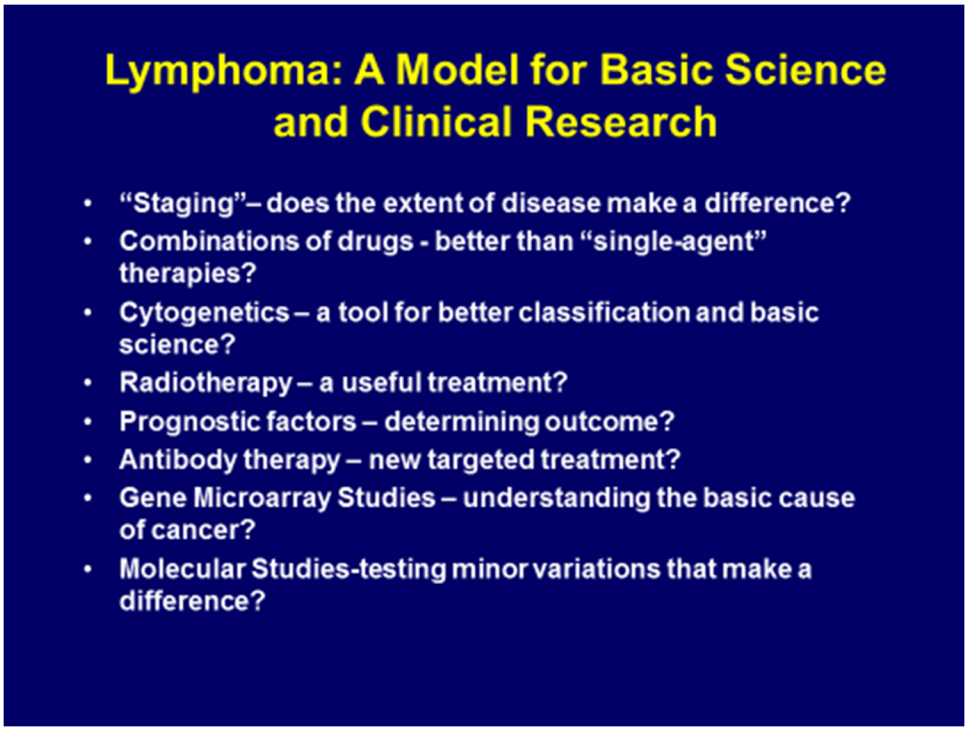
Dr. Hagemeister, I'm now privileged to turn the program over to you.

Fredrick Hagemeister, MD

Thank you, Lizette. I really appreciate both your asking me to do this as well as having Dr. DeGennaro there, and I appreciate The Leukemia & Lymphoma Society for having me, being able to do this. I really appreciate it.



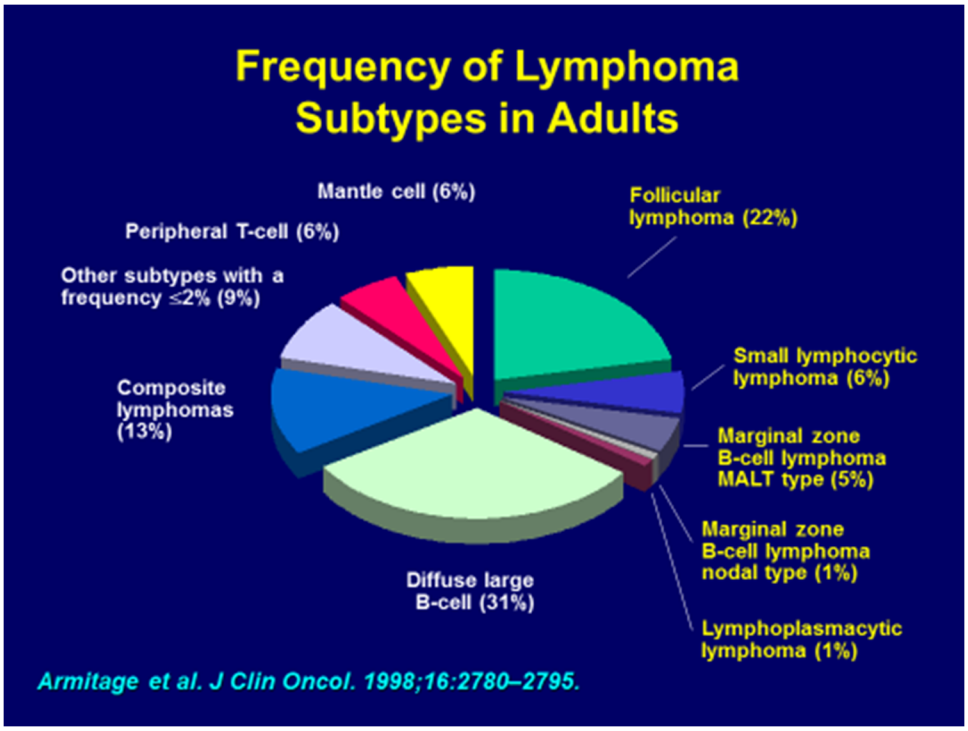
I have no major disclosures for this particular presentation.



I would like to go and get started. There's a lot of information that we have to go over, and I hope that you find much of this information not only interesting but also will spur you on to think about additional

things that might be important in your asking further questions about this and looking more deeply into some of the information which I've provided you.

First of all, I'd like to talk about just in general what we think about lymphoma and how we view it. Lymphoma is really a model for basic science and a lot of clinical research that's going on. You can see listed here many different things that took place in the past and are still being looked at currently in the management of patients with lymphomas. And these have been extrapolated to patients with solid tumors. These days, of course, we're learning things from investigators who look at solid tumors as well because we're finding out that many of those drugs that work in solid tumors are working also in lymphoma. And some of the research that is going on there is making a big impact in the management of patients with both lymphomas and leukemias.

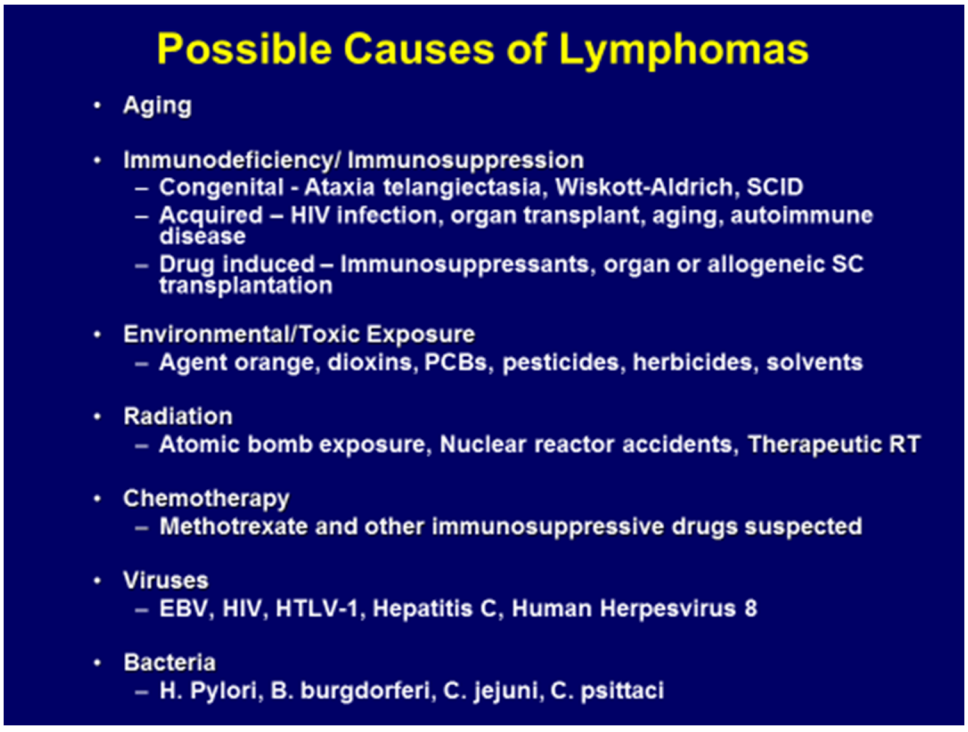


The frequency of lymphoma subtypes shown here has not changed much in many years. I'm showing you some of the lymphomas that have been listed and studied more recently, and you may be very well aware that we're breaking these down into even more subsets. Shown on the sort of right-hand side are follicular lymphomas which represent 22% of patients with lymphoma; and, of course, the more aggressive diffuse large B-cell is shown at the bottom. About 31% in the United States have that particular disorder, who have lymphomas. And somewhere around 60,000 or so new patients will be diagnosed with lymphoma this year in the United States, and that number does climb a little bit with time.

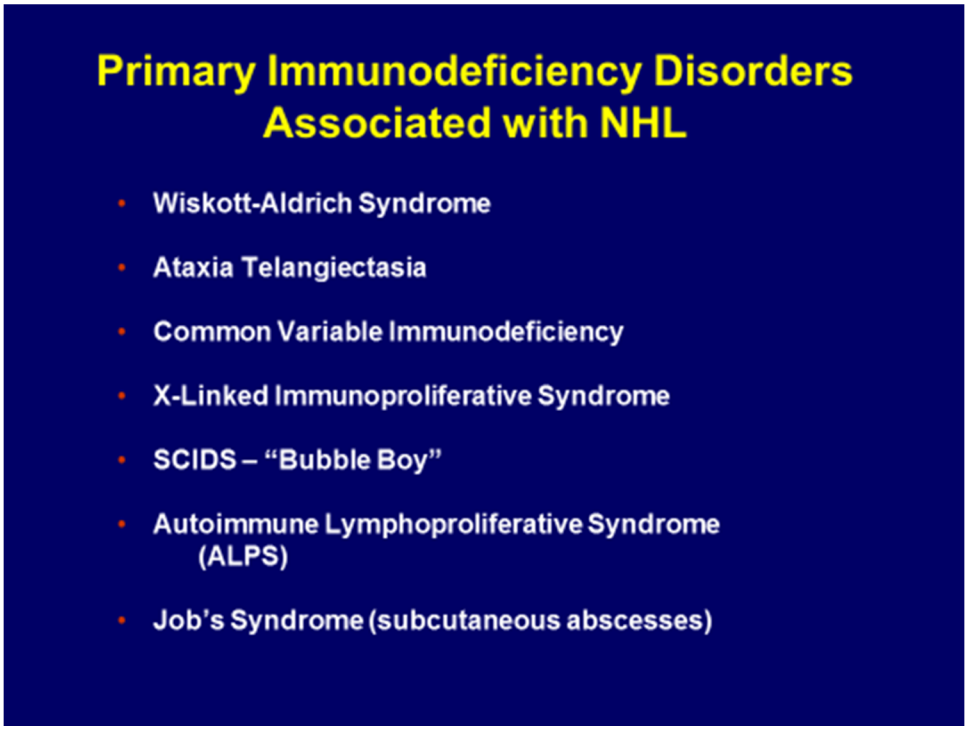
Also shown on here, on this slide, are other lymphomas; and I'm going to cover some of those lymphomas during this presentation. I'm including mantle cell as being one of the indolent lymphomas, although that is arguable about whether it will be or not. But because it is a small cell

lymphoma and not a large cell lymphoma, I've also included it; and I'll also include a little bit about T-cell lymphomas as well, which only represent 6% of the lymphomas in the United States.

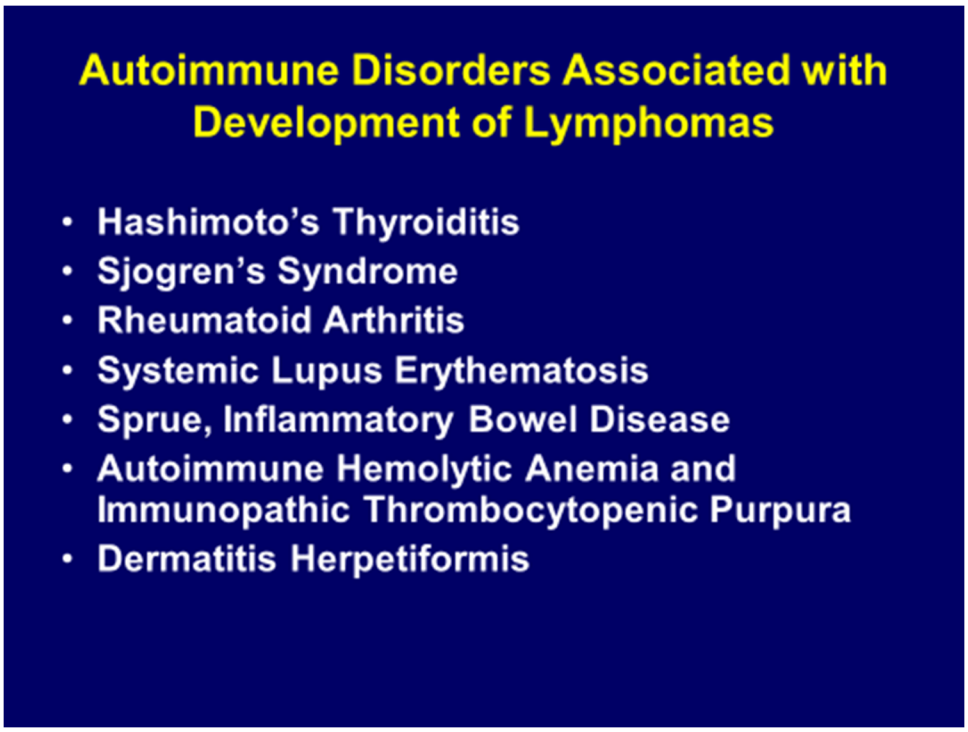
The first possible causes of lymphomas are shown here;



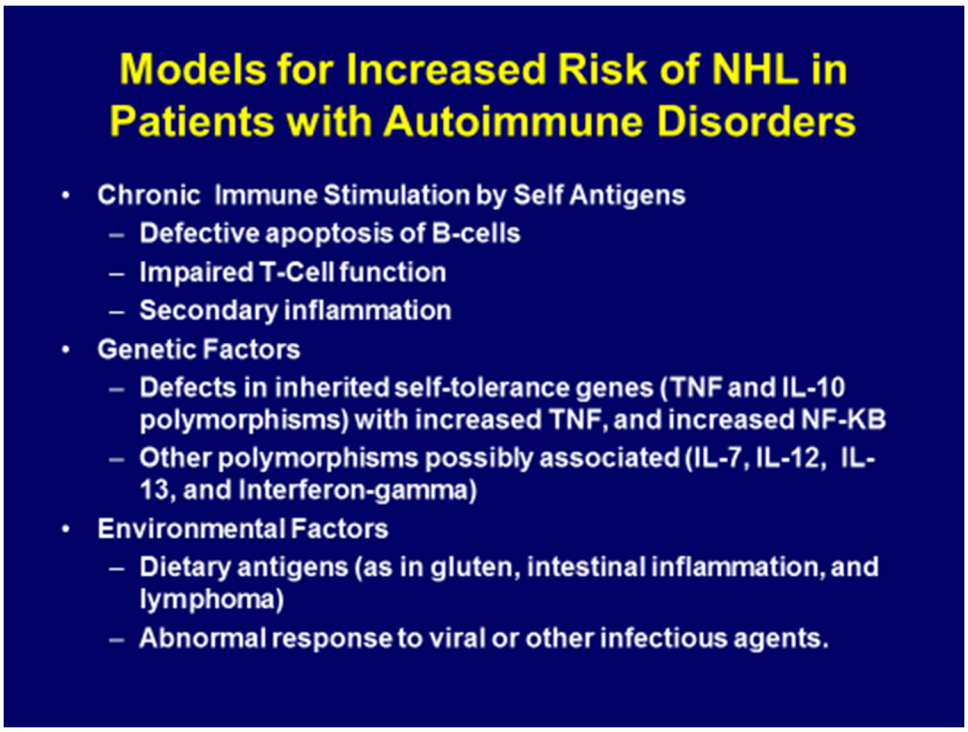
and, as you can see, there are a variety of different possible things that have been linked to the development of lymphoma. What you don't see here are different types of foods or exposure to different kinds of environmental agents, except for Agent Orange, which is still counted as being a major issue for people who have worked in the armed forces. Other things that have been listed, also pesticides and herbicides. The problem is that we don't know exactly which one. If you happen to use pesticides and herbicides on a farm, for example, there is a higher risk of developing lymphoma. It hasn't been very well worked out, but the point is that with this particular slide, all of these are associated with some type of immune suppression. And this is the major key factor in understanding what might be the cause of lymphoma or why patients develop lymphoma. And I'd like to say it's not just having low immune function. It's actually having a dysimmune function. In other words, a dysfunction of the immune system rather than being poor immunity.



There are some primary immunodeficiency disorders that are associated with lymphomas, and they're shown on this slide. They are relatively uncommon disorders. However, all of these have been associated with an increased risk of developing lymphoma. And there are a variety of different possible models as to why these might be taking place. For the most part, there is an overactivity of the immune system; but it is in the wrong direction. So it's not just that the immune function is poor or that there's a really bad immunity. Instead, it is that the immune function is a dysfunctional immune system—kind of like you could think of it as dysfunctional family members and that kind of thing. It's a way to think about it.



There are some autoimmune disorders that have been associated with the development of lymphoma, and shown here are a variety of them. These have been looked at in the past, and there have been a number of patients—we often see patients who have thyroid dysfunction with Sjögren's syndrome. Rheumatoid arthritis has not been easy to pin down, and I'm going to show you a little bit about that. We know that patients who have sprue or inflammatory bowel disease have a higher risk of it, and systemic lupus has been one of those things that's been associated with that disorder as well or with development of lymphomas.

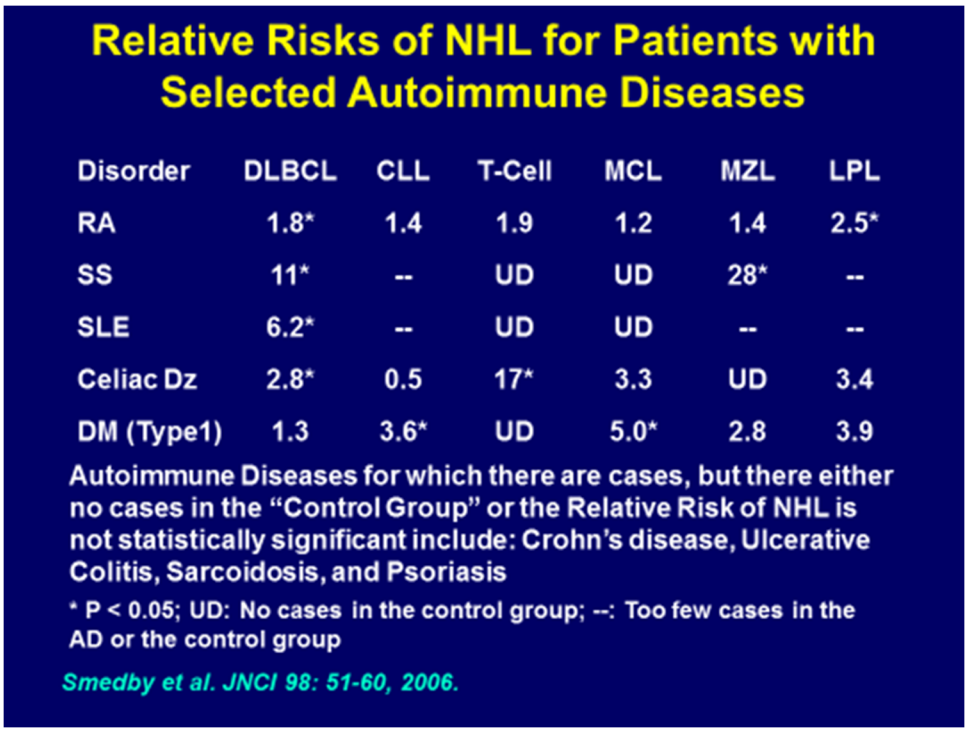


There were some models, as I mentioned before, that might be thought of as being ideas of why this might happen. And, mostly, they either represent some chronic immune stimulation by antigens that are in the body. In other words, for some reason, your joints give you problems; and there's some sort of immune stimulation because of that. But there's some background problem that's caused, that may be developing in patients who have those background antigens in their body that are causing stimulation.

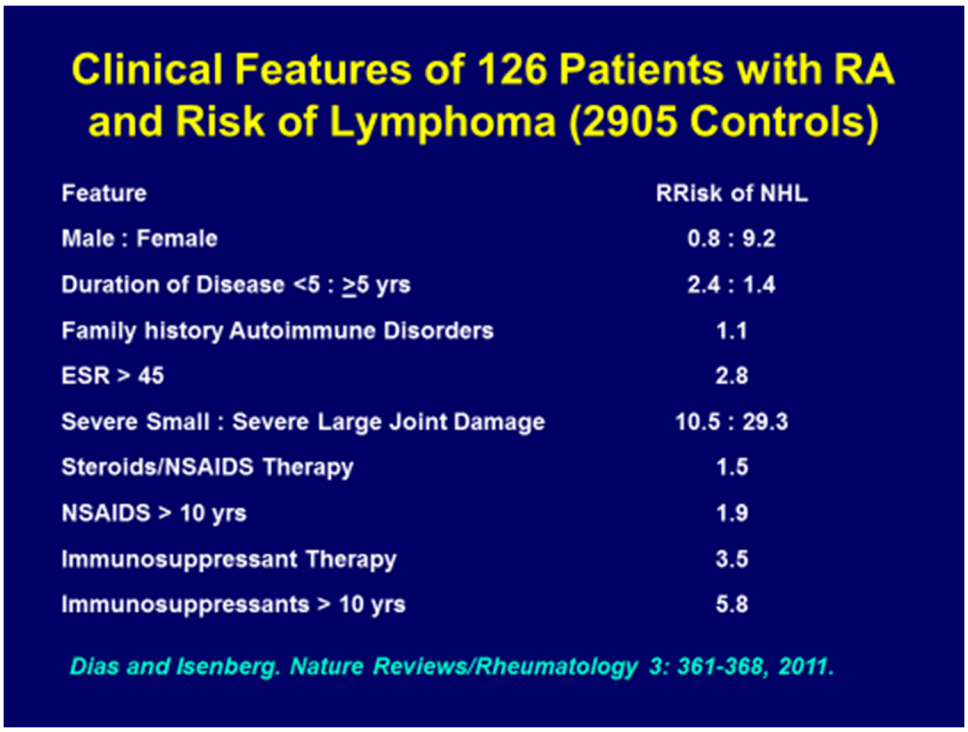
There's some genetic factors that have been associated with the development of lymphomas, but they are not apparently inherited. And one of the problems that we have, and get asked all the time, is this an inherited problem? Do I have to worry about my kids? And we do see some patients who come in whose family members have had some type of leukemia or some type of lymphoma previously. But figuring out exactly what those defects are, are very, very difficult because they are not easily identifiable; and it takes special studies to be able to find those particular commonalities in those patients.

And then, finally, certain dietary factors and that includes people who actually have gluten-associated inflammation of their bowel. They can't eat wheat, and some people who have that are clearly at risk for developing lymphomas.

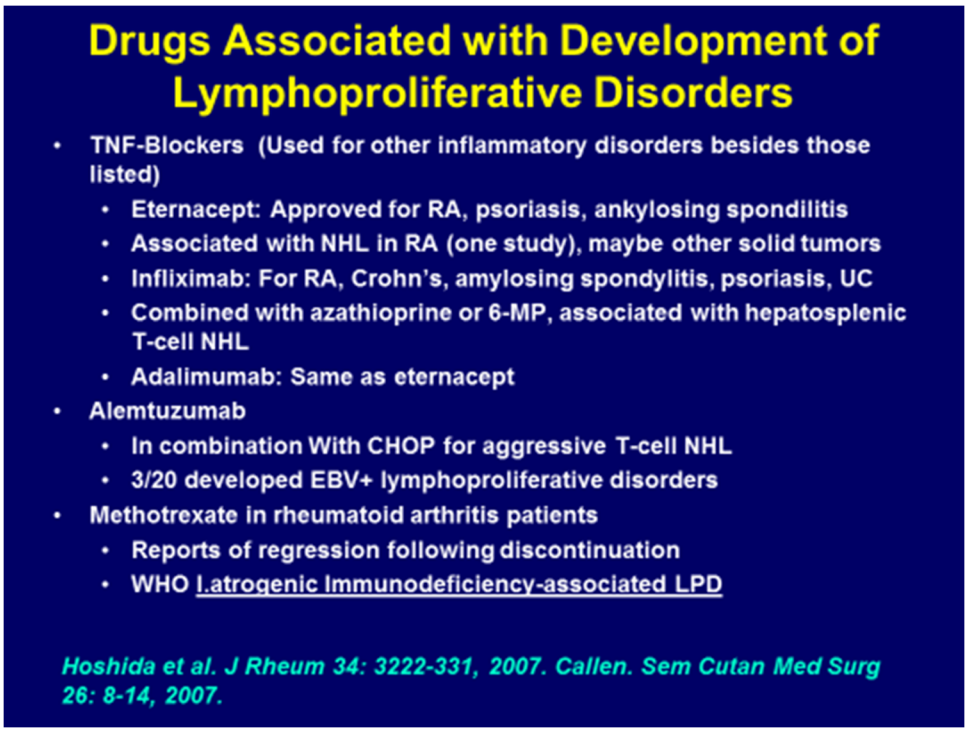
And then, finally, an abnormal response to other viruses or other infectious agents as in EBV.



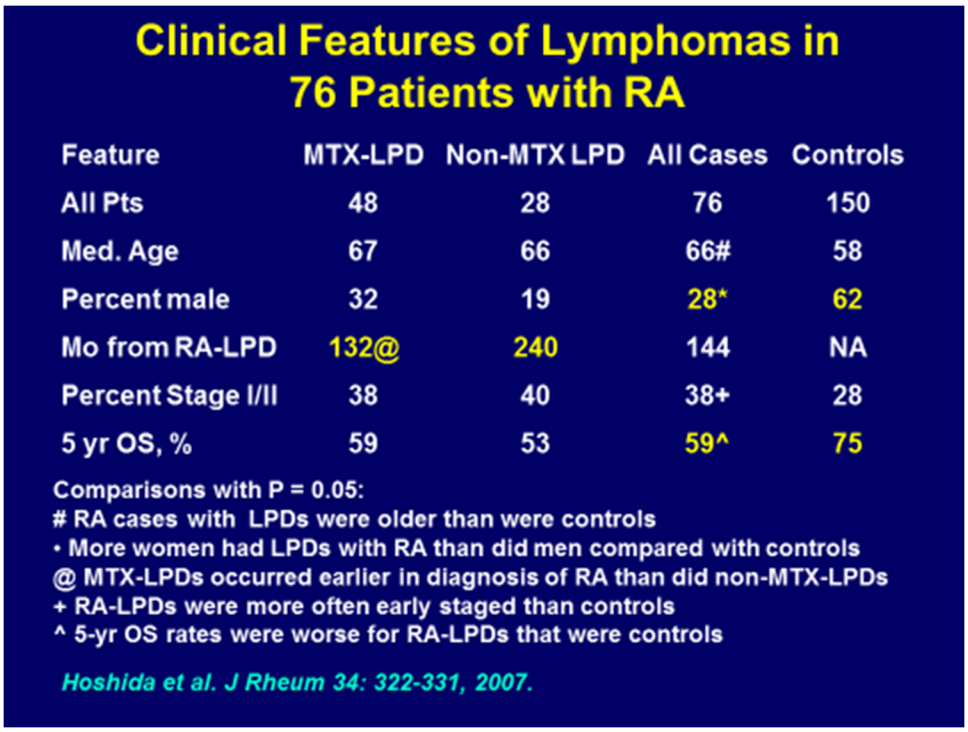
So, this is the risk of development of non-Hodgkin lymphoma in patients who have certain types of autoimmune diseases. And when you see a number that is so very high here, for example, rheumatoid arthritis, on the left-hand side is systemic sclerosis; or SLE, systemic lupus erythematosus; and celiac disease as I mentioned; and DM is diabetes mellitus, which has been associated with the development of some lymphomas. And the number, it shows you like, for example, in the top left-hand side, it says, "For diffuse large B-cell lymphoma, it's 1.8." That means 1.8 times the risk compared to people who don't have rheumatoid arthritis. So you can see across the top that other lymphomas, including CLL (chronic lymphocytic leukemia), T-cell lymphomas, mantle cell lymphomas, marginal cell lymphomas, and lymphoplasmacytic lymphomas are associated with a risk; but it's not very high. And wherever you see the star, that means it's high enough to be significant. The other numbers are not quite there, and so there are other disorders that are not quite yet associated because of mere numbers. The numbers are too small to be able to tell whether there's an increased risk or not.



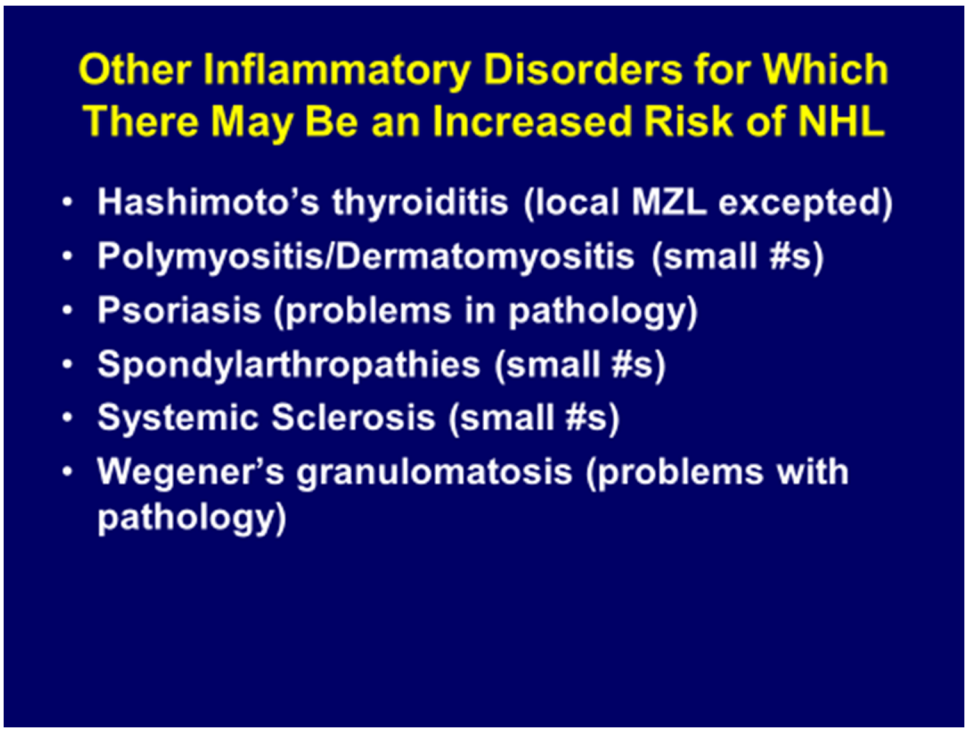
Here's some clinical features of 126 patients who did have rheumatoid arthritis and the risk of lymphoma, and you can see that there are a variety of different issues that are playing a role. At the very bottom, I want you to pay some attention to the immunosuppressant therapy. The risk is 5.8 times the risk if you've taken immunosuppressants more than ten years, and there are a variety of people who take immunosuppressants for various illnesses and increase their risk of developing lymphoma.



There are some drugs that have been associated with development of lymphomas as well, and they include etanercept that's used for rheumatoid arthritis as well as other inflammatory disorders and a variety of other drugs that you can see here. One of the drugs that we use commonly was alemtuzumab for treatment of CLL, for example, and in combination with CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) for aggressive T-cell lymphomas, a number of them develop EBV-positive, that is to say Epstein-Barr virus-associated lymphoproliferative disorders. And, finally, methotrexate, a common drug that is used to treat rheumatoid arthritis; and patients do have and have taken methotrexate and come in to see us with lymphoma; and they've had rheumatoid arthritis. And they ask us, can we get back on our methotrexate? Now that you've cured our lymphoma, and I go, "No, I don't think so. I don't think I would do that." And I wouldn't do that because I don't know that it doesn't increase the risk of their developing that disorder again.

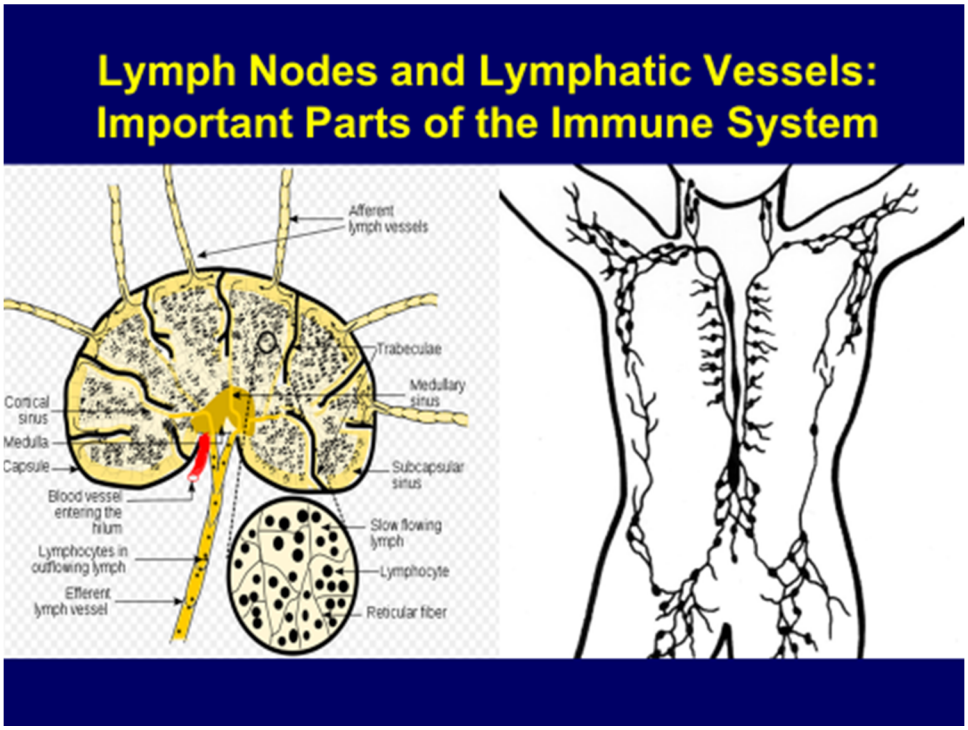


And here are some clinical features I just want you to pay some attention about the methotrexate lymphoproliferative disorder. The months from having taken that drug to development was 132. With the nonmethotrexate, it was much longer. So those patients who develop lymphoproliferative disorders, that is to say lymphomas who had rheumatoid arthritis, they develop their lymphomas much later than do the ones who receive methotrexate. So methotrexate appears to induce it or cause it to be more frequent or more common. And when you compared it to controls, you can see that the overall survival in those patients is lower than it would be in those patients who are considered controls.



Other inflammatory disorders for which there may be an increased risk of developing lymphomas are shown here, but there are problems with all of these in that we expect marginal zone lymphoma to be occurring in patients who have thyroiditis. Polymyositis, there's just not enough people with it to be able to make a definitive statement. Psoriasis can be associated sometimes with development of T-cell lymphomas, and we don't have a lot of information about that because there's problems with pathology. And a number of other issues that means too small numbers to make some sense out of the increased risk or not.

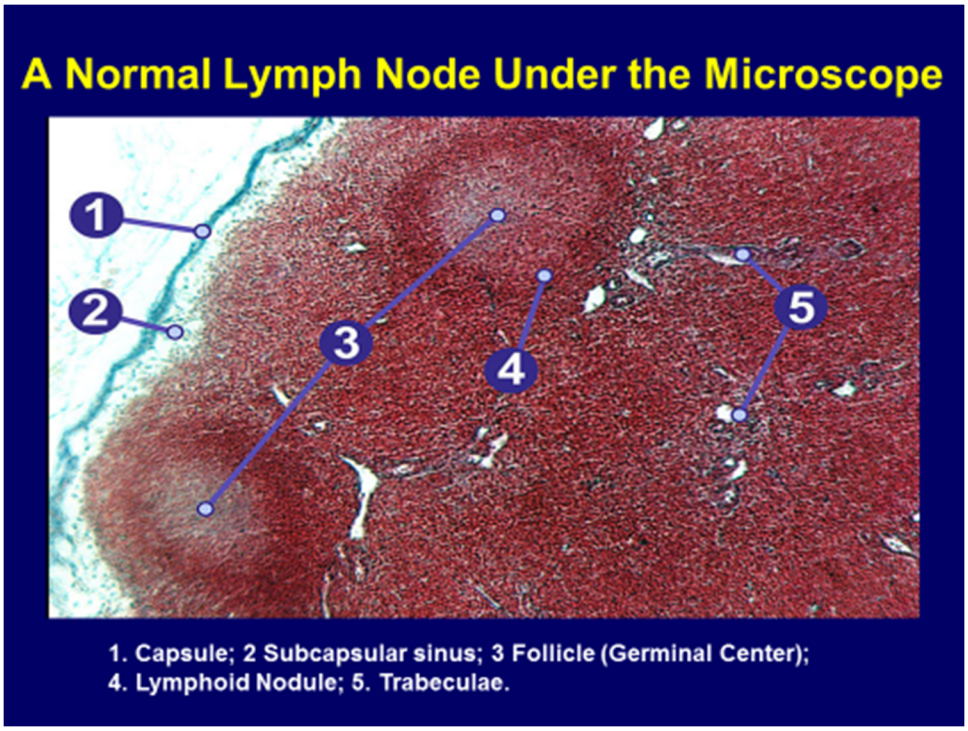
Talk a little bit about pathology.



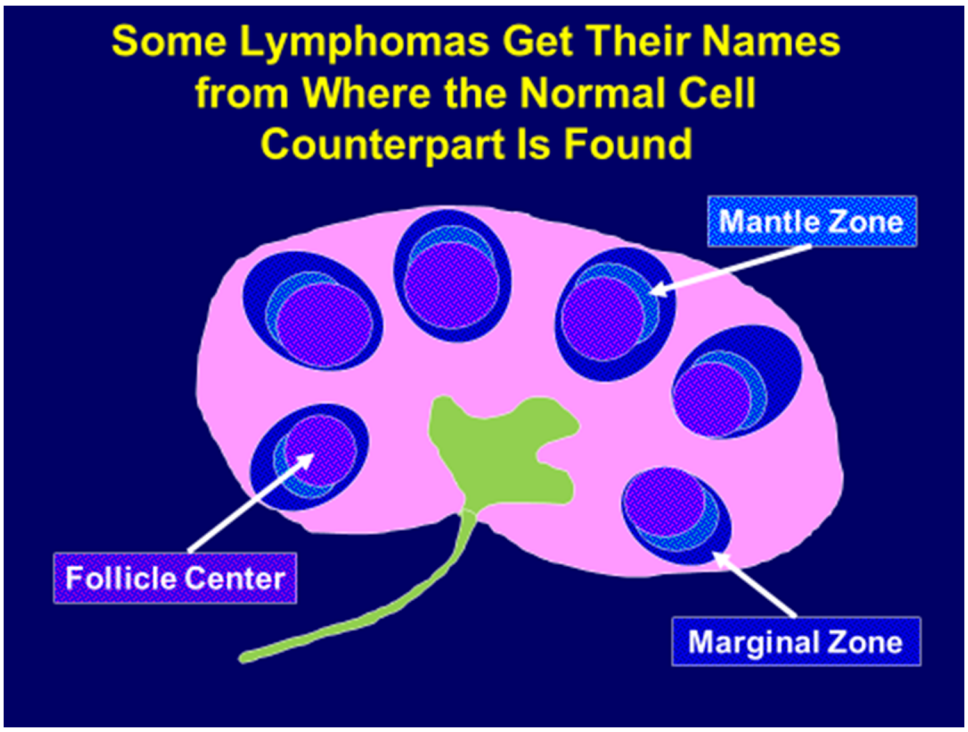
Lymph nodes and lymphatic vessels are very important parts of the immune system, and you can see on the left-hand side, this is a schematic drawing of what a lymph node looks like. There are small

lymph vessels that do connect these nodes, one with the other, throughout the entire body. Afferent means these are the lymph that is flowing into the lymph node, and they flow in from the outside, and you just see the node looks like a bean. It's sort of bean-shaped, and it's divided into various segments by trabeculae and other different supporting structures. And these lymphocytes enter and they eventually decide what they're going to do, how they're going to reduce antibody, if they're going to multiply, whatever they're going to do, depending upon the stimulus. And on the right-hand side, you can see a schematic drawing of the body with all of the lymph nodes that may be occurring.

Sometimes people say, "Well how many lymph nodes are involved?" Well, these are small lymph nodes that you can sometimes not see; and it really isn't important how many are involved in a particular area, although you will see that when you talk about the FLIPI (Follicular Lymphoma International Prognostic Index) score in follicular lymphomas, the sites of involvement play some role in determining how well a patient will do when they receive therapy.

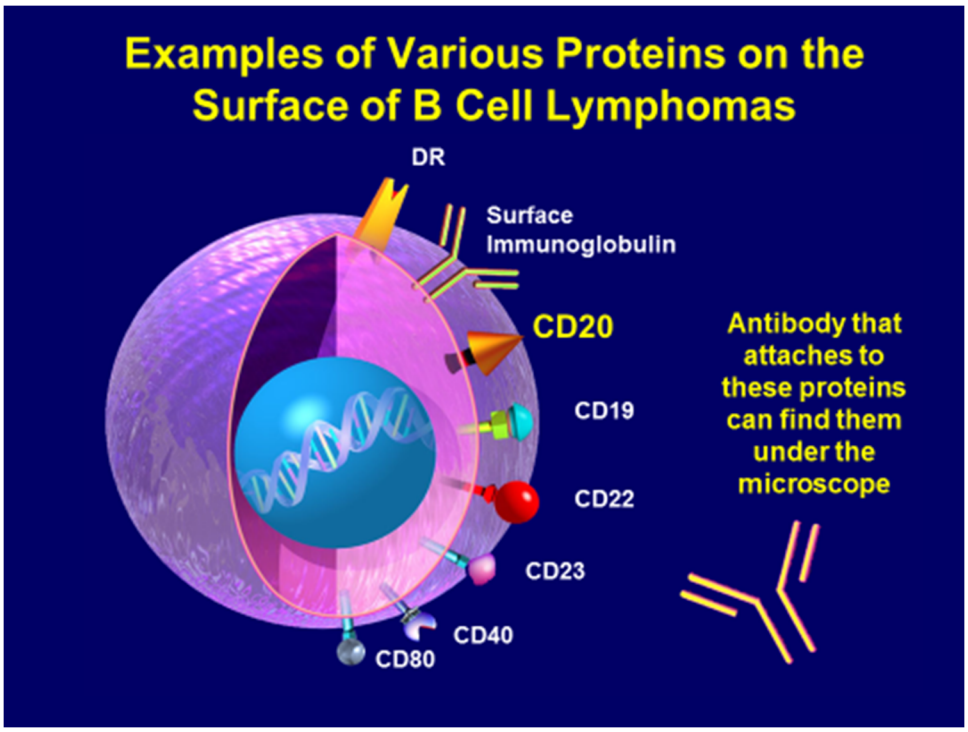


This is a normal lymph node under the microscope, and you can see that there is this capsule that I showed you before, and I want you to pay particular attention to the follicle. This is where normal B-cells go into and they end up becoming whatever they're going to grow up and become ultimately and make antibody. And this is like the baby factory, so we think of it as being a follicle, as in the follicle which is in an ovary where eggs normally reside in a woman. So we're interested in looking at the follicle and sort of figuring out what that might be.

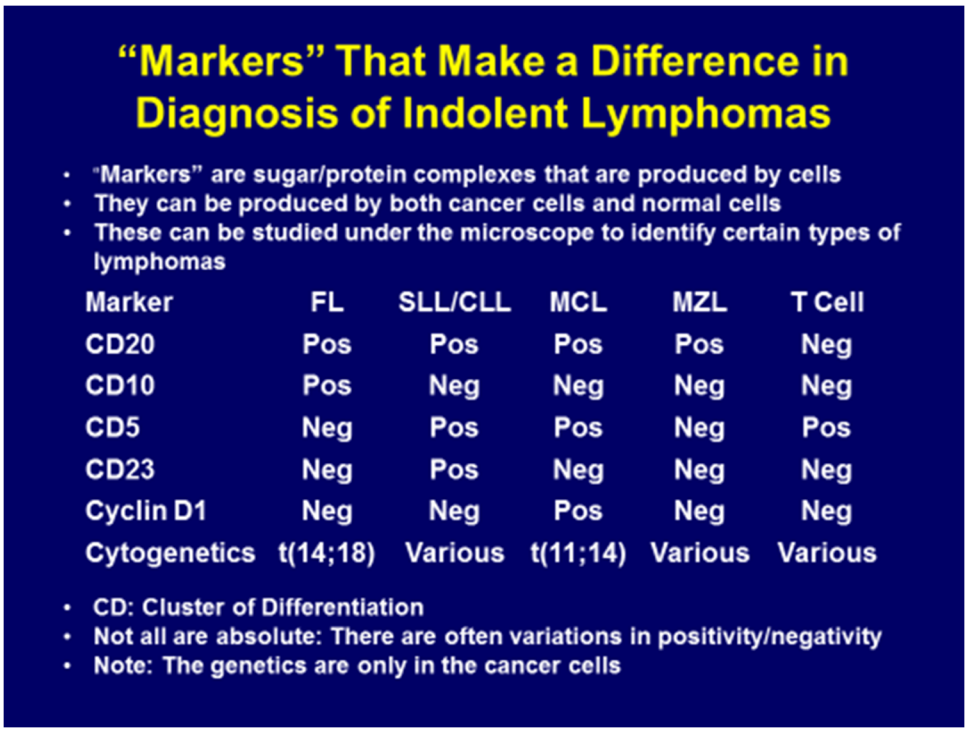


So some lymphomas get their names from where the normal cell counterpart is found in these follicles. And shown here is just sort of a drawing that shows you what those areas are called. And I would direct your attention to the left-hand side where I've got follicle center written, and that's a follicle center which is part of the follicle or part of the germinal center where these B-cells go. And they also go into the mantle zone, shown up on the right-hand side, and then finally the marginal zone. These are all contained B-cells, and there are other B-cells, of course, in the pink area which are the cells that are between the follicles.

So, when these cells that are shown as little bitty dots in these follicles become lymphoma cells, for example, we call them follicular lymphoma. And on the right-hand side, you'll see at the top we call them mantle cell lymphoma when those cells come from that area. And, finally, we call it marginal zone lymphoma because they come from that particular area of the normal lymph node.

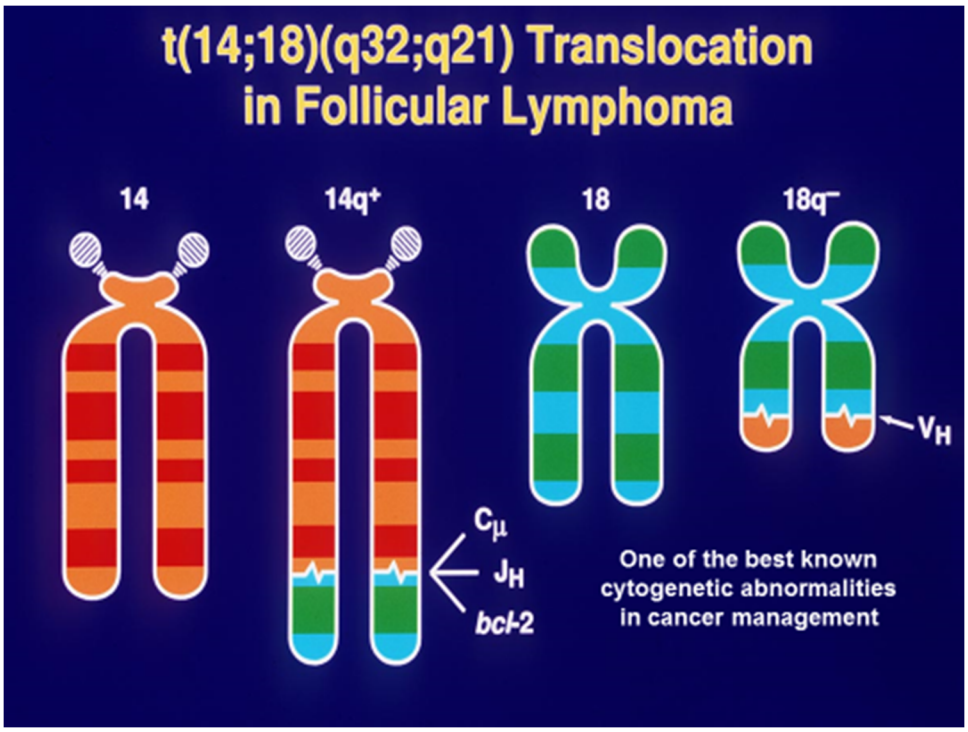


There are also some ways that we identify these cells on the basis of various proteins that are on the surface of these lymphoma cells. And shown here are some various proteins that can be seen on the surface of these B-cell lymphomas. I want you to pay attention especially to the CD20 which is shown on this particular diagram. And CDs, there are many of them. They go from CD1 up to CD250 or even more. These are important. We can find them because we have antibodies that can attach to these proteins, and we can look at them under the microscope and see these antibodies because they have a little target that's attached to them that's florescent and can light up or a dye that shows them. And we can find these proteins on the surface of the microscope, under the microscope and find these cells and define these lymphomas as to what they are based upon these markers.



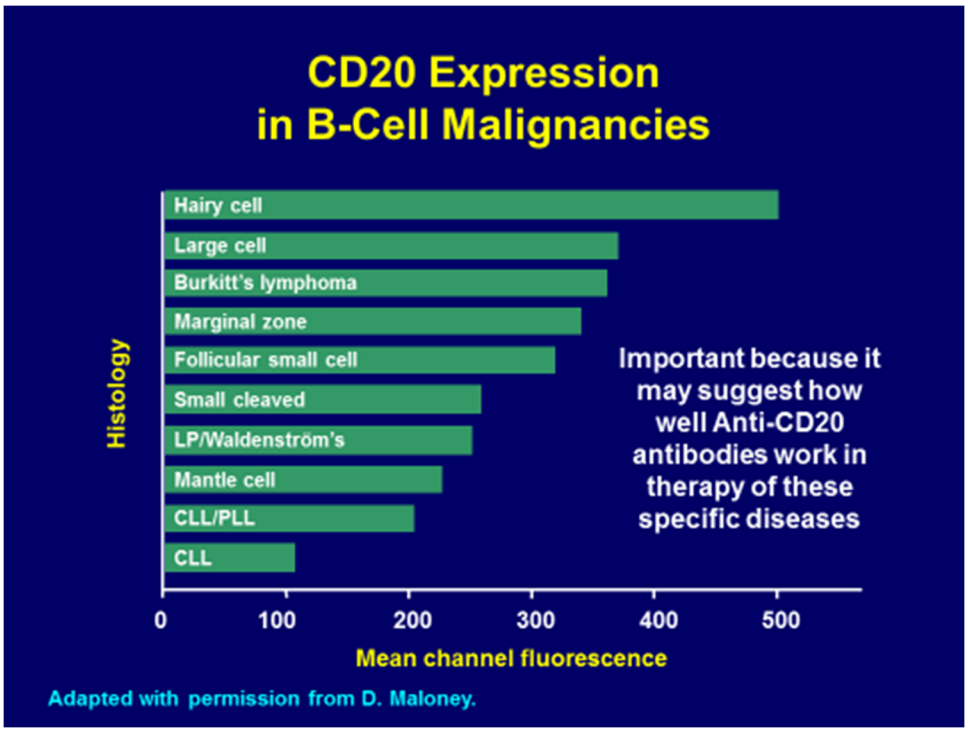
So, here are the markers. CD stands for cluster of differentiation, and these help us decide what lymphoma we've got and what we're talking about. We didn't have these 35 years ago. We have them all available now, and they're used regularly to help determine what type of lymphoma we've got. And you can see that CD20 is positive in all of these. However, CD10 is really mostly positive in only follicular lymphoma. CD5 is negative in follicular lymphoma but is positive in small lymphocytic lymphoma (SLL) or CLL and mantle cell lymphoma. It's also positive in T-cell lymphomas. CD23 is positive also in CLL, but, mantle cell lymphoma is usually negative for CD23; but it can be positive. Marginal zones are usually negative for everything. Cyclin D1 is also positive in mantle cell lymphoma and usually not in the others.

So, the important thing is that we use these particular markers to determine what type of lymphoma we've got, and often we'll get slides and we say, "Well, we're not sure exactly what type it is." And we ask the pathologist, "Can you do an additional stain to tell us what type of lymphoma it is."

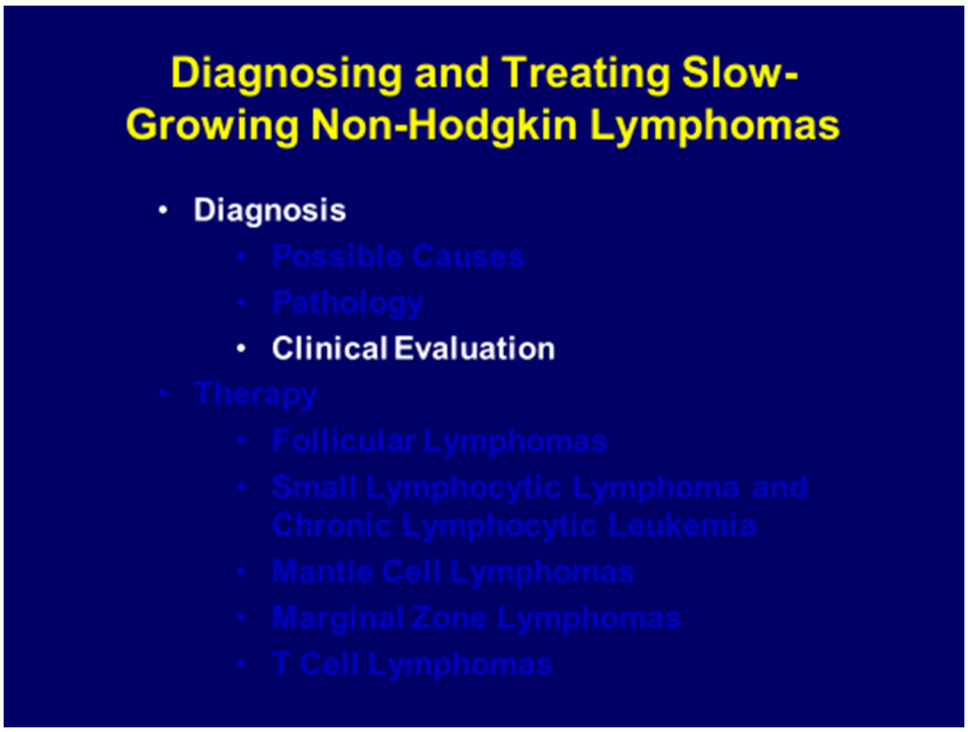


Another thing that's important about these lymphomas is that they often have a translocation that is mean. That means to say here is shown chromosome 14 on the left-hand side and chromosome 18; and in this particular slide, you can see that part of chromosome 14 is broken off and is attached to chromosome 18. And part of chromosome 18 is attached and is broken off and is attached now to chromosome 14. And this is a very well-known cytogenetic abnormality that occurs in follicular lymphoma; and whenever we see this, we can see this translocation also in other types of lymphomas. But in follicular lymphoma, this is almost standard. It's almost required. We can do a lot of testing now, not just looking at the cytogenetics under a microscope, but we can do special testing called FISH (fluorescence in situ hybridization) and other kinds of interesting other ways of looking at this particular cytogenetic abnormality to find this particular marker. And whenever we looked at this cytogenetic abnormality, it's interesting to see that this is the hallmark of this particular disorder.

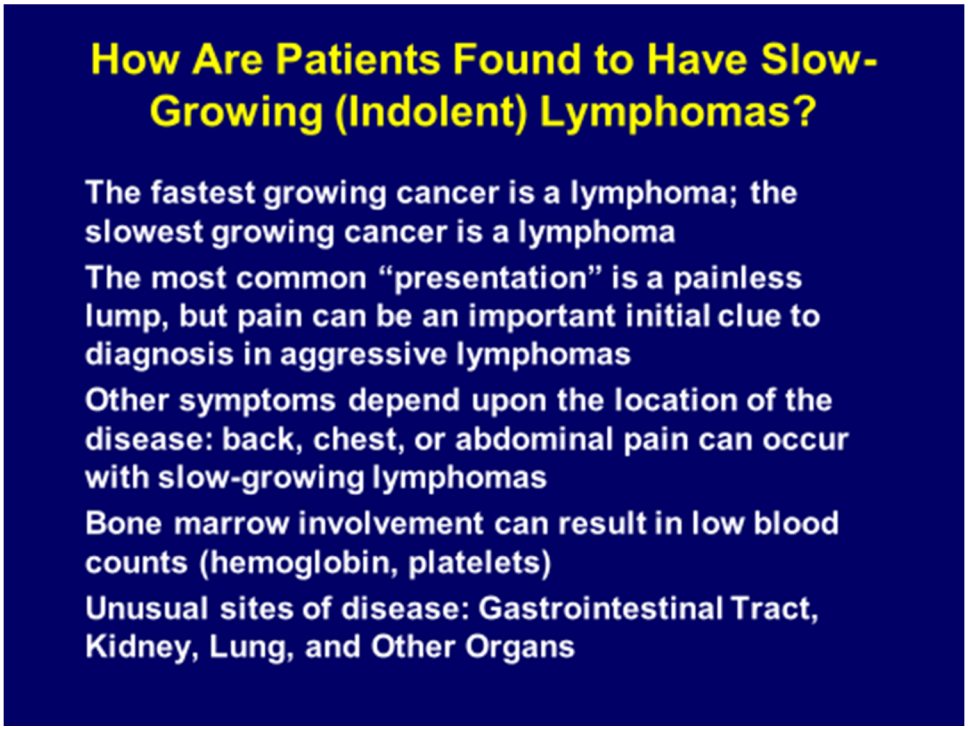
There are others that have also been described; and as you're well aware now, we understand that there can also be changes in these chromosomes that are not detected as a translocation but can be seen as molecular rearrangements. And that's what we look at, mostly when we're trying to test for that.



CD20 is also not, although it may be ubiquitous, that means it's always present or almost always present on B-cell lymphomas, it can be faint, which you can see in patients who have CLL. Their cells don't have a very big expression of CD20. But as you go along, you can see that the ones that have the most expression are large cell lymphomas and hairy cell leukemia. And follicular lymphomas are sort of a little bit less than those, but they're still quite bright in this. And it's important because it suggests that anti-CD20 antibodies may work better in the patients who have greater expression.

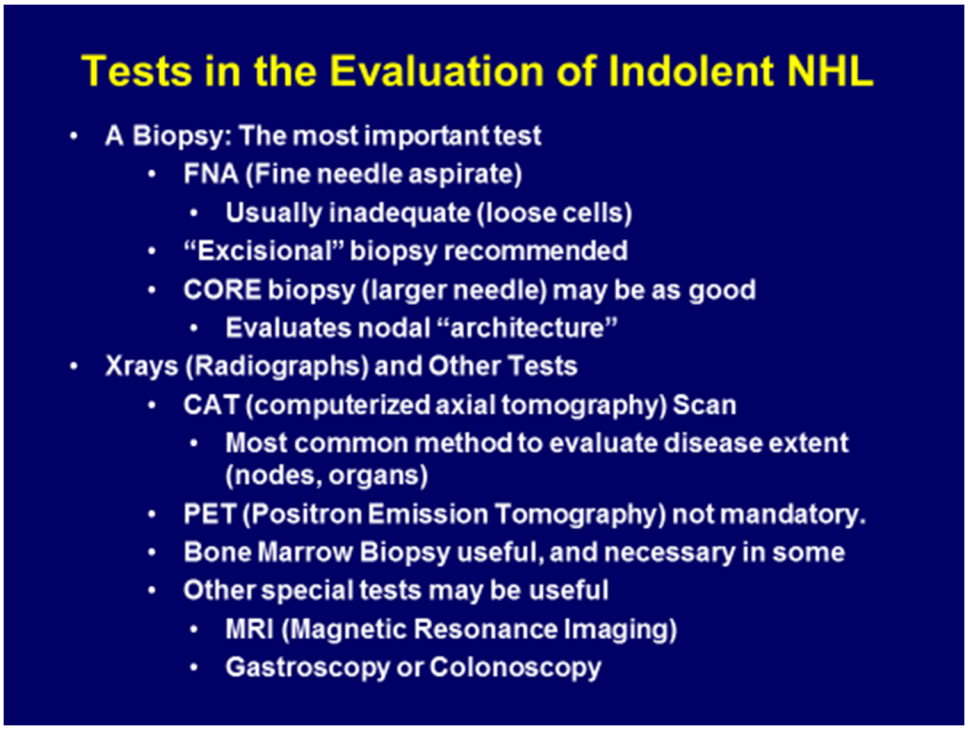


How do we clinically evaluate these?



Well, the slowest growing cancer is a lymphoma and so is the fastest growing cancer. So, we have all types of growth of these. In the indolent lymphomas or slow-growing lymphomas, and I may use that

word to describe these diseases in the rest of this talk, their most common presentation is a painless lump. But pain can also be important in aggressive lymphomas. Other symptoms depend upon the size of the disease and the location. You can get back, chest or abdominal pain. And bone marrow involvement can lower blood counts, and so you can get anemia as well as bleeding. Unusual sites of disease include the gastrointestinal track, kidney, lung and other organs.

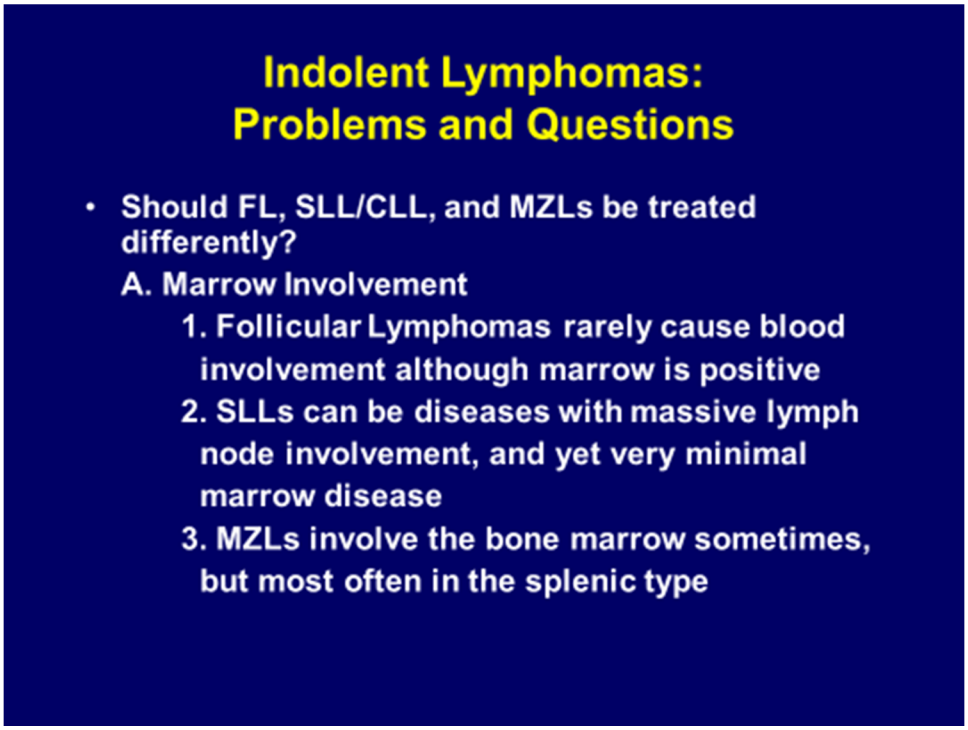


So what's the most important test? It's a biopsy, of course, and getting a good interpretation of that biopsy. Patients who come to our center often have to obtain their slides from the outside because they've already had a biopsy performed, and we will often demand that we get those slides to be able to evaluate and tell these patients what we think their lymphoma shows.

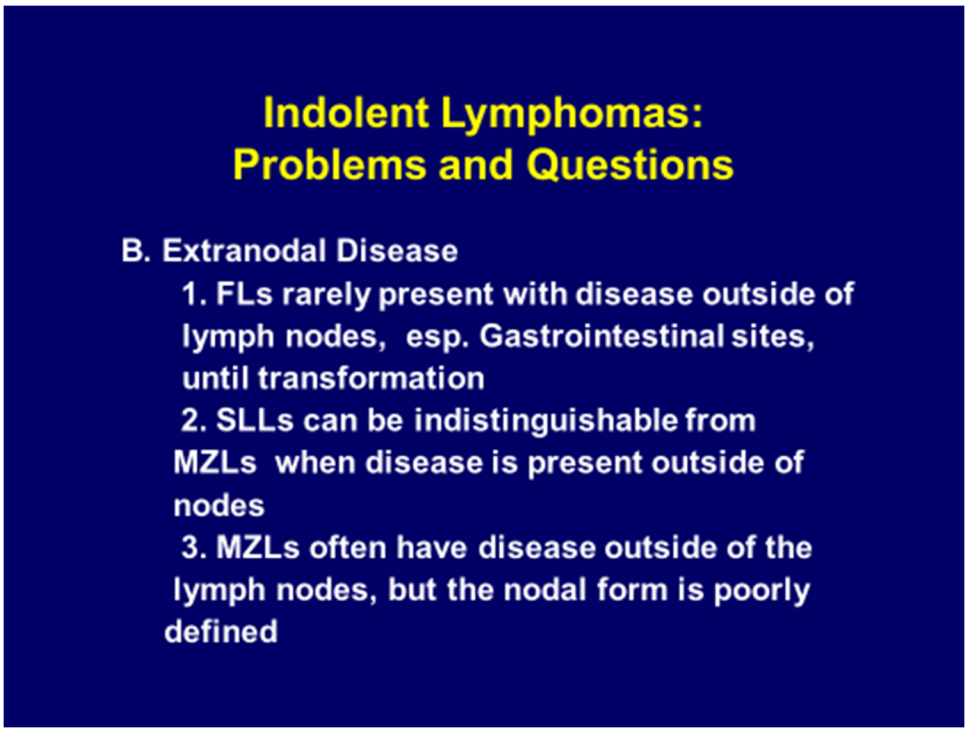
An excisional biopsy is recommended over a fine needle aspiration. Fine needle aspiration merely gets those cells loose, and you can't look at them in association with one another. Now we've become accustomed to looking at what we call a core biopsy where we get a larger needle. It may be as good as doing an excisional biopsy. It does evaluate nodal architecture, and you can also do markers on a core biopsy quite easily.

As far as x-rays and other types of tests, the CAT (computerized axial tomography) scan is the most common method used to determine disease extent. Sometimes the PET (positron emission tomography) scan is used, especially in patients who had disease that is outside of the lymph nodes, that is to say extranodal. Extra means outside of. So bone marrow biopsies are also useful, sometimes necessary if you see low blood counts. And other tests may also be useful, depending upon where the disease is located. MRI is particularly good for muscle and for bone, and CTs are not so good. So we like to use MRIs for determining that extent of disease, and CTs really don't look

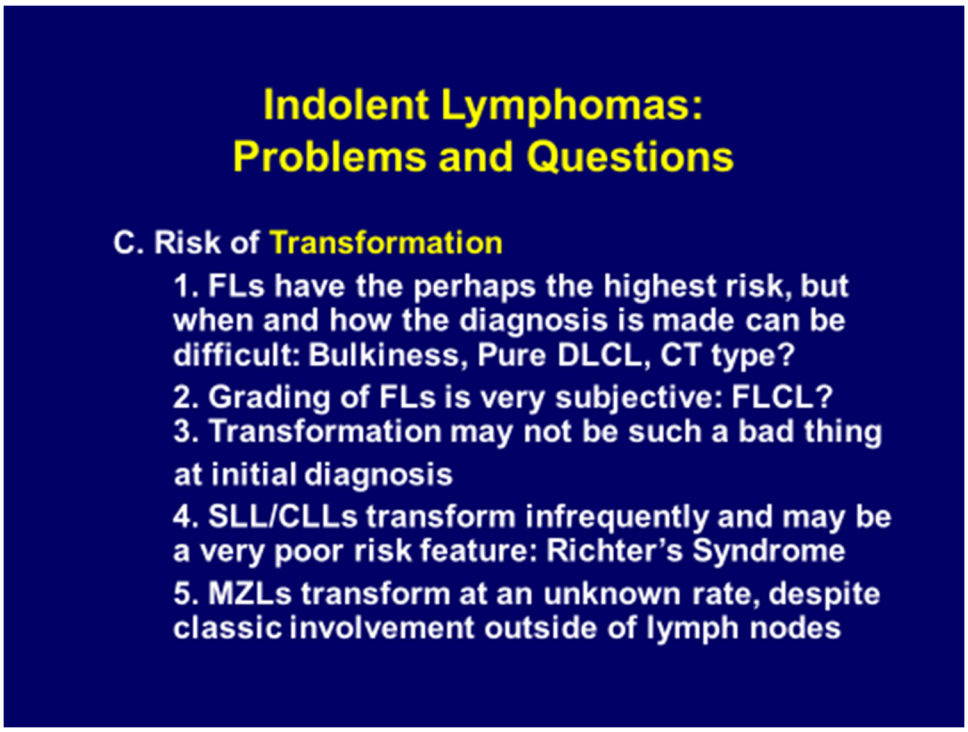
inside the colon or inside the stomach, so it's necessary to do gastroscopies and colonoscopies in patients whom you suspect might have disease involvement in those places.



So should these lymphomas be treated differently? Well, marrow involvement is very common in all of these—in follicular lymphoma, small lymphocytic lymphoma. Of course, that's when we call it CLL. And marginal zone lymphomas. But follicular lymphomas rarely cause blood involvement. Although the marrow is positive, small lymphocytic lymphomas, of course, with CLL can have lots of nodes and have very minimal disease. But CLL will have peripheral blood involvement as well as marrow involvement and very little massive node involvement. Marginal zone involvement occurs, of course. It can also have bone marrow involvement, but they're most often present in the splenic type.



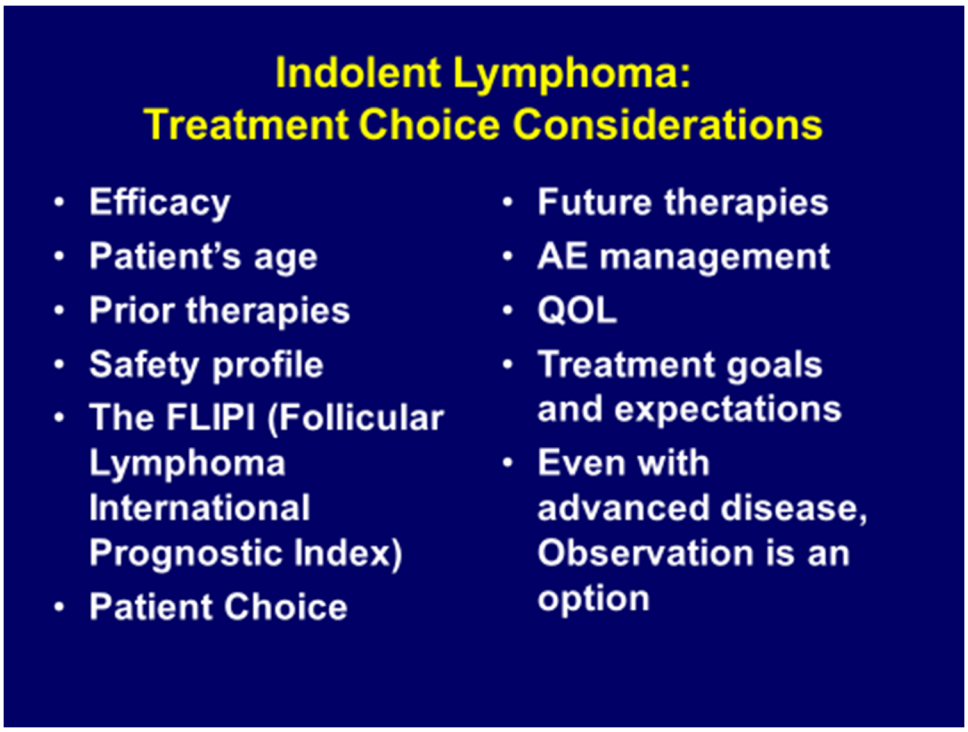
Extranodal disease is also, that stays outside of the lymph nodes. Follicular lymphomas rarely present with disease outside of the lymph nodes, until they develop transformation to more aggressive lymphomas. Small lymphocytic lymphomas can be indistinguishable from marginal zone lymphomas when the disease is outside of nodes and does. It doesn't usually occur; but marginal zones do, of course, involve the disease outside of the lymph node.



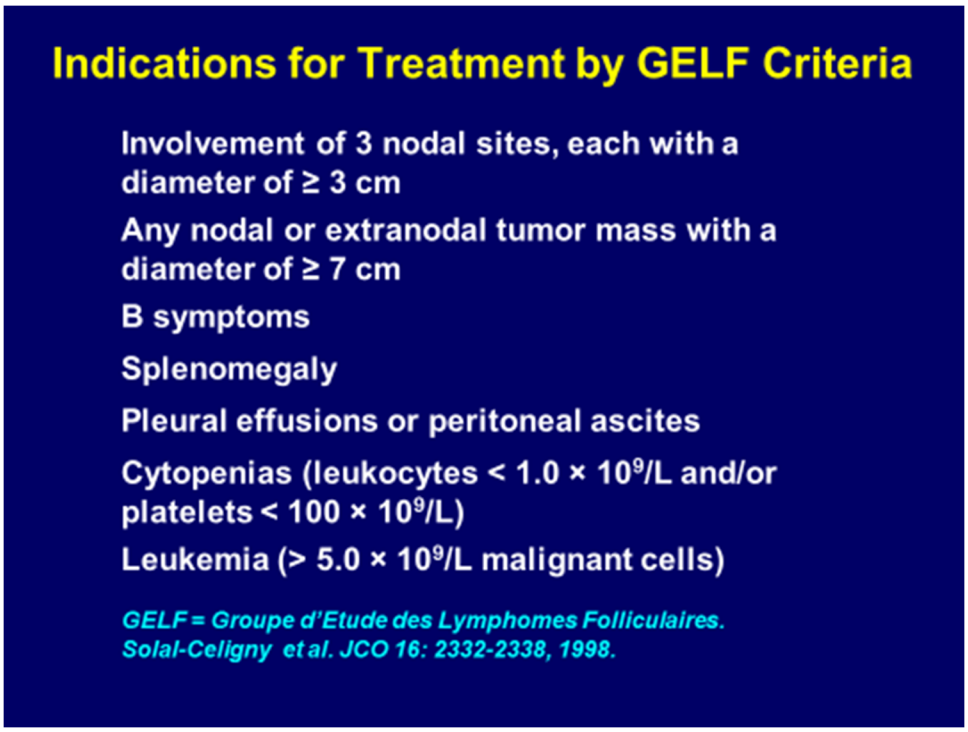
This risk of transformation has often been questioned, and we're trying to figure out why do patients who have slow growing lymphomas suddenly develop a rapidly growing lymphoma. And people have looked at that already and understand that there is suddenly some change in the cytogenetics of the lymphoma cell that makes it grow more rapidly. And then is when it's really a problem to treat because then they have to be treated as if they have aggressive lymphomas. And some of the drugs that we use to treat indolent or slow growing lymphomas don't work as well when they are used to treat aggressive lymphomas. So making that diagnosis of transformation is often very important.

Follicular lymphomas have the highest risk of developing transformation, and it's somewhere between 1 and 3% per year. On the other hand, and it's important, grading of follicular lymphomas is often very subjective. There is a disorder called follicular large cell lymphoma or grade 3b. I will go over that a little bit in just a moment, and it can be a problem in trying to treat those disorders.

Transformation may not be such a bad thing at initial diagnosis. You just treat for the aggressive form and then later on worry about the slow growing variety. SLL/CLLs, however, transform very infrequently; and we use the word Richter's syndrome to describe that particular problem. Somewhere between 5% and 7% at the very most will transform over their lifetime. Marginal zone lymphomas also transform at a very unknown rate. We don't know exactly how frequently that does occur, but it does occur.

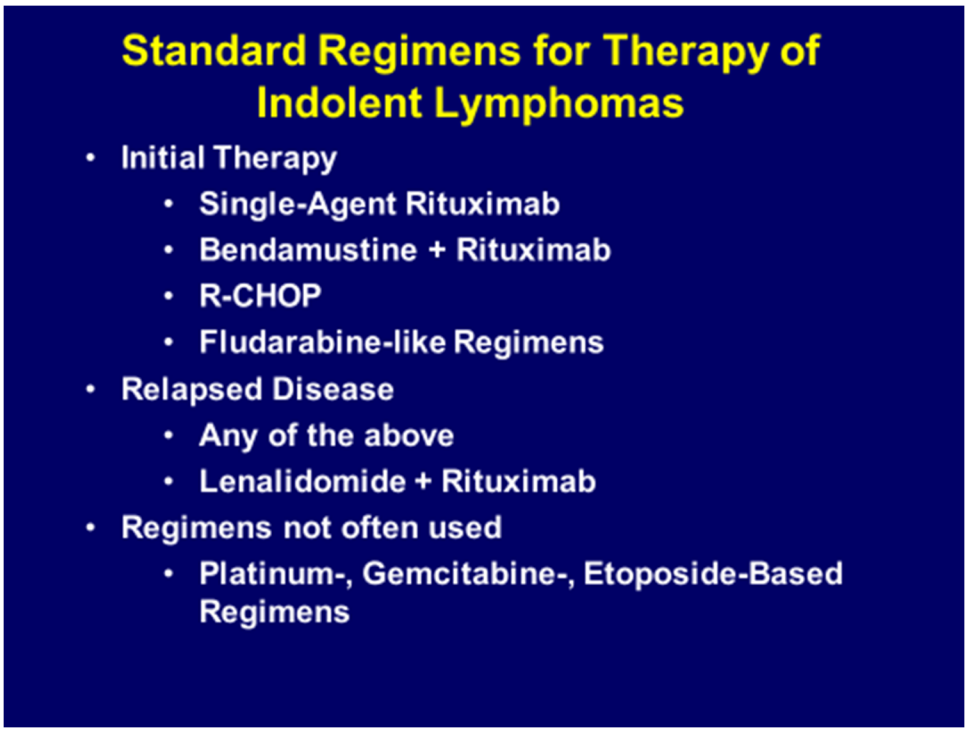


So treatment choices depend upon a lot of different factors here. I would like you to pay attention in particular to the left-hand side of the slide, at the very bottom where it says, "patient choice," realizing that once you understand exactly what you've got and what is going on, it's very important to discuss what type of treatment might be the best for you or the patient, depending upon what is going on as far as all of these other issues are concerned, including quality of life.



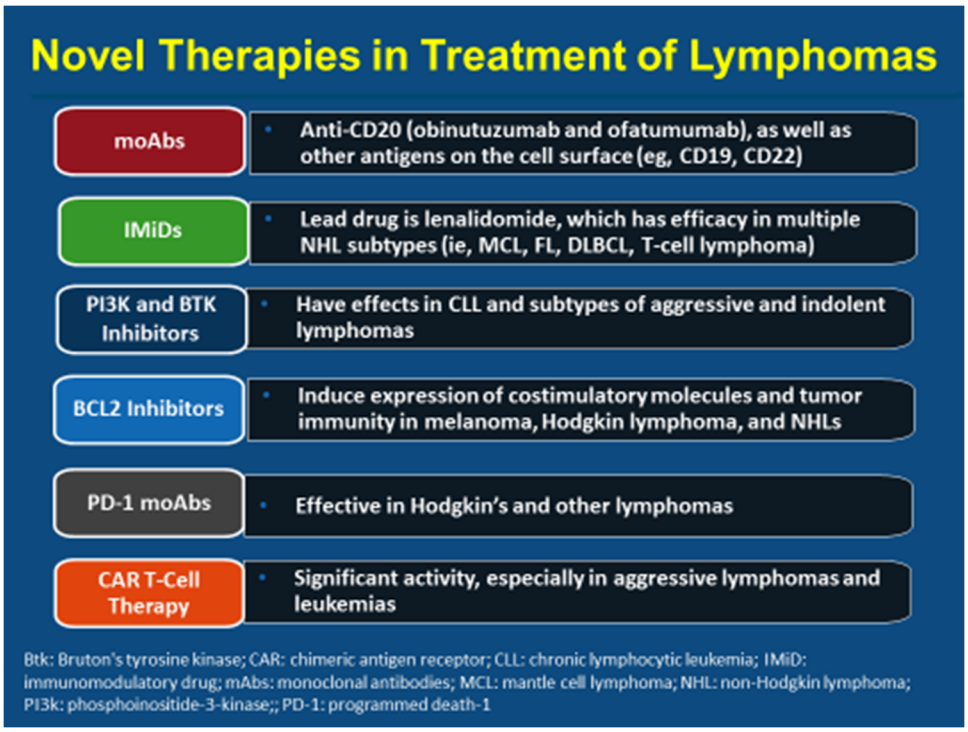
There is also a particular method of evaluating patients to figure out whether they can or should be treated, and this is known as the GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria. This is used mostly for follicular lymphomas since it was described many, many years ago. And it's basically whether patients are symptomatic or whether they have involvement of three nodal sites, each with a diameter of more than three centimeters or any nodal or extranodal tumor mass with a diameter of greater than seven centimeters, which is about three to four inches, in that range.

The rest of these are all patients who would have some sort of symptom. Of course, if you come into the clinic and you have symptoms, well that's an issue; and you've got to be treated. But if you have no symptoms and you have less than what is shown on this slide at the top two parts, then you're a patient who could be observed because it's been already noted that you can watch and not treat these patients at the very beginning because their disease grows so slowly in many cases.



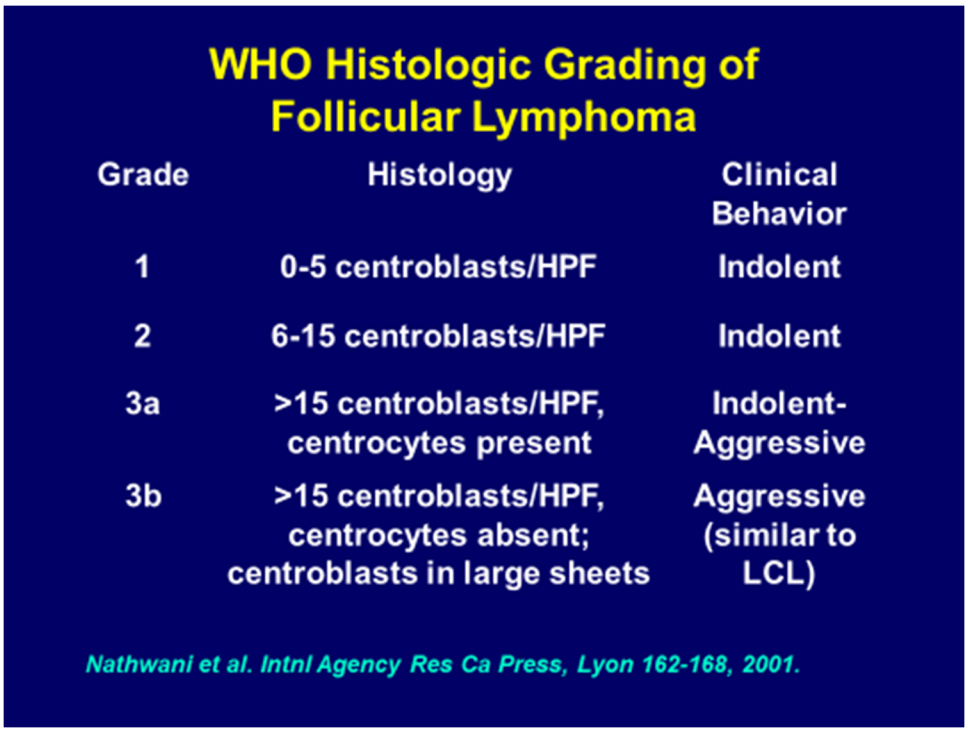
There are some standard regimens that have been used for treatment of indolent lymphomas and shown here, include those today single-agent rituximab, which is an anti-CD20 antibody, now made available by the FDA almost 20 years ago, and certainly started to study 20 years ago. And this has changed the prognosis of patients with indolent B-cell lymphomas in a great deal, so much that, and I'll show you some of the very positive data that shows because of the use of rituximab. Bendamustine, which was used many years ago in Eastern Europe, in particular East Germany, and then came to the United States about eight years ago or so, tends to be a very good drug also and is very well tolerated and is used along with bendamustine to treat patients. And then the standard R-CHOP (rituximab with cyclophosphamide-doxorubicin-vincristine-prednisone). Fludarabine-like regimens are used primarily for patients with small lymphocytic lymphomas or CLL and appears to be a very good regimen and better response is seen with fludarabine-like regimens as opposed to CHOP or even bendamustine. I'll show you that in a moment.

Relapsed disease is treated with any of the above. It depends upon what therapy you've had before. But now we've got lenalidomide. I'll show you some of that data soon, and then there are regimens that we don't use very much, including platinum-based, gemcitabine-based or etoposide-based regimens, which are usually reserved for patients with aggressive lymphomas.



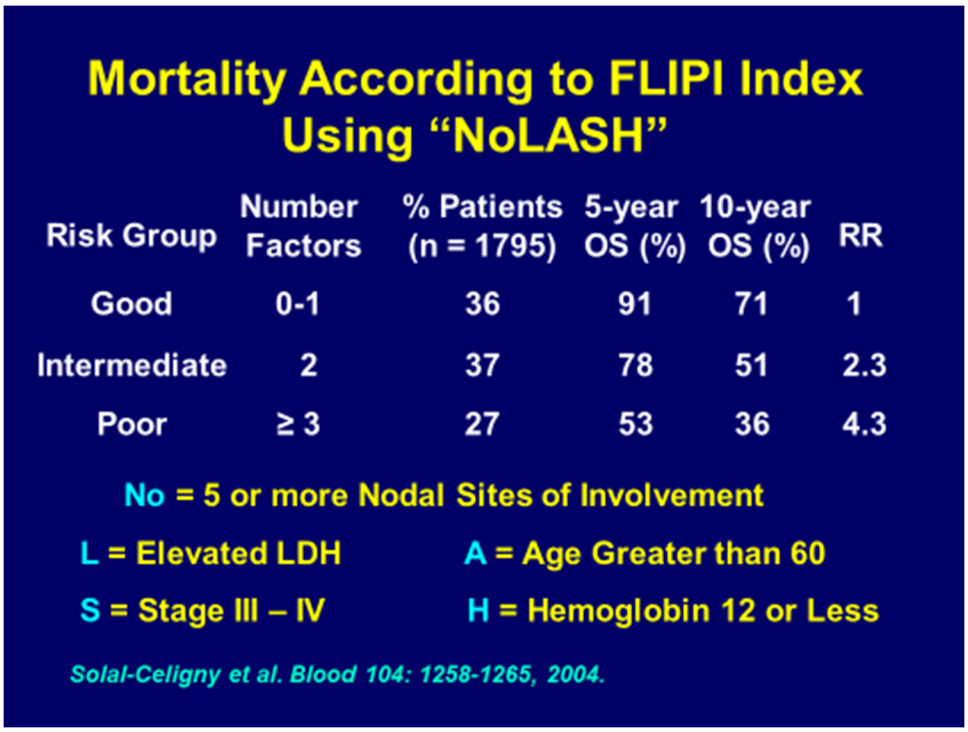
Some the new novel drugs have come along, and I'm just showing you this in one particular slide. We're going to talk about these in a little bit. They include monoclonal antibodies that are novel, but they're all directed against CD20 for the most part. What are known as IMiDs (immunomodulatory agents). These drugs are also effective in a variety of different lymphomas. PI3 (phosphoinositide 3) kinase and BTK (Bruton's tyrosine kinase) inhibitors—all persons who have lymphomas should understand a little bit about those and what they do and why they are effective. BCL2 (B-cell lymphoma 2) inhibitors, there's a new drug that's coming out that's now available for patients who have CLL and will be available soon for other patients with lymphomas, and then PD-1 (programmed cell death-1) monoclonal antibodies and CAR (chimeric antigen receptor) T-cell therapy, which I'm not going to cover today.

So for follicular lymphomas, I already mentioned grade 3b, so this grading system comes from many, many years ago.

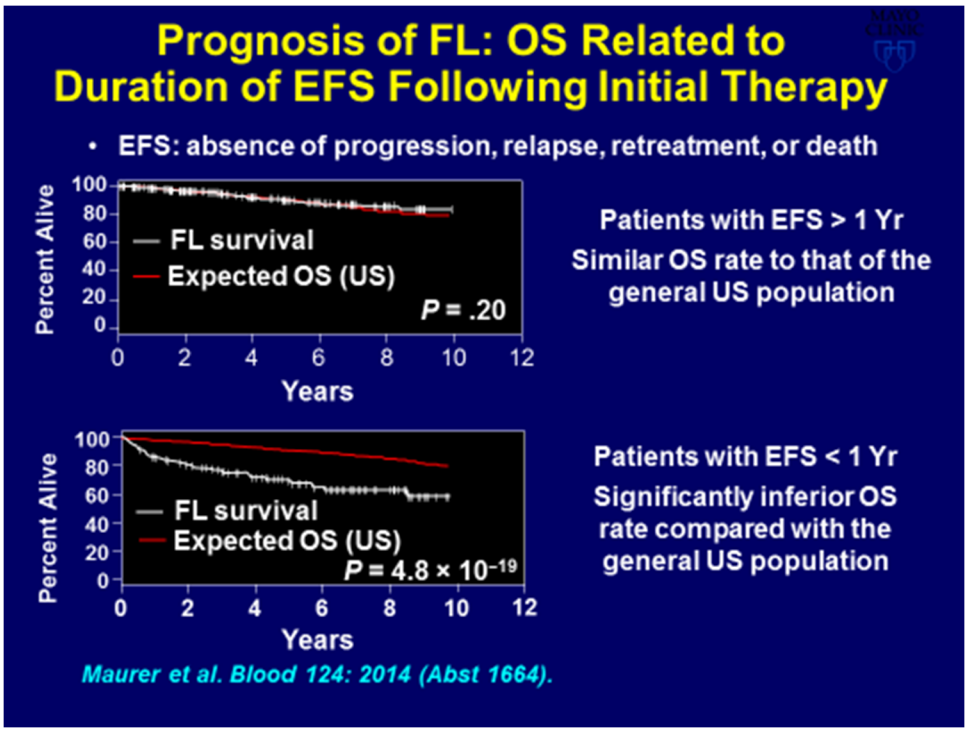


You can see almost now it's longer than 2001. It was described many years before that, and it's based on how many central blasts can be seen per high power field. Central blasts you could consider as being large cells. And I mentioned to you earlier on that large cells are very important because large cell lymphoma tends to be an aggressive lymphoma.

So grades 1 and 2 go together. They are indolent lymphomas. They behave very slowly, and they grow slowly. Grade 3a, we're not quite so sure. It may depend upon other features. Some of those patients have an indolent disease, and some of them have more aggressive disease. But grade 3b is central blasts and large sheets. So these sheets of large cell lymphoma mean they should be treated as if they have large cell lymphoma. And you can see how important it is to come up with this grading system and make some sense out of whether a patient should be treated intensively or not. Grade 3b we often see in association with lower grades, meaning that the patient already had the lower grade disease many years and then developed a more aggressive lymphoma. And, finally, the patient went to the doctor because they had this; and indolent lymphomas can be present in a patient for two, three or even four years before they know they have this lymphoma.

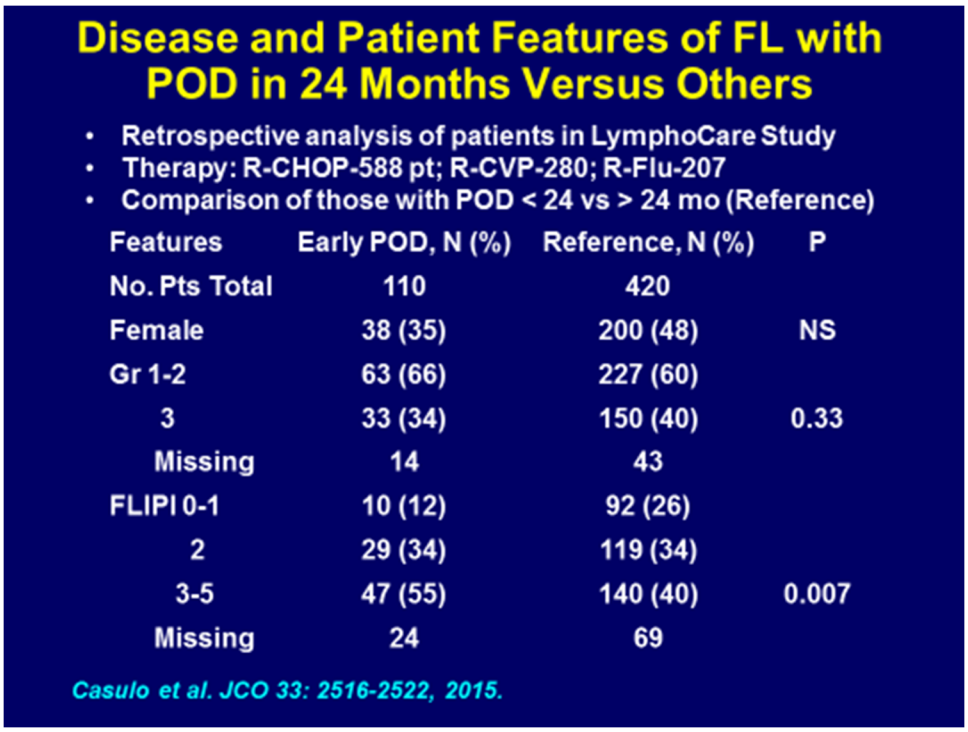


So this is the mortality, that is likelihood of dying according to the FLIPI index, keeping in mind that the FLIPI index was described before rituximab was available. Things have changed dramatically about this, but we still use the FLIPI index to determine how patients will do. And you can see that. It's also known as NoLASH (number of nodal areas, LDH [lactate dehydrogenase], age, stage, hemoglobin level), which is ascribed, it was invented in Europe with a number of different patients who were also accumulated from the United States. And you can see that there are a number of different factors. The more factors you have, the greater the risk, or I should say the greater risk of dying in the next ten years or so. And you can see that the relative risk does go up. Good risk group patients, zero to one. I would say that at MD Anderson, the majority of patients that we see are patients who actually have intermediate risk group disease, that is to say two features. Sometimes we see threes, and sometimes ones. Very rarely good risk. But almost all of them have intermediate risk disease, and many of those patients we observe only because we know that there is no difference in starting them on therapy early because their survival is not going to be any different. Now we've got rituximab, and we believe that. When you give rituximab, the survival is so excellent that we're not even worried about it any longer.

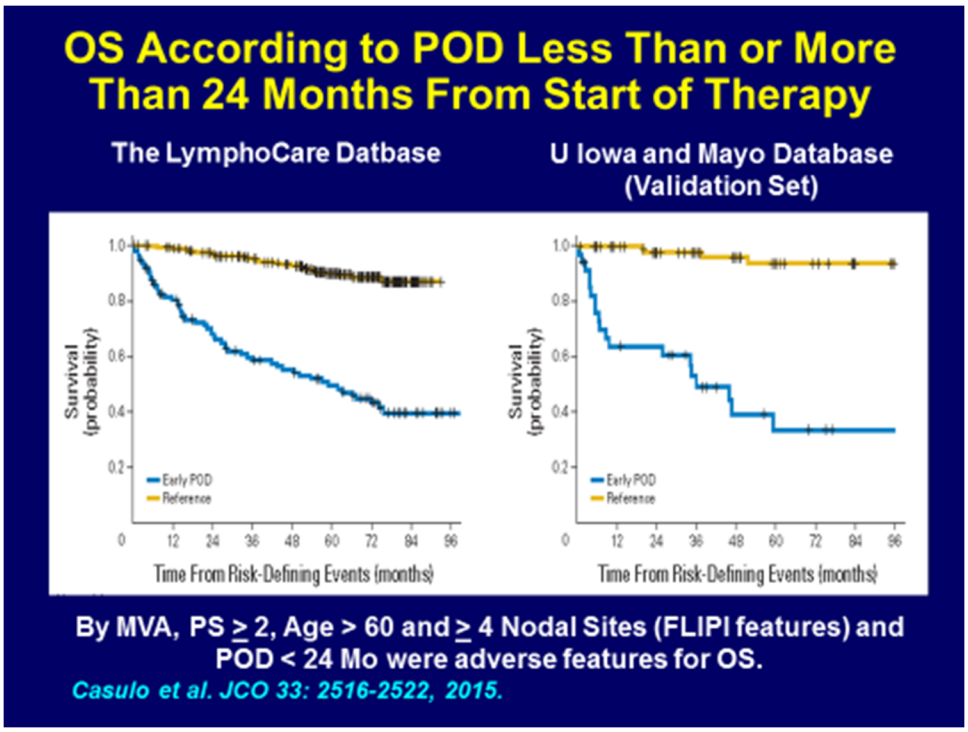


So this is a group of patients who were looked at, collected, and looked back retrospectively in trying to figure out how can you predict how patients with follicular lymphoma—this is the good news. This is, in fact, great. If you happen to be free of disease in this particular retrospective analysis for at least a year, if the EFS, means event-free survival, if it's greater than a year, you're overall survival is going to be similar to that of the general US population. Meaning you're going to live as long as you would live without the lymphoma, if you've never been diagnosed as having lymphoma.

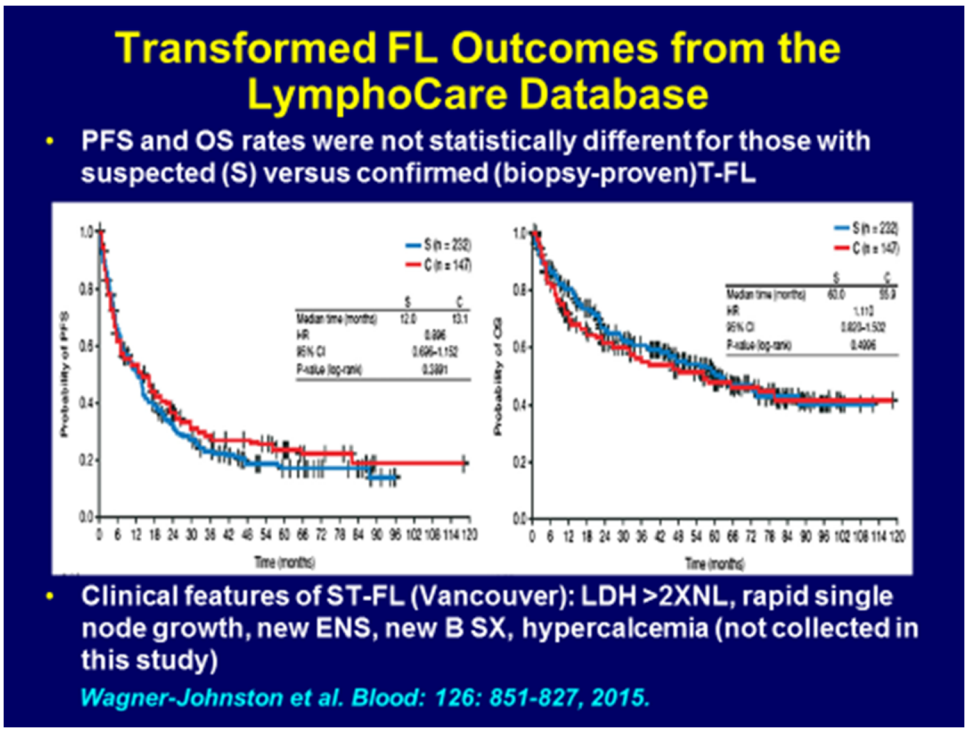
If, on the other hand, you develop progression within a year, you have a significantly inferior overall survival rate compared with the general US population. So now we can tell patients something about it, and make a decision about what kind of outcome they might have if they get treated and then their disease comes back more quickly. And we need to start thinking about how to be able to manage those patients in a better manner.



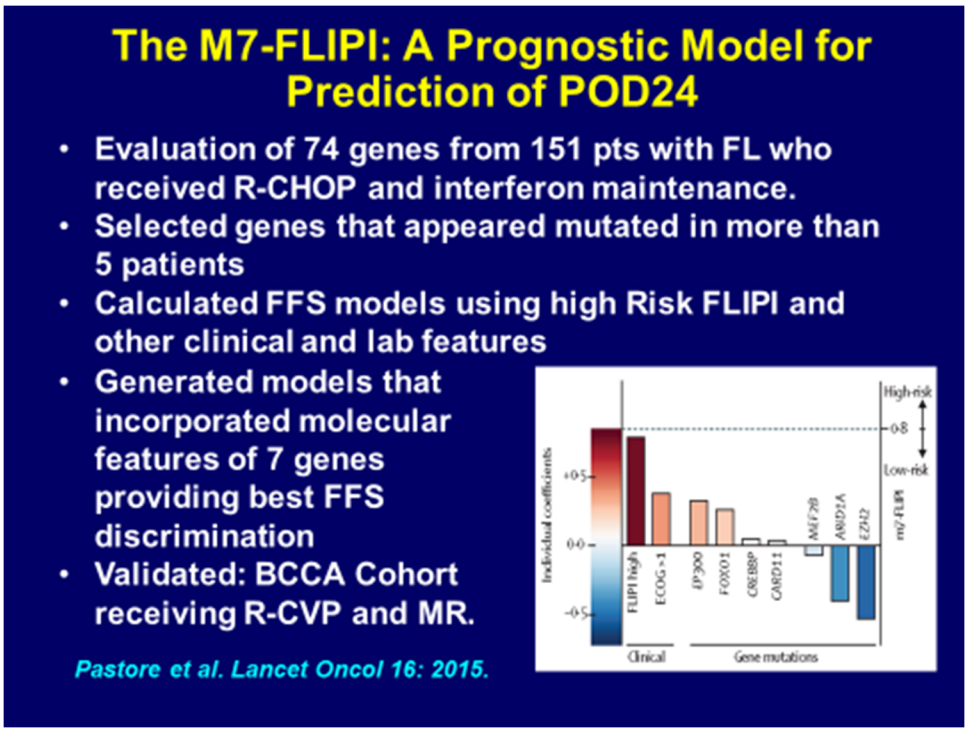
There are others who have looked at this and have looked at what's called the LymphoCare Trial. This comes from the LymphoCare collection of patients that were collected by and that's supported by Genentech. Those patients were looked at in this study. There were a number of different features they tried to figure out that would correlate with whether you have progression of disease within two years or not. And you can see that those patients who actually had a high FLIPI score had a higher risk, and that *p* value on the right-hand side, you'll see it over and over again, this was the only factor that they saw that played an important role. Those who had a high FLIPI score, three to five, were those patients who had a higher risk of developing disease progression within two years, which is thought to associate also with the likelihood of a lower survival.



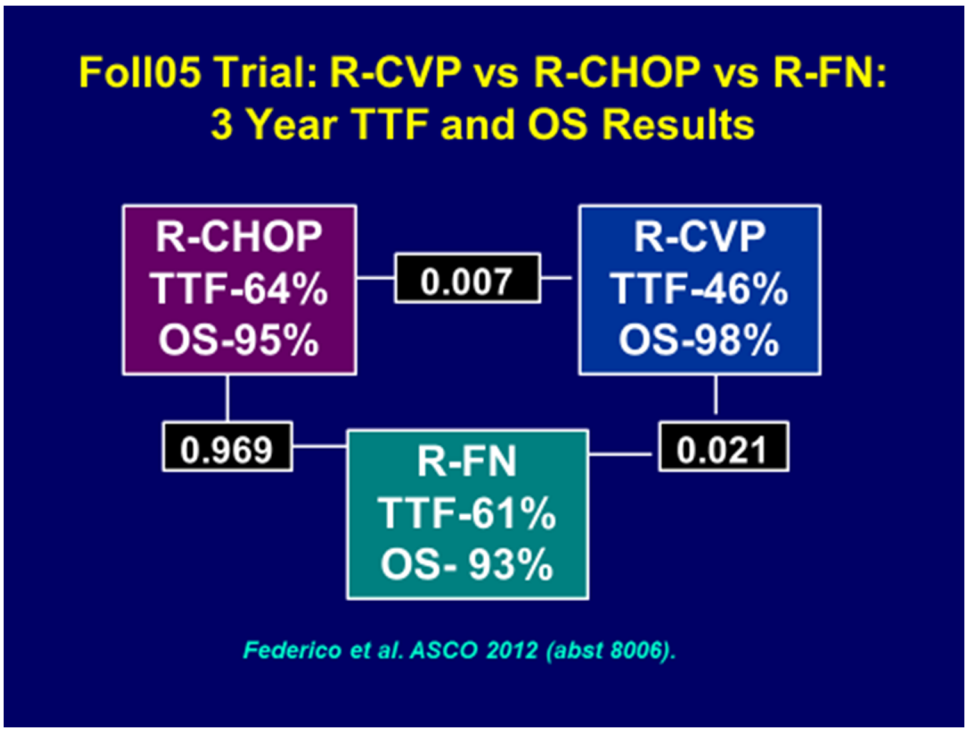
So, we're thinking about how to invent these different programs to come up with this outcome. This was also validated, not only in LymphoCare database, but also in the University of Iowa and Mayo's database. It was published by Casulo in the *Journal of Clinical Oncology*. And you can see the outcomes are quite different for those who have early progression of disease being the survival probability; and you can see there at about five years, it drops to about 50%. Every time the curve drops a little bit in this particular analysis, somebody has died. So you can see that these kind of curves predict the outcome of those particular patients and suggest that they need to be treated with something else earlier on.



Transformation is also not a good sight feature in this particular database. You can see the probability of remaining free of disease on the left-hand side, and the probability of surviving on the right-hand side. And what was important about this is that you may not need to do biopsies to determine whether patients have transformed; so there's certain clinical features that were looked at Vancouver, and they're listed at the bottom of this particular slide. You can look at that later. But the bottom line is that it may be now possible just for a physician to look and say, "This looks like transformation. Your LDH has gone up more than two times normal, or you've had very rapid single nodal growth, so you need to be treated as if you had transformed follicular lymphoma as opposed to indolent lymphoma.

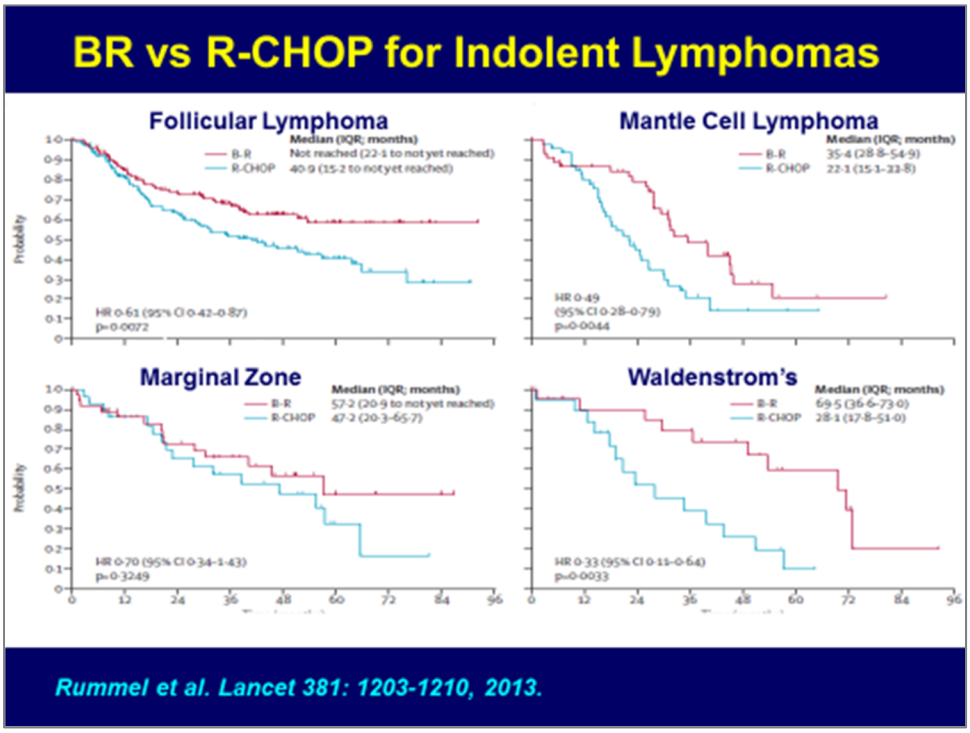


There's another feature that looked at, and all of us are interested in this, this was published not long ago. It comes from the German trials looking at 74 genes from 151 patients with follicular lymphoma who had received R-CHOP therapy. They looked at failure-free survival models, including starting off with a high-risk FLIPI and looked at these genetic features. And you can see these genetic features are listed on the right-hand side of that slide at the bottom. And you add all those together or in some cases where it's blue you subtract some of those, and you come up with a number that gives you an idea of what the risk of that person progressing within 24 months happens to be. So you can see the patient at the very beginning don't have to wait for 24 months to see which patients will survive or get into that risk group, and perhaps we can take those people using the M7 FLIPI now and figuring out how can we predict those people at the very beginning, looking at their lymphocytes, looking at their follicular lymphoma and figuring out, looking at their molecular features and trying to figure out. So it's very important to start thinking about this. It's not yet available, of course, but something that's going to be used on a regular basis. But it is definitely something to think about in the future.



So what kind of chemotherapy works the best? This is an Italian trial that looked at three different types of regimens—R-CHOP, R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) and fludarabine-based therapy. It turned out that the time to treatment failure was significantly better with R-CHOP than it was with R-CVP in patients who required therapy for their follicular lymphoma. The overall survivals, look at that, that's excellent at three years. And I can tell you that those features for those patients who receive R-CHOP, those patients are probably not going to hit 50% by ten years. It may be longer than that as far as survival rate. Now we tell patients that if they haven't had it relapse within five years, it may be 20 years that they will survive—that is to say no different from the average population.

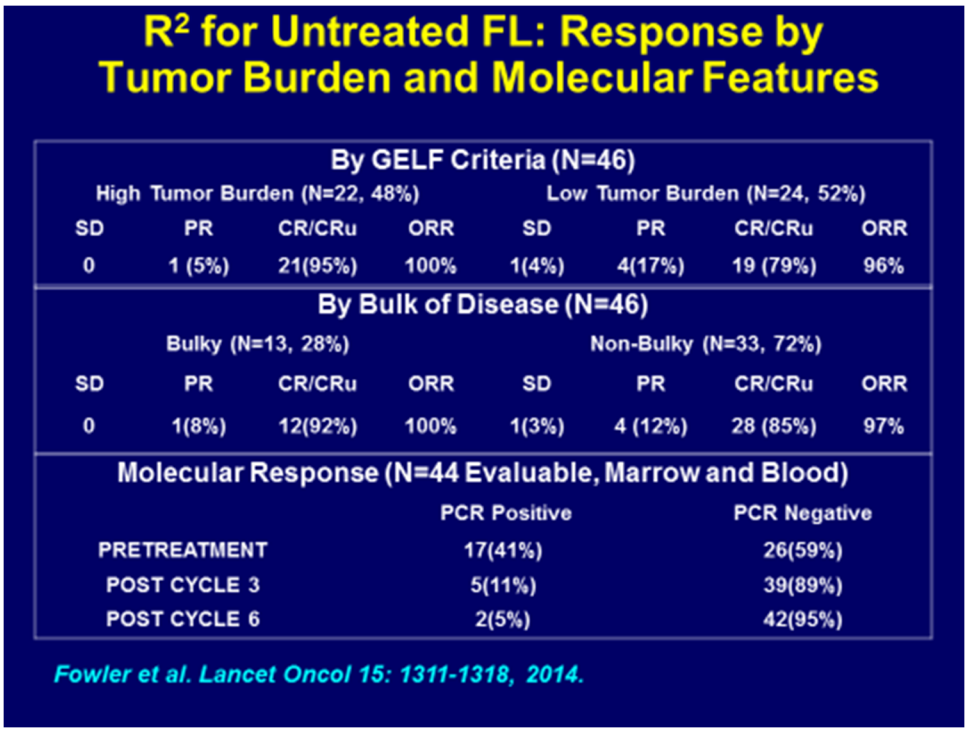
In addition, it turned out that the follicular lymphoma patients who were treated with FN (fludarabine-mitoxantrone) had a time-to-treatment failure that was similar and an overall survival that was similar to R-CHOP, but it was more toxic. So then their fludarabine-based regimen sort of lost in follicular lymphomas in this particular trial.



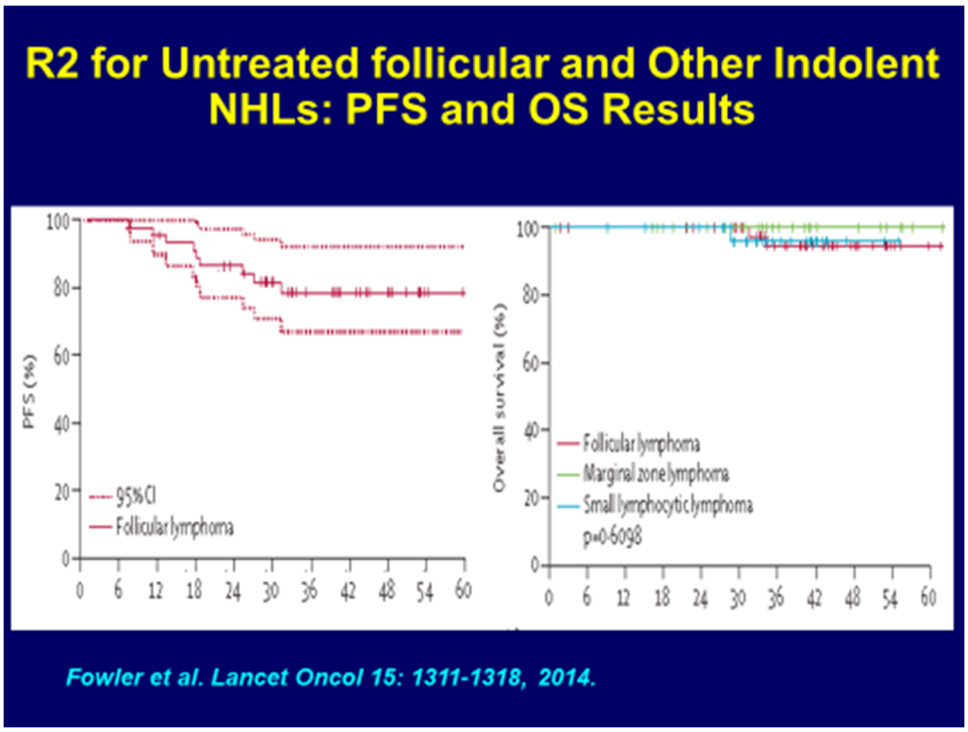
With bendamustine-Rituxan® (BR), a study that was done in Germany, and run by Dr. Rummel, a very important trial that demonstrated that patients who receive BR had as good results or perhaps better results than did patients who received R-CHOP, and BR was rapidly adapted in the United States and thought of as being an important regimen for follicular lymphoma patients and is used often for patients who have only nodal involvement and no extranodal disease.

American studies have not yet corroborated this information, and there has been some critique about this particular study because the R-CHOP treated patients, which is shown up on the left-hand side of this slide. Those in blue did not do as well as other people would have predicted.

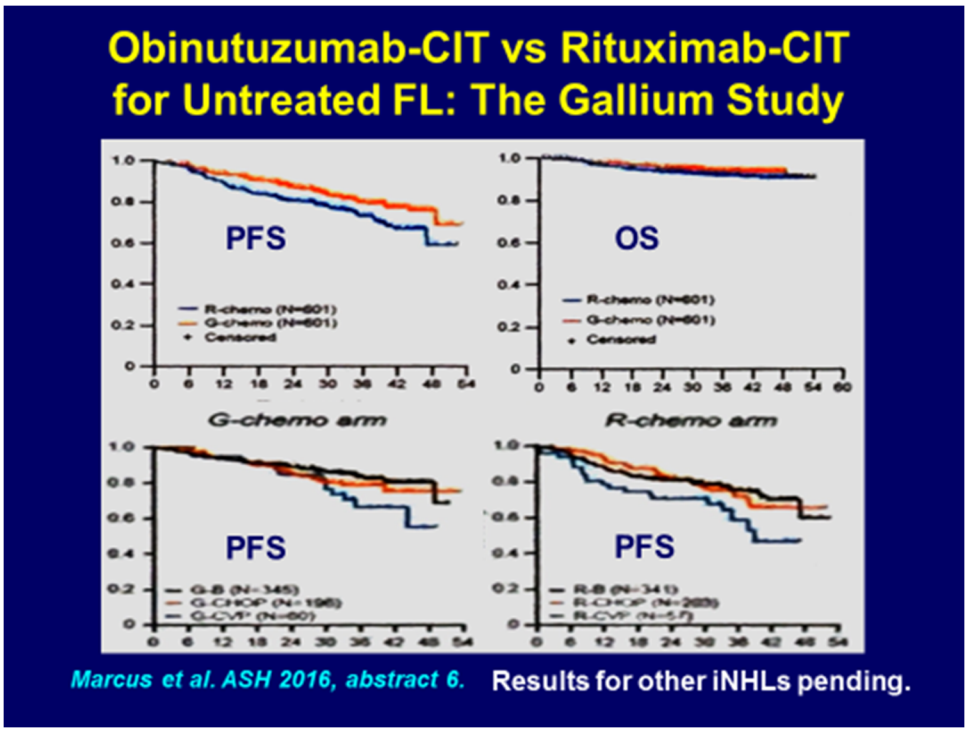
Mantle cell lymphomas, they didn't do very well with either, BR or R-CHOP. You can see that ultimately most of the patients did develop progression of their disease by five, six years. Marginal zone lymphomas did as well with either regimen, and Waldenström's also did better with BR. So it's an interesting group of patients that were treated, and it did set the stage for bendamustine-Rituxan to become a standard of care in the United States.



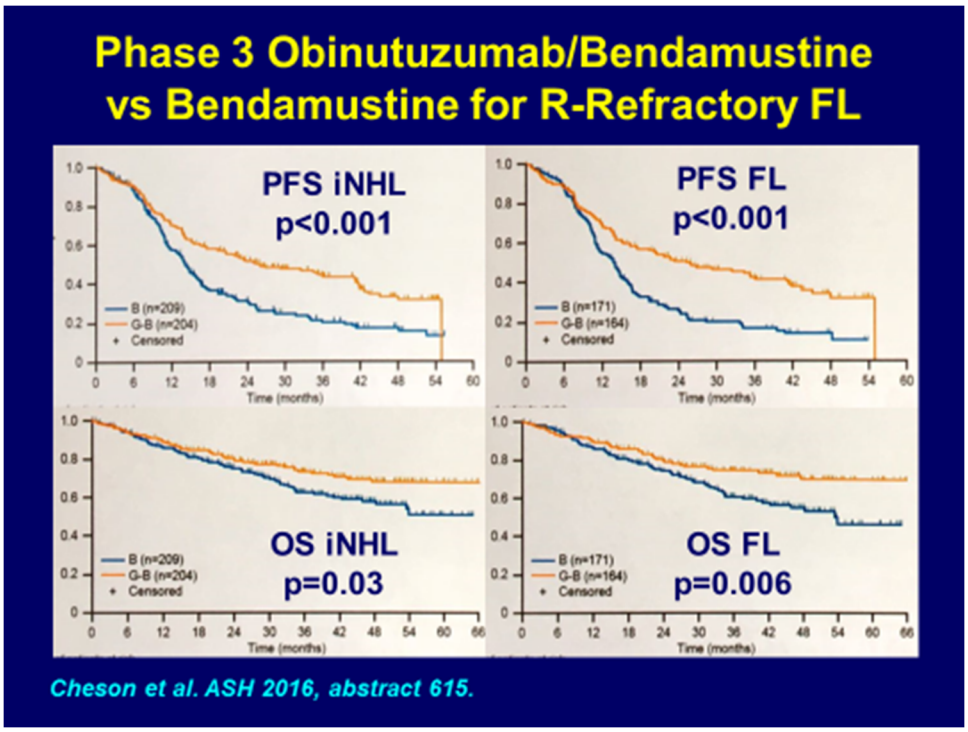
R-squared (rituximab) with lenalidomide was studied at our center for untreated follicular lymphomas, and you can see we treated these patients, regardless of what their disease was, and they had the indolent disease, all of them. However, they needed therapy; and you can see that patients who had high tumor burden, the complete response rate at our center was 95%. This is a pill and rituximab. Those with low tumor burden also had very high complete response rates. Even patients with bulky disease had high overall response rates and complete response rates. And we found that the molecular remission, that is to say having patients ending up with no signs of the disease on a molecular basis in their blood or bone marrow, was very high by the time they finished six cycles of treatment—95%. So we're very, very excited about that particular regimen.



There is a randomized study that is ongoing right now, or at least, I should say, it's been completed and we're waiting for the results comparing Rituxan and lenalidomide or R-squared versus rituximab and chemotherapy. And I am able to get lenalidomide for many of my patients based on this data. This shows you just what the progression-free survival was for follicular lymphoma patients. That looks very, very similar to R-CHOP. Notice at five years, that is 60 months, somewhere around 75% of these patients or so are still free of disease and haven't developed disease progression, and the survival rates over on the right-hand side, it just doesn't get any better for these particular groups of patients—with marginal zone lymphoma, SLLs or follicular lymphomas.

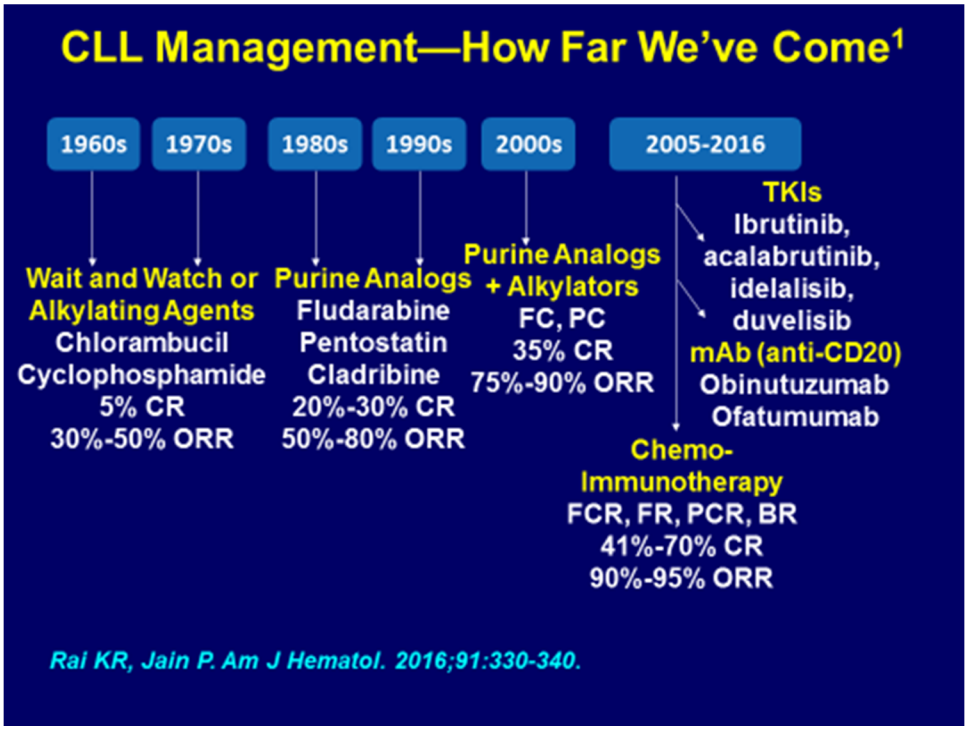


Obinutuzumab is a CD20 antibody just recently presented at ASH, American Society of Hematology, and it's a new monoclonal antibody. It's been around a while. It is rituximab bioengineered to work a little bit of a different way. And I want you to pay attention to the curve on the left-hand side, upper part. It shows you that those patients who received obinutuzumab, that is to say Gazyva®, that's the orange curve, did better when they got that drug plus chemotherapy versus those patients who got rituximab and chemotherapy. And the chemotherapy in this particular study was either bendamustine, CHOP or CVP (cyclophosphamide-vincristine-prednisone). Down at the bottom you can see that CVP sort of loses out completely, again, with either Gazyva (G) or rituximab; and that that little blue curve is lower than the curve with the other two. That is to say that G-CHOP or the R-CHOP or the GB (Gazyva-bendamustine) or the RB (rituximab-bendamustine), the overall survivals don't make a difference for R versus G. So you may see some pushback on this particular issue about survival because survival is better or survival's the same. You don't want to change from rituximab because rituximab is going to be cheap.



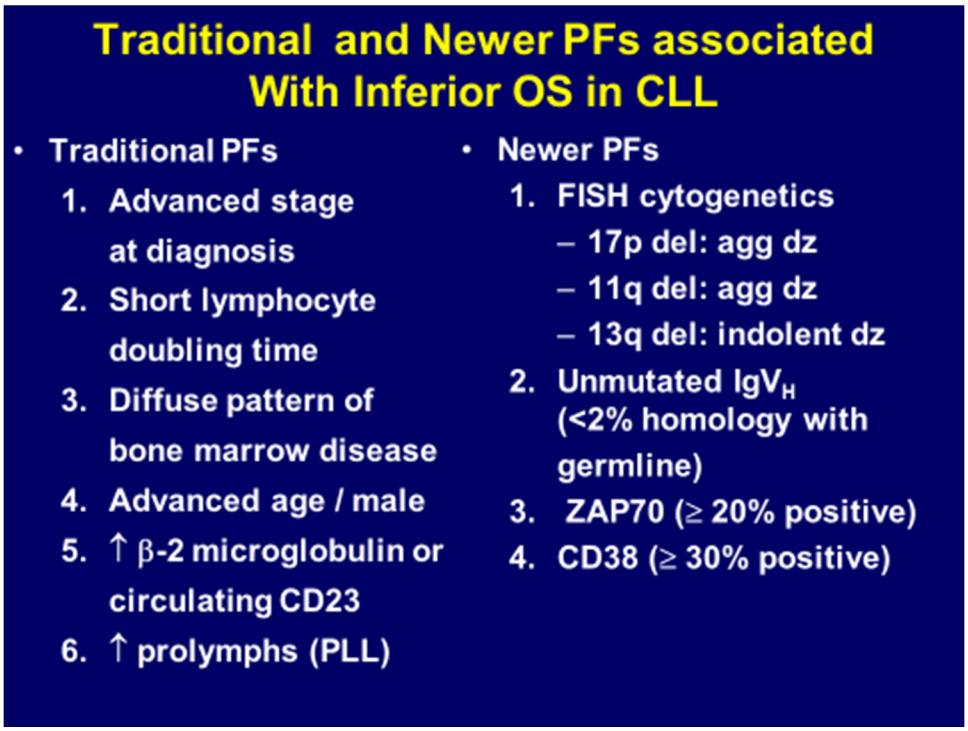
This is just additional data that was presented also for obinutuzumab, this new drug, plus bendamustine versus bendamustine for patients who have already been demonstrated to have rituximab-refractory disease. The progression-free survival was clearly better when patients received Gazyva plus bendamustine versus bendamustine alone. It was also better for the follicular lymphoma groups, and now the overall survival is also better. So if you happen to have disease that progresses with rituximab, you don't give rituximab for those patients. You give them Gazyva plus bendamustine if they haven't received bendamustine previously.

For CLLs and SLLs, we've changed a lot in how far we've come in management of those patients.



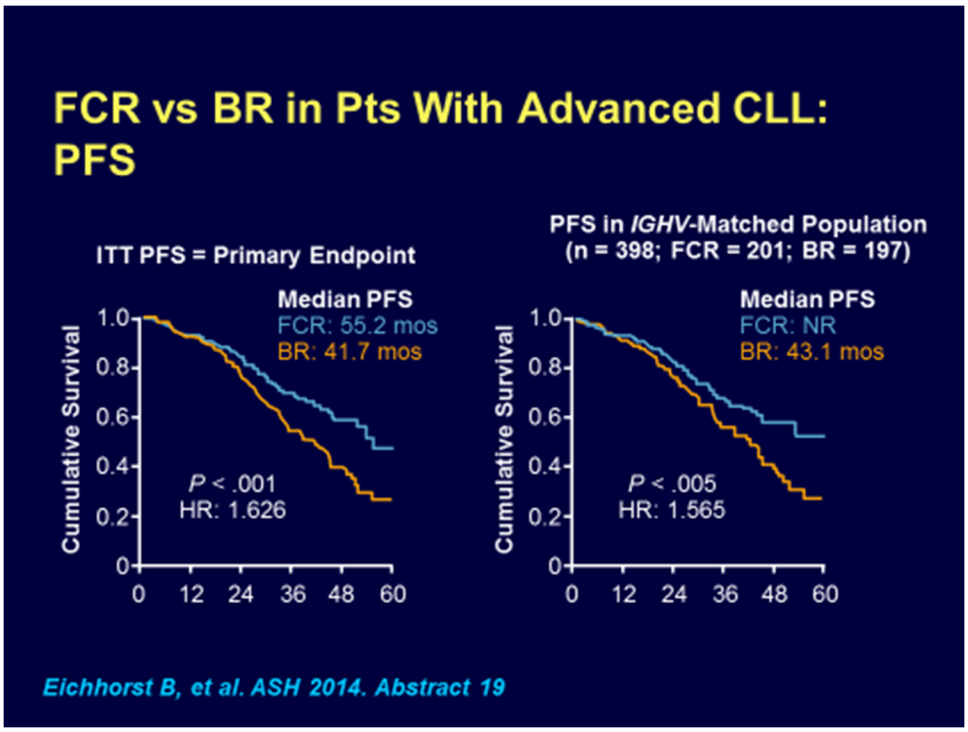
And shown here are kind of the CR rates and overall response rates we had in the '60s and '70s with some of the first drugs when we came along with the purine analogs.The overall response rates went

up, so did the CR rates. In the year 2000, we came up with FCR or I should say FC or pentostatin plus cyclophosphamide, and their CR rates were good and the response rates went even higher. And you know now that patients who receive chemoimmunotherapy can enjoy a 90 to 95% overall response rate and somewhere around a 50 to 70% complete response rate with those therapies. But now we've got all these other agents which are new, which are going to make a big difference in the management of patients with CLL and already have.

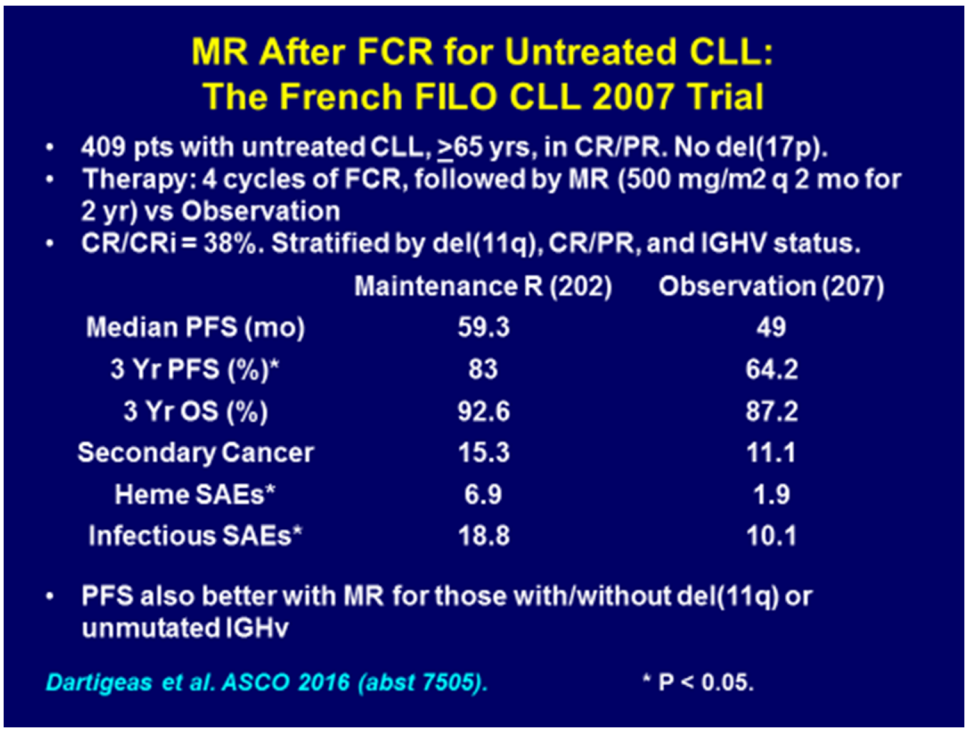


There are some prognostic factors that we associate with an inferior overall survival in CLL. Shown on the right-hand side are some traditional prognostic factors, but on the right-hand side are some features that I think are very important. It's the most important part of this slide. Prognostic factors include now cytogenetics of the lymphoma cell, of that CLL cell.

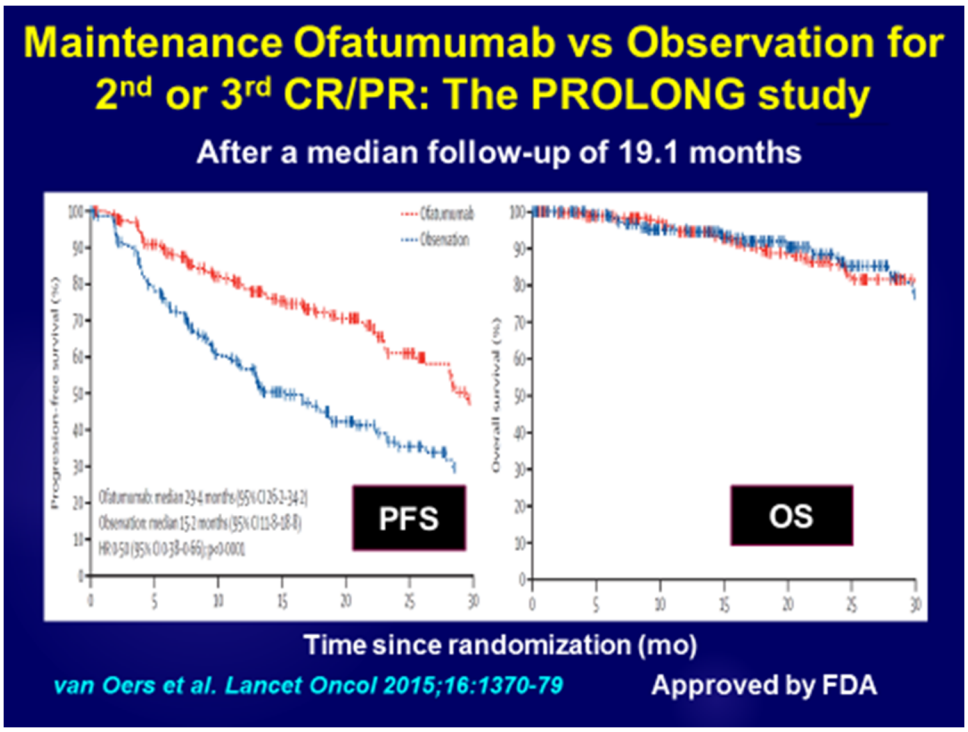
And in the recent analysis and we questioned, I didn't question or we didn't at MD Anderson, but those have questioned how often do you obtain cytogenetics in your patients with CLL? And it turned out that physicians in private practice only obtained cytogenetics on their patients with CLL in 25% of their patients. I think that's wrong and that needs to be something that needs to be pushed more. I think that now because we have drugs that will depend upon the cytogenetics of these patients, in particular 17p deletion that now we're getting patients getting more cytogenetics done on their cells. Also, mutational status plays an important role in the management of these patients; and we're finding out more that whether they're mutated or not makes a difference. If they're mutated, it's good. If they're unmutated, it's not good. And I would suggest that you ask further questions about that from your physician ultimately about what that may mean.



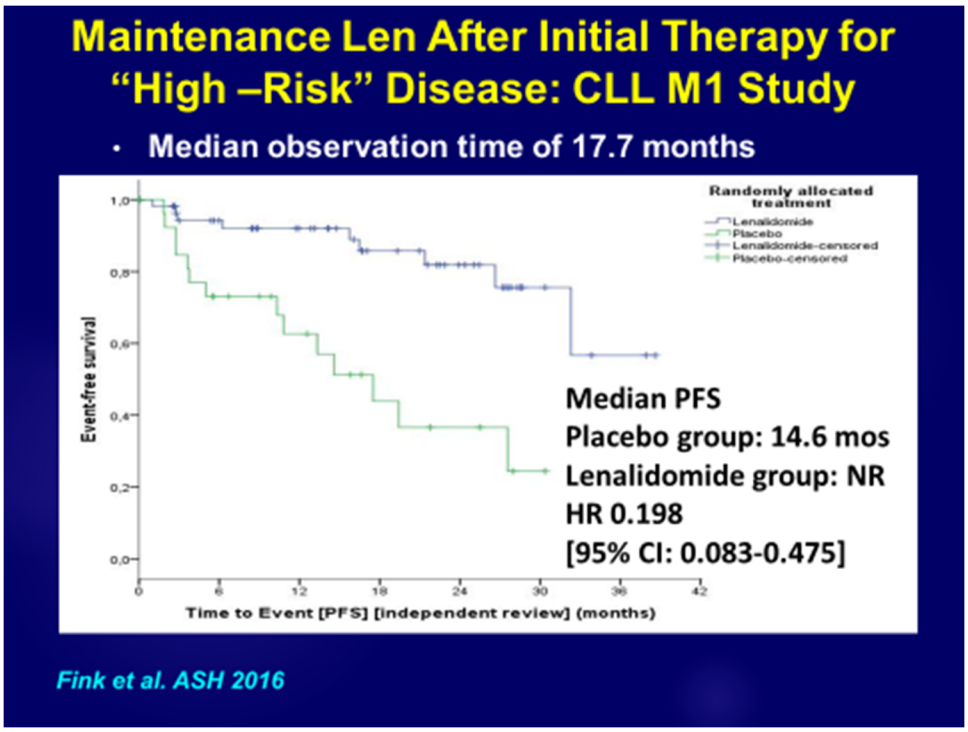
This is a study that looked at FCR, that is fludarabine, cyclophosphamide, and rituximab versus BR in patients who had advanced CLL. The progression-free survival still is better with FCR than it is with BR. BR was chosen and said, "Well, we can try to give bendamustine for those patients, but it's not as good as FCR, even in patients who are older." But still, patients who are older don't tolerate FCR as well as they do BR, so BR is chosen usually for patients who are older.



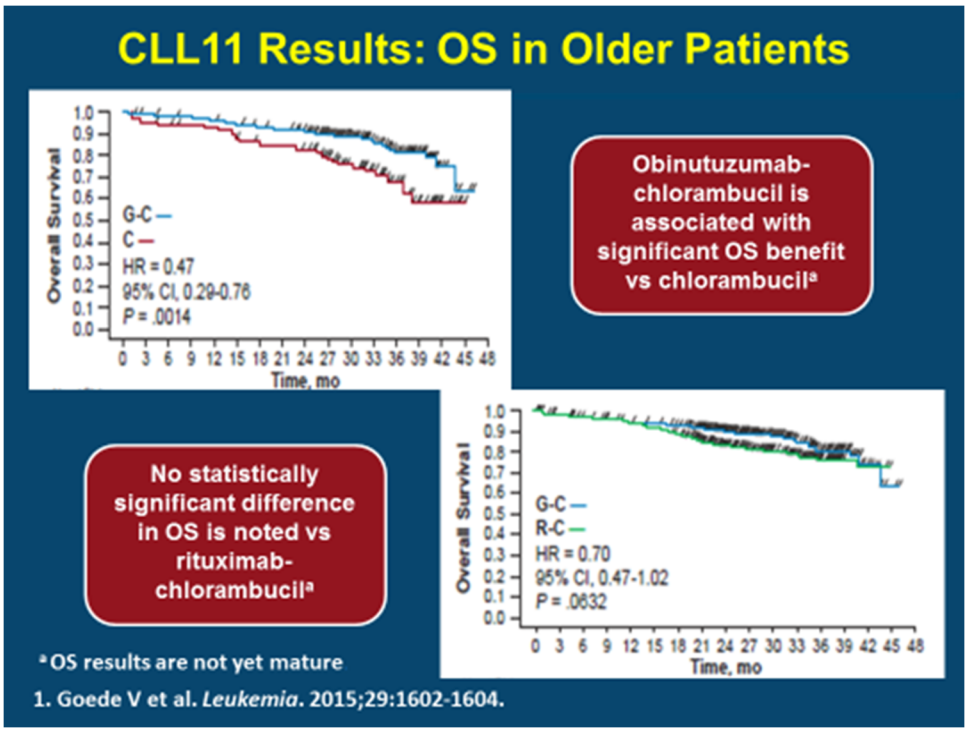
This is a study that looked at maintenance rituximab for patients who had untreated CLL, and it turns out that progression-free survival is better if you give maintenance Rituxan for CLL. We never thought that it would be so useful because rituximab is not, as a single agent, a very good drug for patients who have CLL. But it turns out that as maintenance, it appears to be a very, very good regimen. You can see that the progression-free survival at the sort of middle of the slide, the progression-free survival is really great, is 83% versus only 64% for those who are on observation. And the overall survival, also, looked like it might be better, although marginally improved by about 5% because these patients, you'll have to follow them out for five or even ten years to see whether there's a major difference.



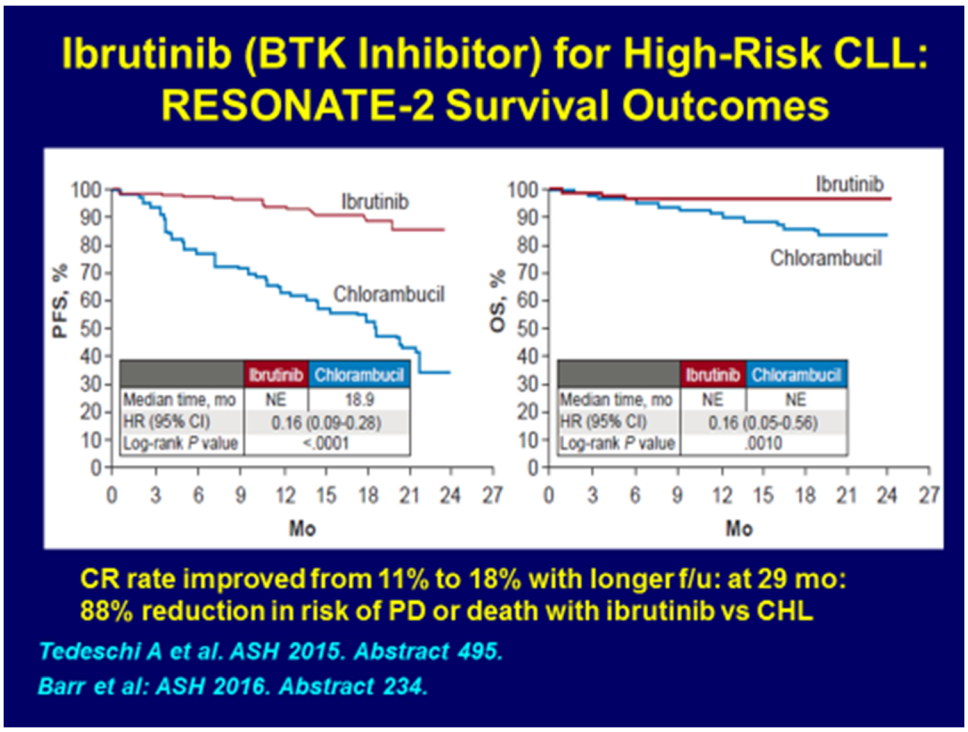
Also, ofatumumab has been studied in patients who have relapsed CLL, and look at this. This is patients who are in second- or third CR or PR. It's called the PROLONG study. It was recently published in *Lancet Oncology*. And those patients who received ofatumumab, another antibody that is directed against CD20 turns out to be a very good drug to keep the patients from developing progressive disease. This is something we wouldn't have known had not clinical trials been performed. Unfortunately, in the United States, it's very difficult to perform clinical trials. Only about 3 to 5% of patients with lymphoma go on to clinical trials ultimately; whereas in Europe, it's 50%. They can do these studies.



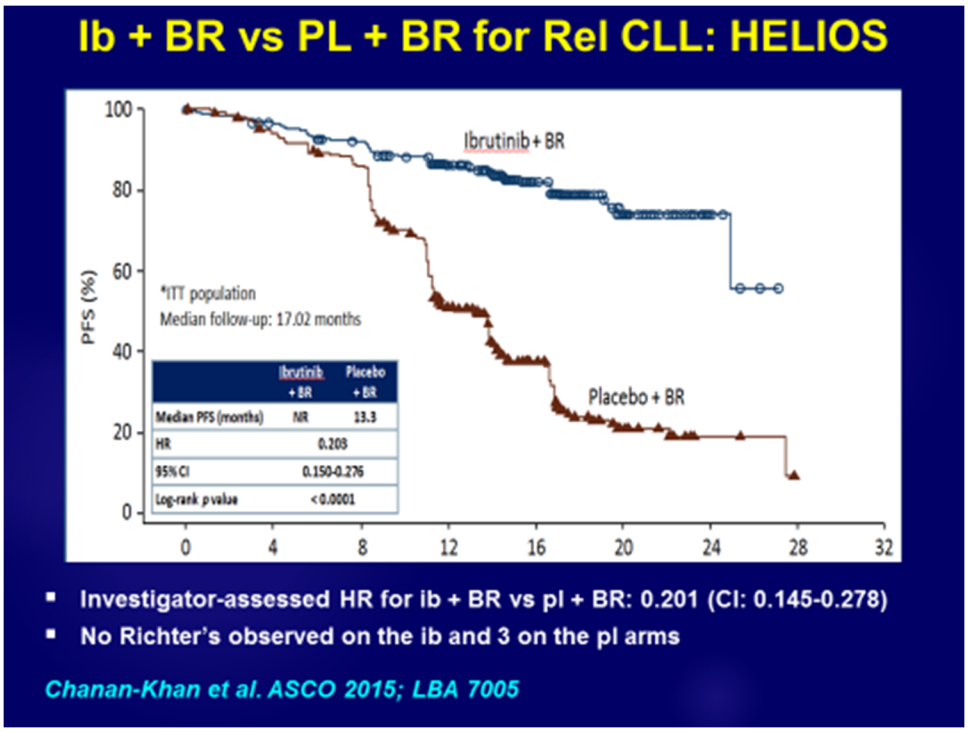
Lenalidomide has also been studied after initial therapy for quote "high-risk CLL," and the difference is very striking here, with the progression-free survival being quite good in those patients who received lenalidomide after having been induced into remission with therapy versus placebo. So, again, you've got to ask yourself is it worth taking these particular drugs over a longer period of time?



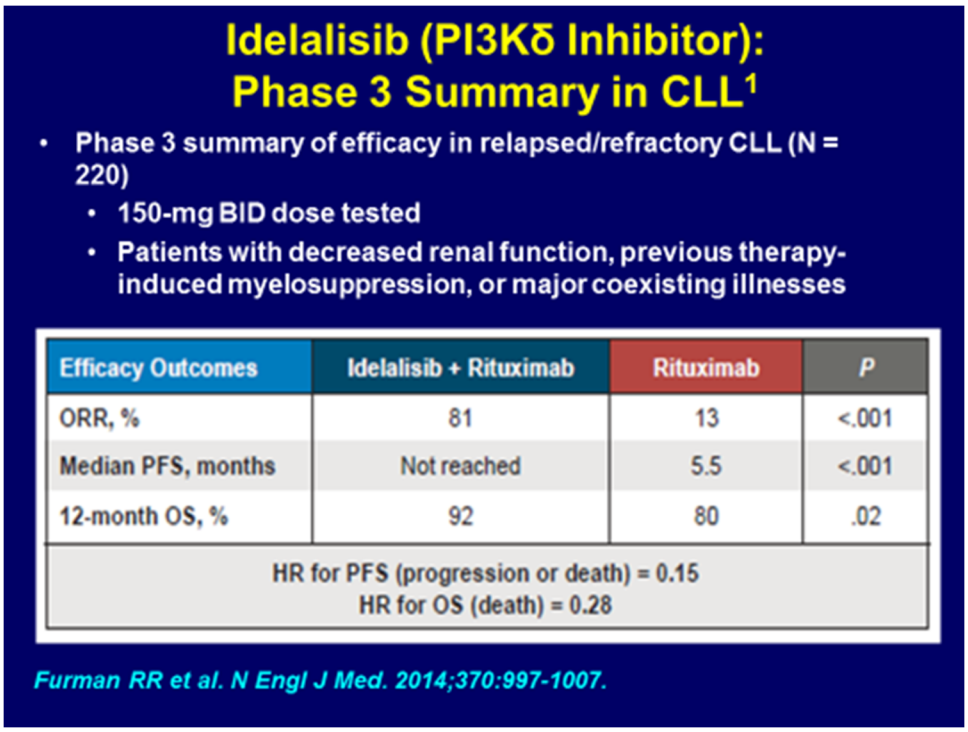
These are results in older patients who also received obinutuzumab plus chlorambucil, just looking at how that did versus chlorambucil alone. It's why obinutuzumab-chlorambucil was judged to be a better combination than chlorambucil alone. And why did they choose chlorambucil, because it was a drug that was approved by the FDA. So obinutuzumab and chlorambucil became a standard of care. Overall survival was significantly improved and now is a treatment choice for patients who are older.



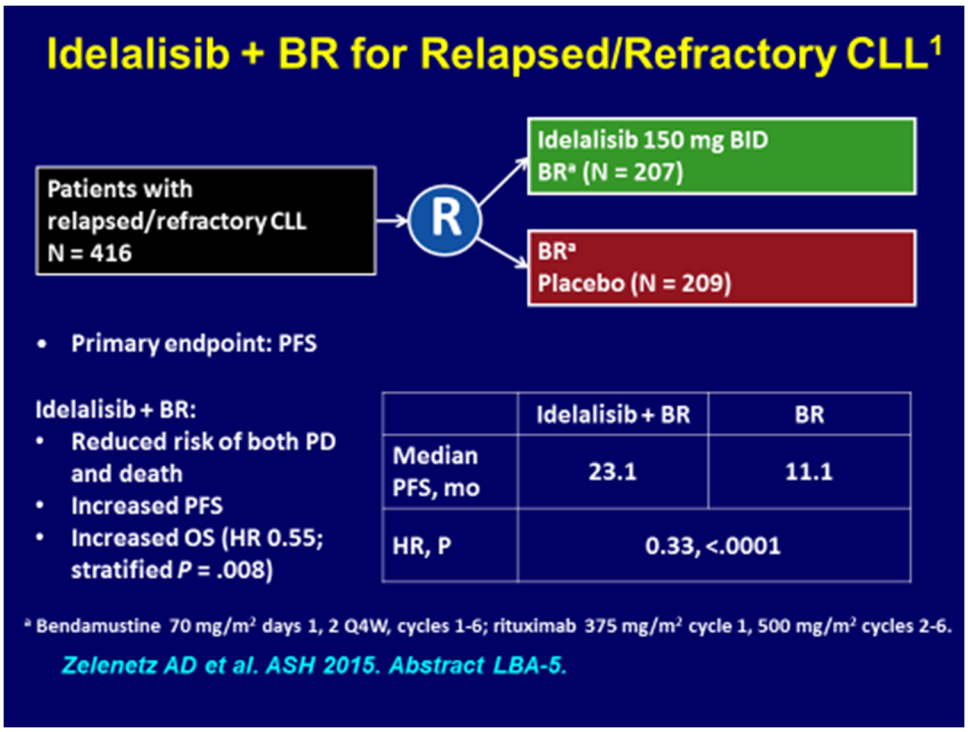
But there may be better therapy coming along. And that happens to be this particular drug, ibrutinib. This looked at patients who received either chlorambucil or ibrutinib for their disease. And look at not only on the left-hand side is the progression-free survival, which is striking, but on the right-hand side, survival. So once you see survival outcomes, you all of a sudden say, "Oh, my gosh, this is a drug that we've got to take. You can't take chlorambucil." Whether the combination is better is a question, but I don't know how you're going to get at survival and progression-free survival that looked like that top curve does on either side of the slide by giving the combination.



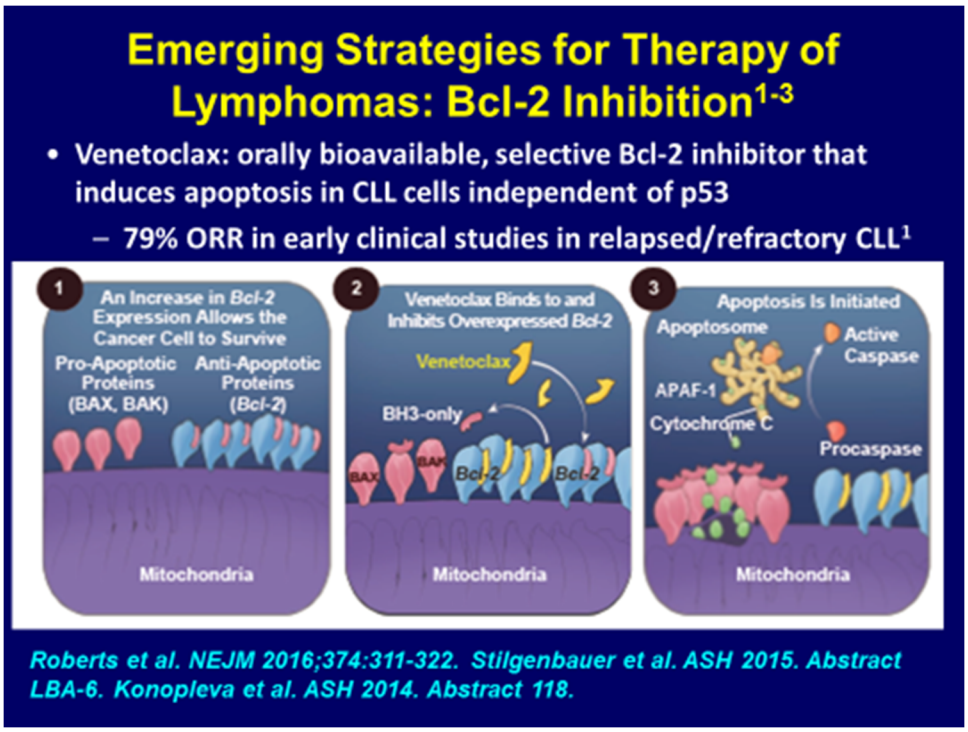
This is ibrutinib plus the bendamustine-Rituxan versus placebo versus, plus bendamustine-Rituxan for relapsed CLL. And you can see the ibrutinib adds a lot in here. We don't know how ibrutinib versus BR will eventually compare. That study has never been done. But I would bet that, and everyone's betting on ibrutinib is a great drug, is going to work great in CLL. So everybody's getting ibrutinib now and no chemotherapy at all.



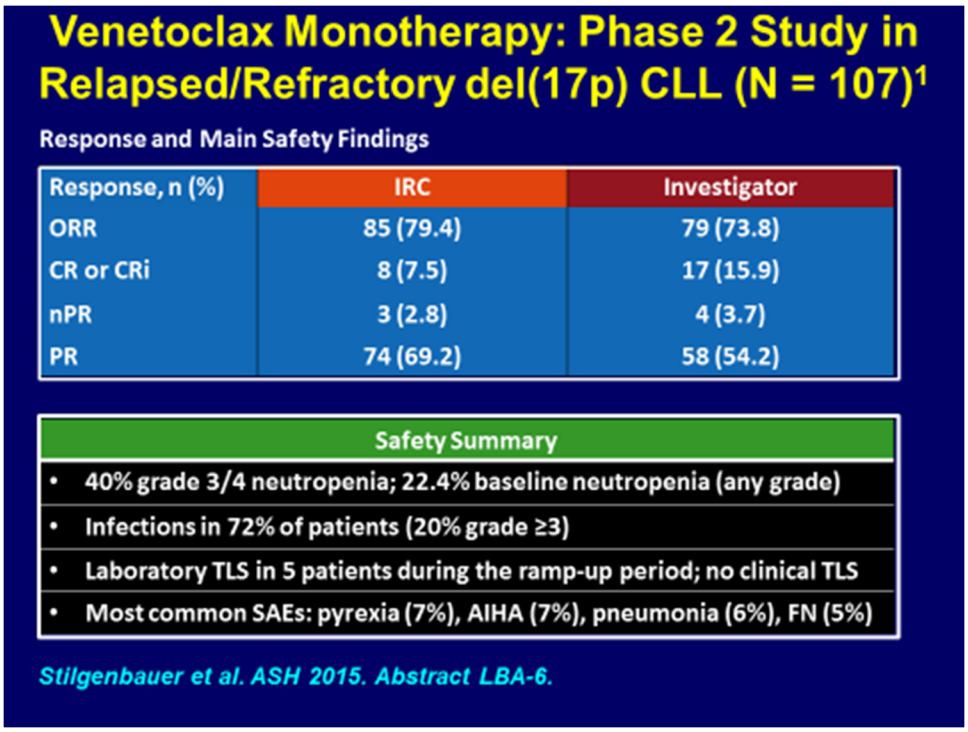
Idelalisib is another inhibitor that looks like it may be better than just standard chemotherapy. This is a study that looked at idelalisib plus rituximab for relapsed disease, and you can see that it's way better. The overall response rate's 81 versus 13% and overall survival is 92 versus 80% at a year.



So this drug was also approved for treatment of CLL in relapsed. It's also been studied in combination with bendamustine-Rituxan versus bendamustine-Rituxan alone. I didn't want to leave this study out because you can see that it's clearly better as far as progression-free survival is concerned. But this was a study that was presented, 416 patients presented by Dr. Zelenetz from Memorial Sloan Kettering.

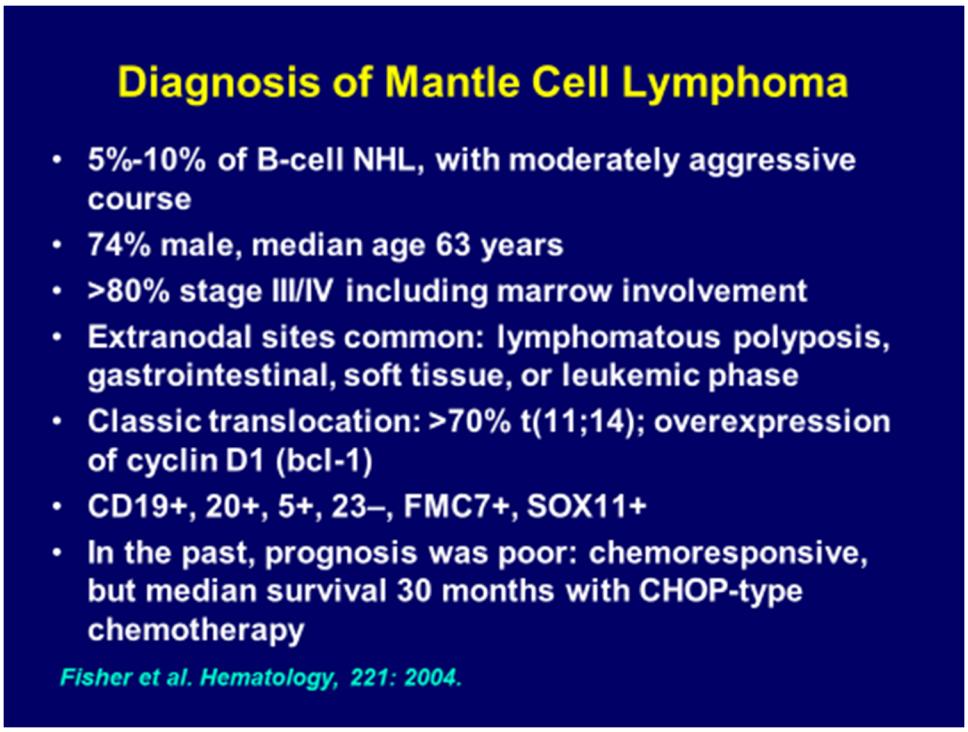


I have to mention venetoclax. It's an anti-BCL2 drug, and just shown here is the whole concept between BCL2 and BAX. They're two different kind of proteins that can be expressed by cancer cells. On the right-hand side of each of these little boxes is BCL2. This is the protein that keeps cells alive longer than they would be if they didn't have it expressed. In the left-hand side shows you the BAX, which makes cells die. If you happen to block BCL2 expression, than BAX becomes more prominent, and the cell dies. And so we haven't used that where BCL2 is overexpressed.

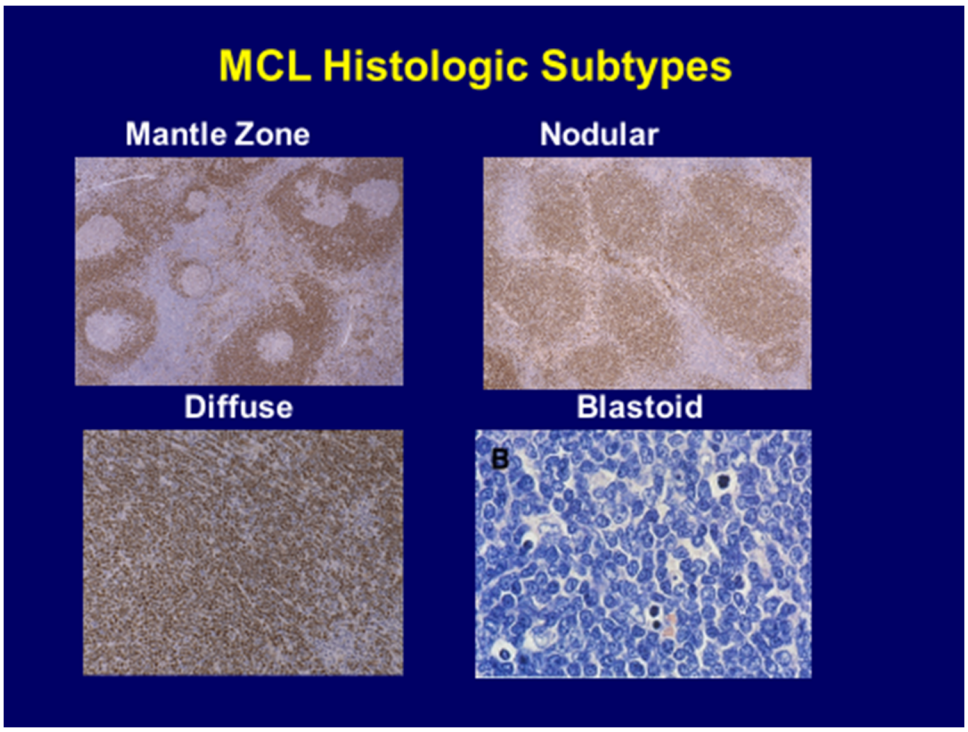


This is a study that looked at venetoclax monotherapy in high-risk patients, and the overall response rate was extraordinarily high. The complete response rate about 10% overall.

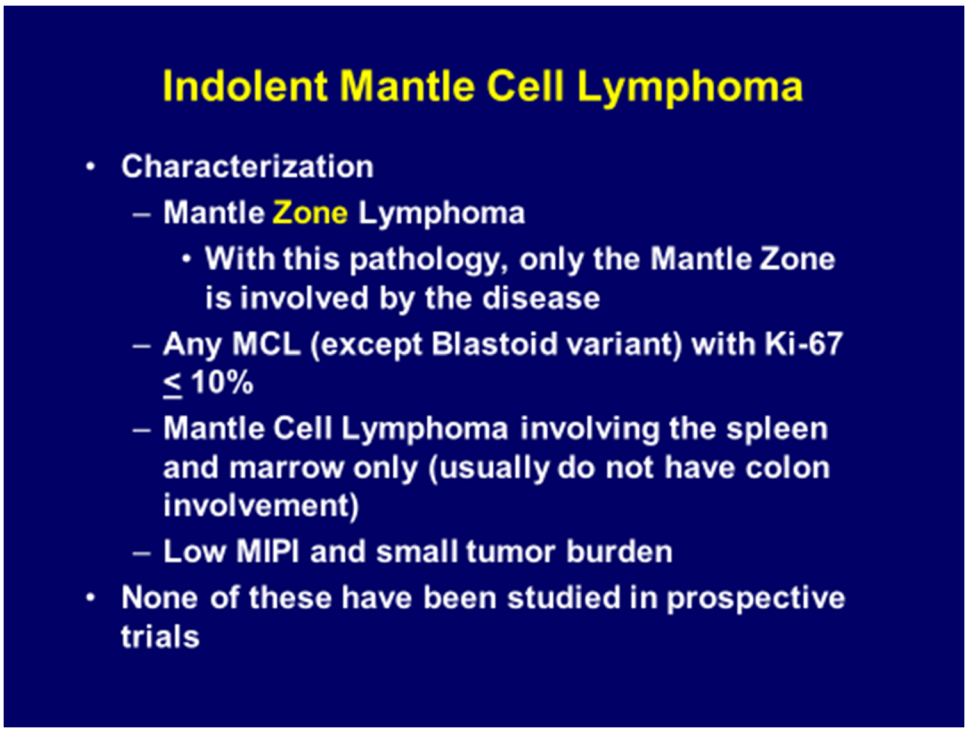
I just want to show you a little bit about mantle cell lymphoma.



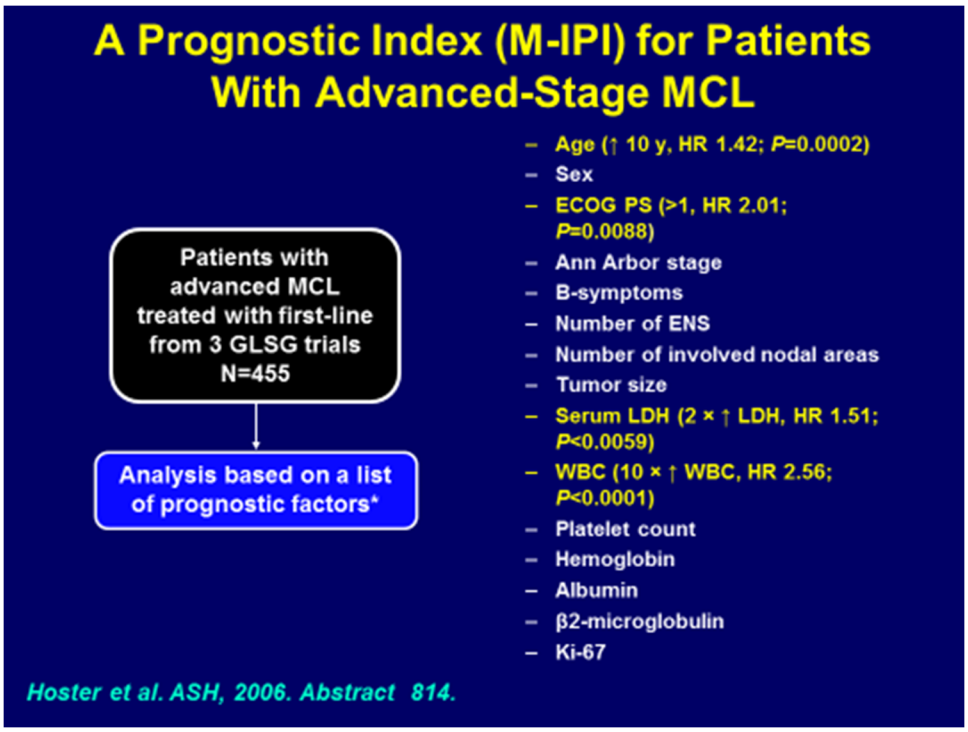
It is relatively rare at our hospital, not rare. For some reason, it mostly occurs in men; and most of them have marrow involvement and extranodal sites of disease, that is to say gastrointestinal tract are very common. It also has the classic 11;14 translocation. They look like this.



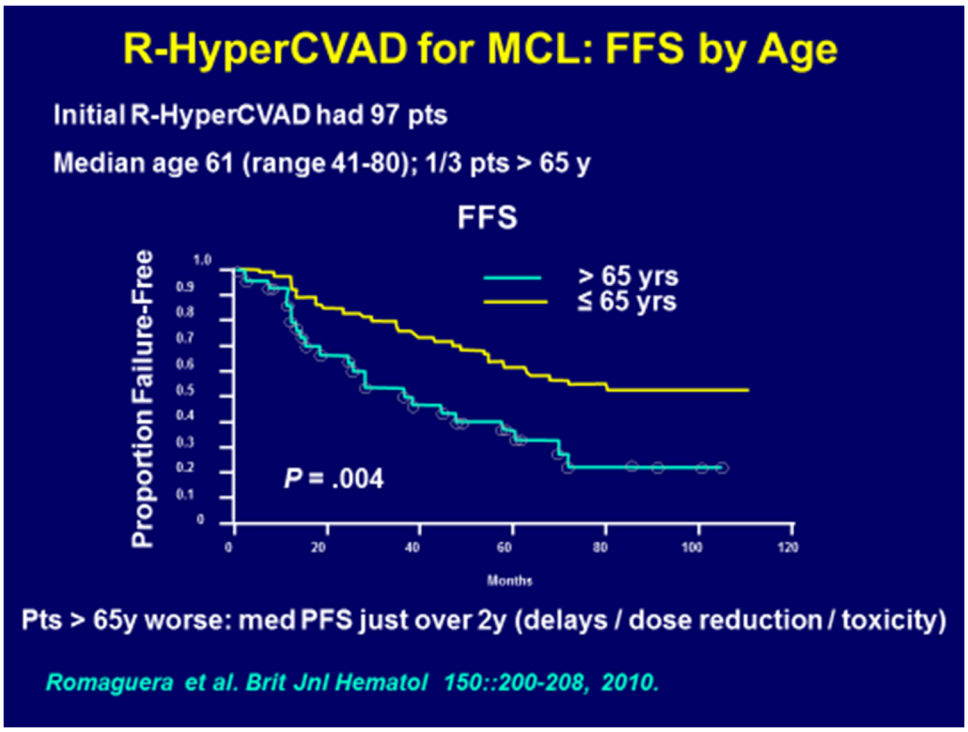
On the left-hand side is mantle zone involvement only, nodular mantle cell diffuse as it involves the lymph node and then blastoid variant, which is a bad risk disease.



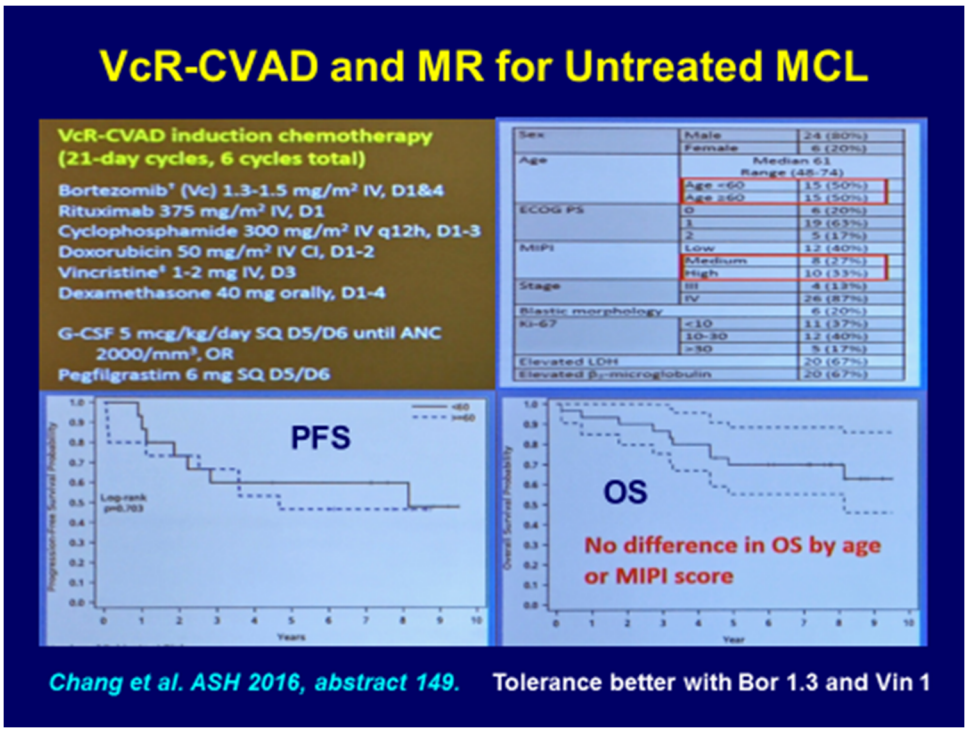
Mantle zone lymphoma is a very slow growing disease, and I'm going through these slides because the end of the hour is getting close.



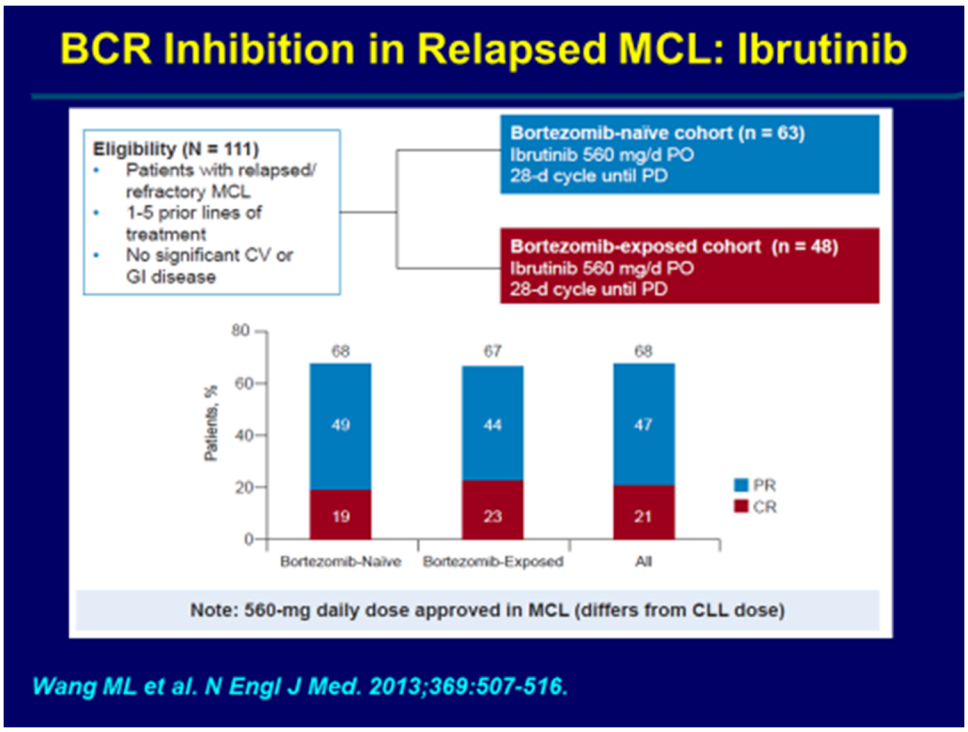
There is the MIPI (Mantle Cell Lymphoma International Prognostic Index) score that has also been used to try to tell us which patients will do better. It looks like the FLIPI in a way. It was devised specifically for mantle cell lymphoma.



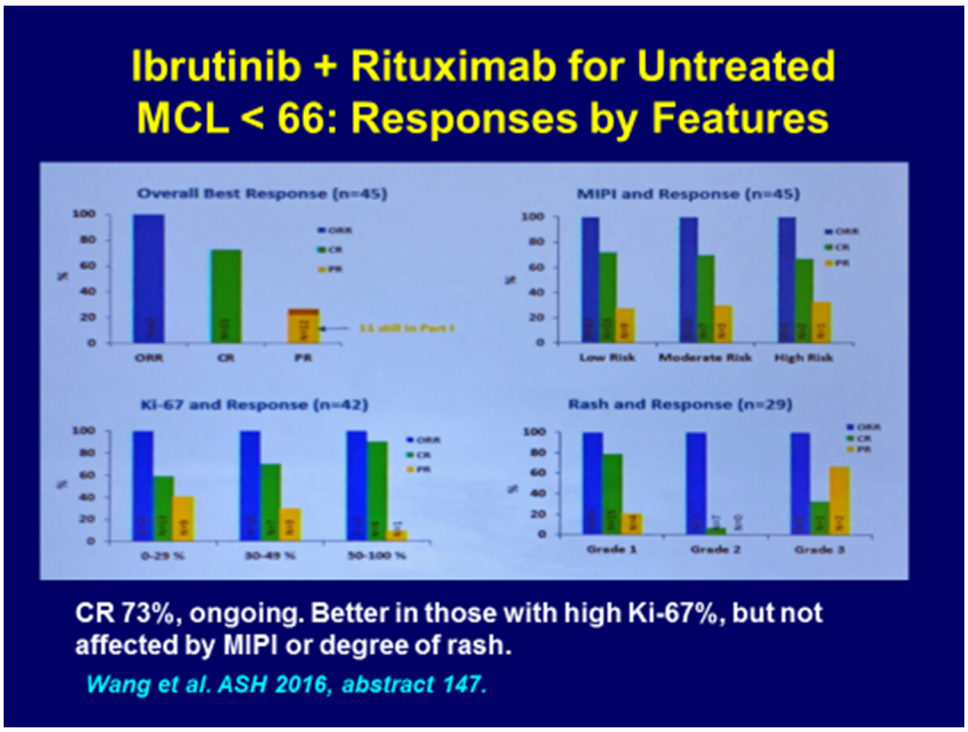
R-hyperCVAD (cyclophosphamide, vincristine, doxorubicin) has also been used for mantle cell lymphoma and was the regimen used at our center for a long period of time. And you can see that patients who are over 65 don't do as well with this particular regimen. That's why BR came along.



When you add Velcade® to the R-CVAD regimen, you may do better without giving the Ara-C (cytarabine)-methotrexate. In this study they also gave maintenance rituximab.

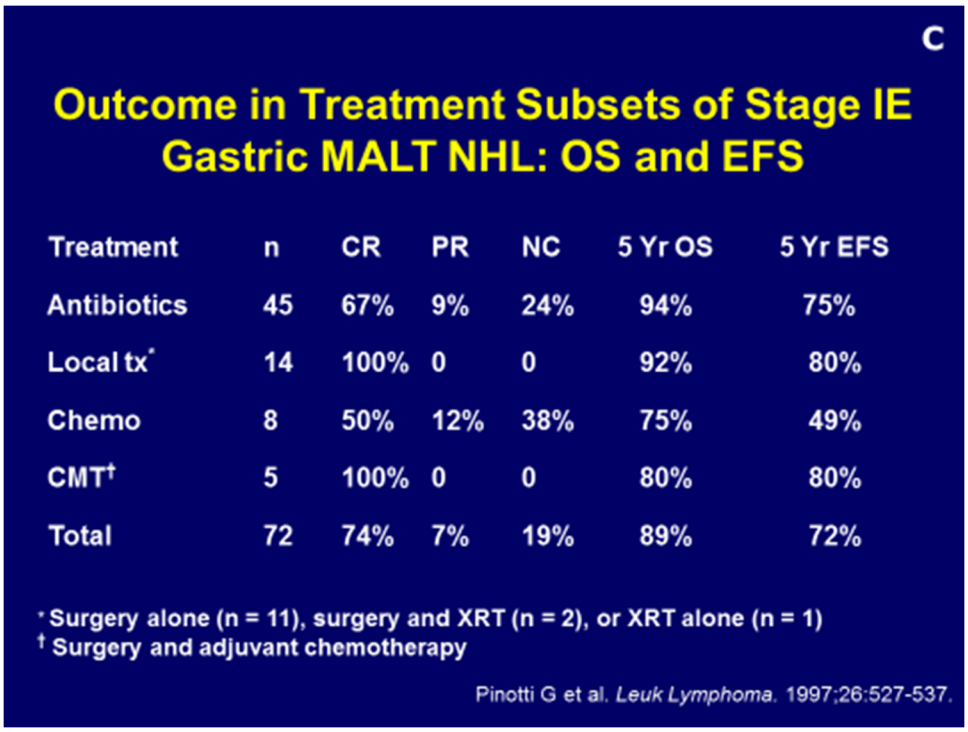


Finally, ibrutinib came along; and here you can see ibrutinib is used in bortezomib-treated, that is Velcade-treated patients or those who didn't have exposure to Velcade before. And mantle cell patients responded regardless of whether they had previously received that drug previously.

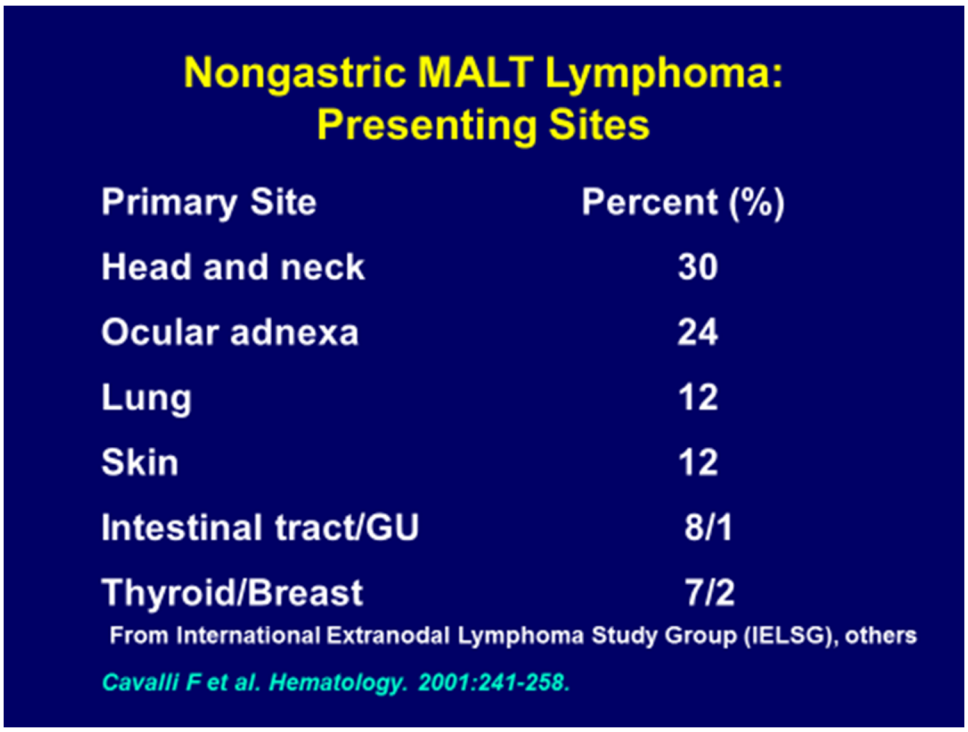


I'm just going to skip that slide because I know that the time is close here at the end.

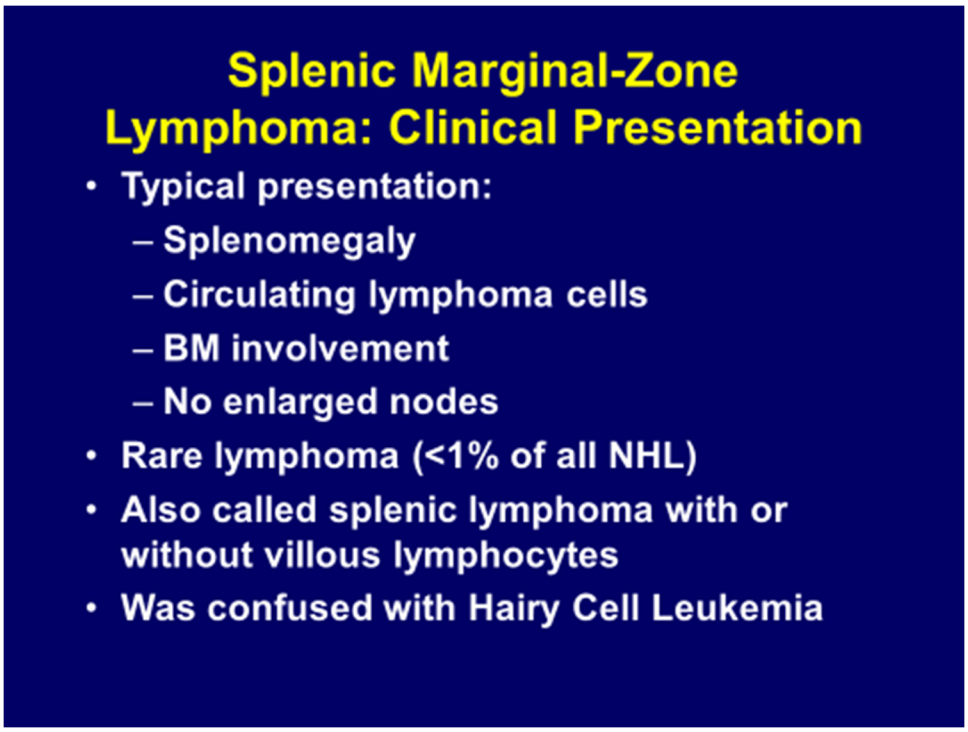
Marginal zone lymphomas, because I know there may be 10% of patients who have lymphoma have a marginal zone lymphoma. It has not been studied very well. The reason is because it is so different, the way that it presents.



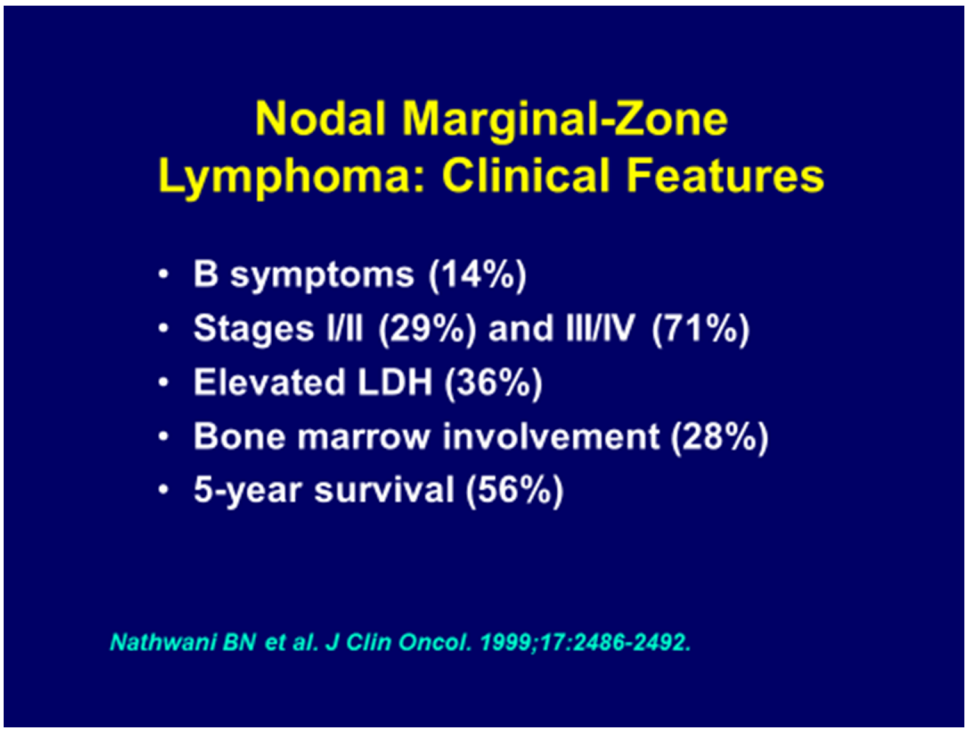
The gastric marginal zone lymphomas are often treated with antibiotics and go into remission. They're very slow growing lymphomas and do quite well.



Nongastric lymphomas, marginal zone lymphomas or MALTs (mucosa-associated lymphoid tissue), can present in any particular soft tissue area—bone, they can be in breast, they can show anywhere in the body and they usually occur because of some inflammatory process that is ongoing.



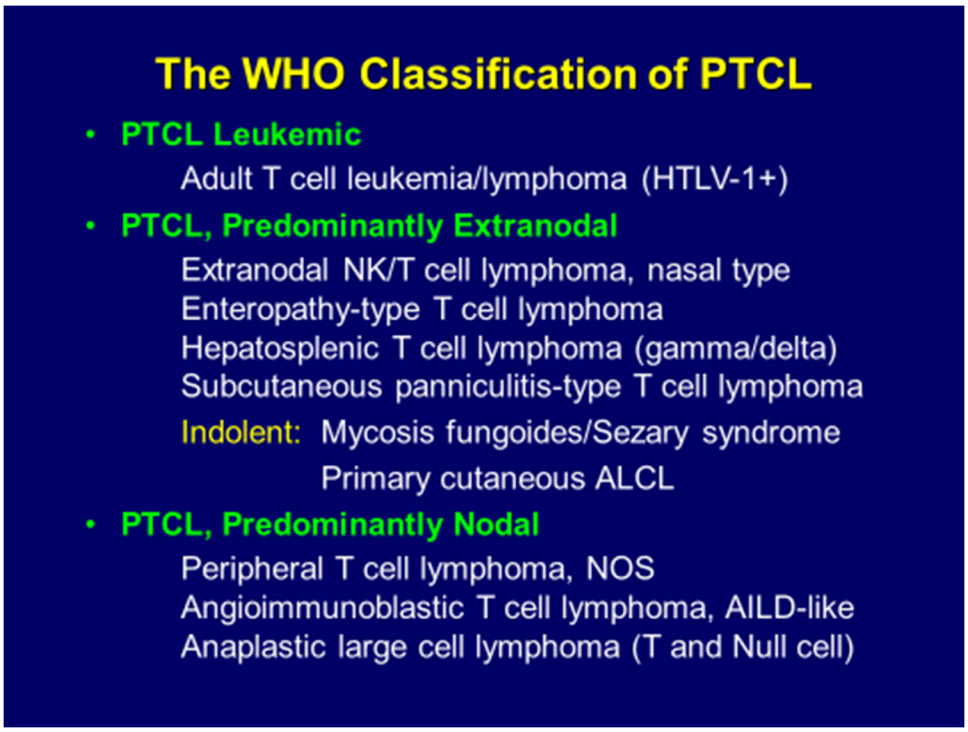
A typical presentation for a patient with splenic marginal zone lymphoma is a big spleen, circulating lymphoma cells, and is very, very easily treated with rituximab these days and is considered a treatment of choice for this particular disorder, rather than removing the spleen.



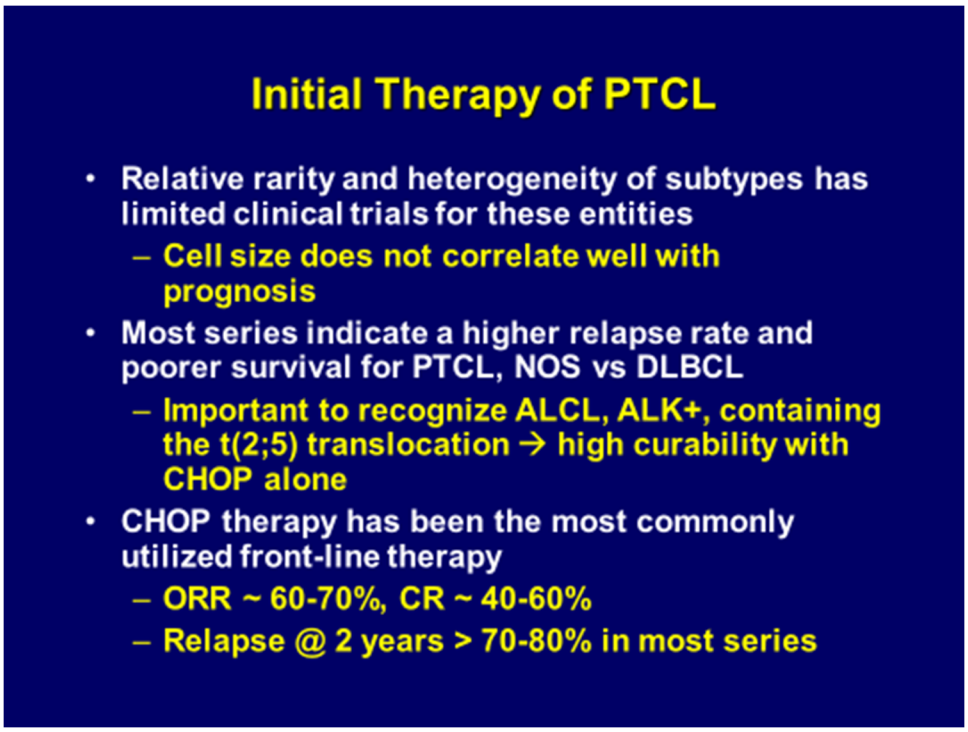
Nodal marginal zone lymphoma, which is the other variant, a third variant, nodal varieties, extranodal, and then splenic marginal zone lymphoma. The nodal variety is one of those that is supposed to have a lower survival. I think it's been confused with aggressive lymphomas at some time, and we're not really sure how to best manage those patients at the current time.

Therapy is very difficult to decide. It is individualized. At the bottom you can see that radiation therapy often works for patients. Single-agent rituximab or BR also works, and some of these newer agents also work.

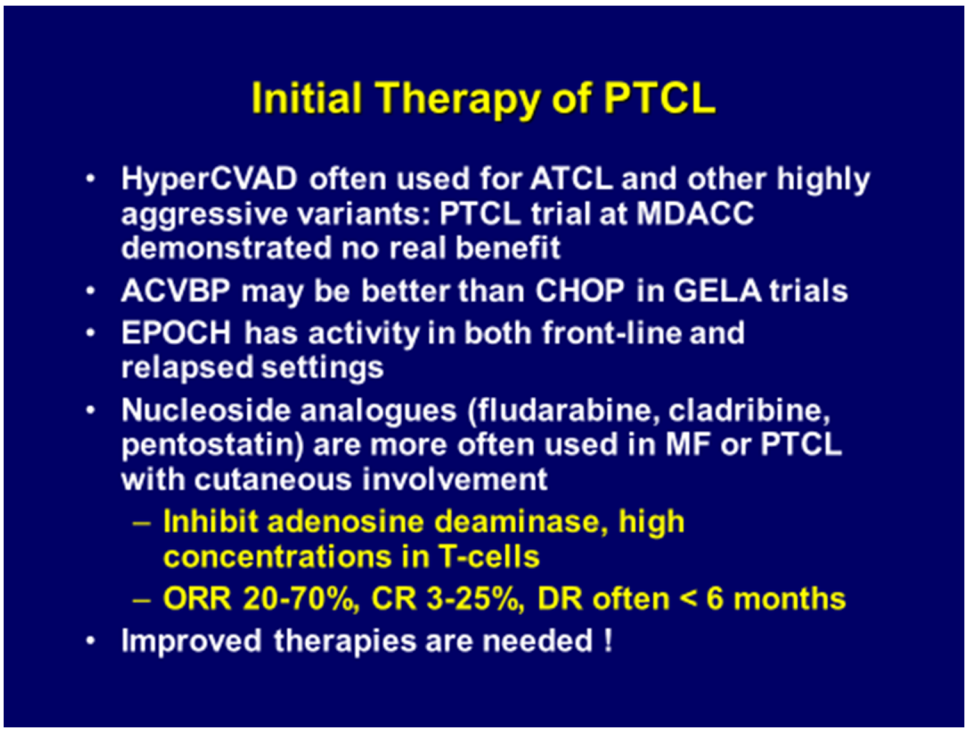
I want to pass on T-cell lymphomas a little bit because one of my patients told me that they would be watching this.



There are a variety of different PTCLs or peripheral T-cell lymphomas, interestingly, that they are usually diagnosed according to where they occur in the body, as opposed to different markers. And we're still trying to figure out how to best determine how to classify these illnesses. The cell size of these cells doesn't correlate well with prognosis. It is important to notice whether they are ALK- (anaplastic lymphoma kinase) positive as far as a marker.

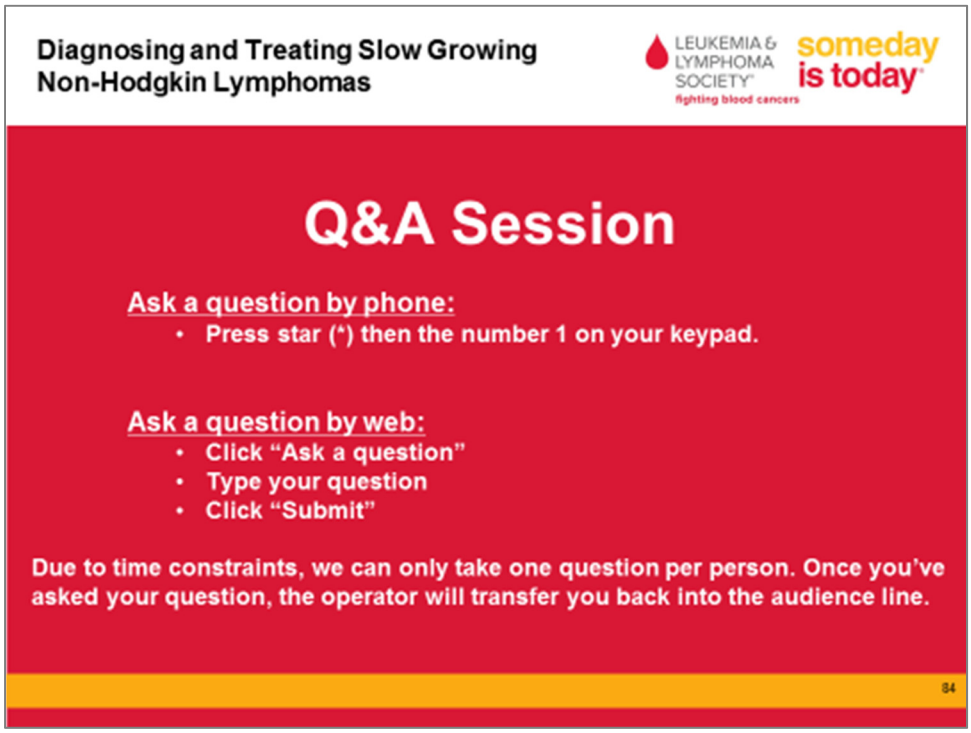


Those appear to be highly curable with CHOP therapy alone, but a very small percent of patients will be ALK-positive. And CHOP has been used as the standard of care for most of these patients.



There are other regimens that have been attempted, and purine analogs appear to be doing better than these others.

QUESTION-AND-ANSWER SESSION



Fredrick Hagemeister, MD
So I want to open up now the rest of the time that we have, and I'm willing to go a little bit more, a little bit longer, certainly, and discuss some of the questions that came through not only the Web but also on the phone.

Lizette Figueroa-Rivera, MA

Thank you so much, Dr. Hagemeister, for your very clear and informative presentation.

Lizette Figueroa-Rivera, MA

Our first question comes from the Web. Dana asks, "How do I manage the stress of watchful waiting and how do I know when and why to call my doctor?

Fredrick Hagemeister, MD

That's a really good question. Most people whom I have who are, well, I will say, once they come to me and see me and I say, "You know, you don't really need therapy right now." And I will often try to reassure them and say, "You know, what we're going to do is, we'll see you. You had this disease for a while. So if you've had it for a while and you're not getting sick from it, then what's another four months going to do?" And so they eventually understand well let's look at it again with CT scans in

another four months. In other words, it doesn't mean waiting and ignoring. It means waiting and being certain that it's not getting out of hand or that something's not happening.

In one study that looked retrospectively at patients even who were observed, 8% of those patients actually went into some type of remission, just by observation, meaning their own body took care of the lymphoma for some period of time. Eventually those patients developed progression and needed therapy, but the bottom line is unless your nodes are not big enough, three centimeters is like one-and-a-half inches in diameter. It's really small. So you have to realize these are small nodes that are not causing problems. If you have pain or something new happens, realize that you're going to get back to your doctor; and your doctor needs to tell you, "Hey, if you've got a problem, just call me and I'll see you right away."

Lizette Figueroa-Rivera, MA

Thank you, doctor, and the next question comes from the telephone audience.

Operator

Thank you. Our question comes from Tom, calling from Colorado. Please state your question.

Tom from Colorado

I'm going every four weeks for an infusion with rituximab, and then I'm also using at home twice a day a pill called Zydelig®. I just wondered if he had any comment on what the Zydelig, a relatively new but I didn't hear you mention that, at least by the name Zydelig.

Fredrick Hagemeister, MD

Yeah, yeah, because that is idelalisib, so that I did mention. It's used commonly in patients who have small lymphocytic lymphoma or who've had CLL, and it is approved for treatment, second-line treatment or more for patients who have had previous treatment for their CLL. Right now in the United States it's also available as a single agent by the FDA in patients who have indolent lymphomas that have developed recurrence; and it's been available about a year and a half or two years almost and is a very valuable drug in the management of patients. You do have to watch for some side effects, including diarrhea, which can become a problem after you've taken it for some period of time, as well as some other issues that I'm sure your doctor has discussed with you.

Tom from Colorado

Thank you very much.

Lizette Figueroa-Rivera, MA

And thank you for the question. Doctor, our next question comes from Eugene. Eugene asks, "Is it common for the time between recurrence to decrease? Is there an average rate that represents this decrease?"

Fredrick Hagemeister, MD

So, the point is that many years ago there were some studies on patients who had indolent lymphomas. What was found out is that when you gave the first treatment, the remission would last a particular period of time. And then when you treated a second time, when you decided to treat it, the time that the patient was in remission was shorter. And the third time it was shorter, and the fourth time it was even shorter than that.

Well, that's true, but in that previous setting many years ago, they were giving the same therapy every time. They had no additional new drugs, so that has to be asked again. That question has to be asked over and over again. And we don't really have definitive studies that show that in any way on a longitudinal basis, although there are some sort of retrospective analyses that suggest, yes, that if you've had this disease for a while, you know, and you've been in remission, the second time the remission is shorter.

But now we've got new agents that are changing all of that, including newer antibodies. We've got venetoclax. We've got all these inhibitors, these protein inhibitors and all of these new immunotherapy things that we're all in a whole completely new era. So who knows how things are going to happen, and I wouldn't be disheartened by that particular idea that there are going to be problems if I'm on a new therapy, and I'm going to develop recurrence soon. Because we see patients having a partial remission or perhaps a response to therapy, and then the disease stays the same. It doesn't get bigger; it doesn't get any smaller. It just stays the same size. And so we may be changing these illnesses into something that progresses or ultimately stays the same size for a long time and the patient just doesn't progress, and that's what I think is happening with a lot of these new agents.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And Marilyn asks, "I notice that psoriasis was a possible cause of lymphomas. Does that hold true for eczema?"

Fredrick Hagemeister, MD

No. You know, the diagnosis of these different kinds of disorders can be very, very difficult; and there are many patients whom we have who have psoriasis specifically who come to see us, and they turn out that they've had T-cell lymphoma for a while or T-cell lymphoma can be confused with psoriasis. I'm not sure that eczema specifically might be associated with the development of lymphoma. It's not

one of those that's listed, but eczema can be confused with psoriasis as well. So getting a biopsy is very important in patients who have persistent disorders of the skin that do not respond well to steroid therapy or other types of management.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And Gary asks “Are side effects of steroids within the biological and chemo treatments cumulative or do they subside over time?”

Fredrick Hagemeister, MD

Those usually go away with time. It's usually not a real issue. We found, actually, when we give steroids with chemotherapy, those people usually receive bolus doses. Mostly they get a big dose and then they're off for a while. And then a big dose and they're off. That's how it's given with chemotherapy. So usually the side effects from the steroids are not long-lasting and within two or three months, if you've had chemotherapy and it receives steroids, those side effects are gone.

Some patients who are diabetic, who get treated with steroids, their diabetes gets worse. And they ultimately never get back to where they were before. And their diabetes gets a little bit out of control, perhaps so they may find that they have to take more insulin or take more drugs in order to try to control their blood sugars. But, in general, the side effects of steroids completely resolve with time.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and our last question, Suzanne asks, “If you can discuss CAR T-cell research as a cure for follicular non-Hodgkin lymphoma.”

Fredrick Hagemeister, MD

There was a study that was just presented. It was 14 patients who have been pulled out of a larger series of patients who were treated with aggressive lymphomas. And they've also used it to treat CLLs, although that has not been as successful with CLL as it has with other lymphomas. And CAR T-cell therapy is not something to be taken lightly. This is a program where a person's own T-cells are taken out of them, collected, and then they are sent to a company. The company then gets them ramped up, makes them very, very hungry to kill the lymphoma cell. And then they multiply. They get lots of them. They make them grow. And then when they reintroduce them back into the patient, they may introduce say five million cells, but within five days, it's five billion cells because these cells grow very rapidly. Patients are in the hospital; they are always hospitalized when they're treated, and this rapid growth of these T-cells that are now bioengineered, their own T-cells that are bioengineered, these T-cells now attack the cancer cell and destroy it. And by one month, these patients get repeat PET scans, and their PET scans are negative. These are patients who have very, very refractory

disease, very difficult disease to treat with standard agents. They're patients who often have also already had transplants, and this new type of therapy should be and is only being investigated in major centers. However, we're going to learn how to be able to make those better tolerable; and in the follicular lymphoma subgroup, it turned out to be extremely favorable. And those patients had really great responses to that particular therapy, and certainly longer follow-up is necessary in a longer number of patients to figure out how well they will do on a longer basis, a longer follow-up basis. But the follicular lymphoma patients do very, very well when they are treated with that particular type of management.

Lizette Figueroa-Rivera, MA

Well, thank you, Suzanne, and thank you all for your questions.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

Thank you, Dr. Hagemeister, for your continued dedication to patients. You and your colleagues' research successes have made a really positive impact on people's lives. If we weren't able to get to your question today, you can call The Leukemia & Lymphoma Society's information specialists at 1-800-955-4572. Information specialists are available to speak to you from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org. We can provide information about treatment, including clinical trials or answer other questions you may have about support, including questions about financial assistance for treatment.

Again, we would like to acknowledge and thank Bristol-Myers Squibb, Genentech and Biogen, and Pharmacyclics and Janssen for their support of this program.

Again, thank you, Dr. Hagemeister, for sharing your knowledge with us today. To all of the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us today. Goodbye and we wish you well.

ADDITIONAL QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA

Thank you, Dr. Hagemeister, you've agreed to answer more questions from our program. The first question is from Robert. Robert asks, "After being diagnosed with mantle cell lymphoma, what should I expect?"

Fredrick Hagemeister, MD

Well, let's see. That goes from the standpoint of have you been through staging? The standard staging is, of course, what I mentioned on already the radiographs, although sometimes people will get x-rays of some kind that include a PET scan. And it does depend upon where the disease is located. Some people will do a colonoscopy. At our center, we know that the colon is usually involved, especially if it is not just the indolent type or the variant, as we call mantle zone lymphoma. That's only 5% of lymphoma, 5% of mantle cell I should say.

So it's more common that we assume that the colon is involved, but the more important thing is that once a patient has completed therapy for mantle cell lymphoma, that the original sites of disease should be looked at. So we would always do a colonoscopy to confirm that the patient is in complete remission, we would do a bone marrow more than likely because the bone marrow may have been involved at the very beginning. We also usually get a bone marrow at the very beginning to see how much of the bone marrow is involved when they start on therapy. But it would be the same type of workup and evaluation as we do for any patient with a lymphoma.

The only thing that might be slightly different is getting, making certain that you have the proper stains done on the biopsy itself showing that it is, indeed, cyclin D1-positive on the immunostains and that it also, that FISH has also been done and shows that it is, has the 11;14 translocation.

Lizette Figueroa-Rivera, MA

Thank you, and our next question comes from Mary Katherine. She asks, “Does a deep tissue body massage cause problems for a person with lymphoma?”

Fredrick Hagemeister, MD

Well that certainly depends upon where one is as far as therapy is concerned. For example, if one is taking chemotherapy and is going to get a body massage, I would suggest that's a real big problem because you may have low platelets and, therefore, bruise easily and have bleeding, either superficially or internally. And I absolutely would not recommend that a patient who is starting on therapy or has had some sort of treatment go through a massage. I don't think that's a very good idea at all. However, if one has completed therapy and is in remission, one should go about one's business as if one never had lymphoma. That means if you want to get a massage, get a massage.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And Shirley asks, "Can a person be too old to have a stem cell transplant?"

Fredrick Hagemeister, MD

Age probably isn't as important when deciding whether a person has to go through a stem cell transplant, that is a chronologic age, as is physiologic age. There are some patients who are younger who really haven't taken care of themselves and are in bad shape, people who are perhaps even 50 or perhaps under 60 at least. Those patients can sometimes not go through a stem cell transplant because their lungs aren't in good shape or they've got heart problems or other kinds of issues that are not under control. And so medical problems generally will indicate whether one can or cannot go through a stem cell transplant.

Also, general physiologic condition, that is to say if one is eating and walking about and is physically active, even patients who are in their 70s who exercise—and I have a lot of patients who do that and they exercise on a regular basis—those patients would absolutely be good candidates for a stem cell transplant.

I would say that people who are over 80 or 85 are usually not judged to be very good candidates because they have some sort of kidney dysfunction, heart dysfunction, or in some cases pulmonary or lung dysfunction that will stand in the way of their being able to get through a stem cell transplant. So it does depend upon one's physiologic age, as opposed to chronologic age. We have transplanted patients who are up to 80 and even slightly older than that at our center.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and Liza asks, "Can extended chemo with fludarabine and Rituxan cause permanent organ damage?"

Fredrick Hagemeister, MD

Well, the problem with fludarabine and fludarabine alone, not perhaps Rituxan but fludarabine-extended treatment can cause problems, of course. But that would be the same with any chemotherapy. There just is a bigger risk perhaps with fludarabine. Fludarabine is known to affect not only T-cells, that is to say it will deplete T-cells from the body, and those are the major organizers of things and, therefore, increase the risk for getting viral infections and other types of fungal infections and what we call opportunistic infections but also can cause problems with marrow function. And sometimes fludarabine, in particular—the other drugs can cause it too; purine analogs can cause it—can affect the bone marrow very adversely and make it so that platelets will go down and don't recover very easily. So multiple cycles or extended treatments over a long period of time, that is to say more than four or six cycles of that treatment, depending on the dose, would be problematic and

perhaps cause problems that might be considered quote "permanent" because they just don't recover very quickly and might last for as long as six months or even longer.

Lizette Figueroa-Rivera, MA

Thank you and Francis states that, “Compared to other indolent lymphomas, there seems to be very little information out there about splenic marginal zone B-cell lymphoma. Could you please discuss any current research being conducted, results, and where this information can be found?”

Fredrick Hagemeister, MD

Yeah, so as I mentioned during my talk, splenic marginal zone lymphoma and other marginal zone lymphomas, there are very, very few clinical trials that are open or that are available. There are a variety of reasons for that more than likely. One is that splenic marginal zone lymphoma is relatively rare, and so collecting patients and entering them onto clinical trials is somewhat difficult. Patients with marginal zone lymphoma often get enrolled into phase I/phase II trials of single agents or sometimes of combinations of drugs, which, in general, collect lymphomas of lots of different subtypes to see if there's perhaps a key or a clue that shows up as to whether it might be effective or not.

The largest series that was ever collected was actually from Europe where they collected about 80 or 85 patients, retrospectively collected. So there's no clinical trial that's really looked at a large number of patients with that particular entity. The other issue is that patients with splenic marginal zone lymphoma generally have such a very favorable outcome, now, especially since we have rituximab, they often respond to multiple different types of therapies and have prolonged and extended survivals, such that there may be some investigators who also feel that it's not necessary to do clinical trials because certain therapies are so effective, in particular, rituximab, which can put patients into remission and keep them there for a very long period of time.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And Mehmet asks, "Does non-Hodgkin lymphoma run in families? Do you consider it to be inherited?"

Fredrick Hagemeister, MD

I think that I sort of tried to address that early on in that we do have families who come in, in our center. We did a study a number of years ago just asking patients when they walked in the door if they had a family member who had either a leukemia or a lymphoma or some hematologic malignancy. And it turned out that about 10% of our patients told us that some family member happened to have a lymphoma or a leukemia or myeloma or even an AML (acute myeloid leukemia), that is to say a different kind of, not a lymphoma or a lymphoid malignancy, but rather a myeloid malignancy. And they just told us that, and so we thought that there might be some relationship.

But the problem is that there have been yet no cytogenetic abnormalities in the blood. As opposed to breast cancer, where we find that 10% of women with breast cancer will have an inheritable breast cancer that they can pass down to their daughter. But that's not true in lymphomas. We have not yet found a recurring genetic abnormality in human beings body, in the body or in the blood or wherever it happens to be that we test that tells us that there's something that can be passed on to a child. When we look at the second-degree relative, let's say a cousin, that's when we start seeing this increased risk or an aunt or someone says, "My great-grandmother had something." But the problem is that many of those stories are not exactly very well worked out. So getting records and getting that kind of information can be difficult, and that's why we don't have either some sort of analysis that looks at just patients and trying to understand what's going on. But we also don't even have any analysis of genetic factors in the human being that tell us that this is a transmissible lymphoma.

The truth is that there may be mutational differences that we don't have an understanding of in large cell lymphoma. For example, there are over 300 different mutations in the lymphoma cell that are responsible for directing traffic and for understanding something about how that lymphoma cell behaves. So doing such a comprehensive analysis in human beings normal cells is not really possible and not easy to do, and just sending it off and saying, you know, to some company and saying, "Here's my cheek swab for my DNA. Do I stand a risk of developing lymphoma?" we don't have that. So, obviously, then we don't have a way to tell whether it passes on from one family member to the next.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and Bonita asks, "Does the age of the patient impact the effectiveness of treatment that is monoclonal antibody based?"

Fredrick Hagemeister, MD

Well, the answer to that is yes and no. The age itself does not necessarily play a role. There is some thought that some of the drugs are cleared more rapidly through some mechanisms that are still not very well understood. So one person may get a higher dose inadvertently, and one person may get a lower dose. That may account for some of the toxicities that we see. So the drugs are usually not tolerated as well in older patients, and it may be because they clear some of these drugs more slowly. That is true of rituximab, for example, and it's often thought that people, actually, rituximab may work better in some people because, or antibody therapy, antibody alone may work better in some people who are older because they have bigger levels in their blood.

The same is true of women. Women appear to not clear rituximab so well, and these are primarily from German trials, suggesting that women may do better than do men. And some retrospective analyses have suggested that as well most recently when they received rituximab-based therapies.

So, in general, chemotherapy is generally not tolerated by patients as well who are older. Their doses have to be reduced in effect, possibly partly because their bone marrow function is not as good as

younger patients. So it can be an issue in older patients as far as response is concerned. But as far as there being a genetic definition of why the patients don't respond as well, that's not yet known either. So we're still looking into those kind of things, and there are a lot of studies that show that older patients don't do as well; and the reason for that is not really clear. Probably because their doses have to be reduced in order to be able to be effective, and we just lose the response in such patients who are older.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and David asks, "Is there anything within a patient's control? For example, stress reduction to improve the immune system that can reduce risks for some or all slow growing non-Hodgkin lymphoma?"

Fredrick Hagemeister, MD

Thank you very much for that question. One of the things that we know, stress does not cause cancer. I understand that, I get a lot of patients who come in and ask me and say, "Well, I should reduce stress so that I don't get, so my cancer goes away faster." Not really. Stress causes a number of different things—cardiovascular disease, it's associated with different kinds of other things, diarrhea, bowel problems, certain kinds of colitis, certainly with hypertension. Stress is associated with that as well. And so we know that certain body functions are associated with stress, but it has not yet been associated with the development of cancer.

There are four things that are associated with the development of cancer, and if you fall outside of those relatively, not very narrowly defined features, you're at higher risk. And those higher risks are higher BMI, that is to say greater than 27 Body Mass Index. Number one, it's not what you eat insomuch as it is carbohydrates are an issue because your Body Mass Index goes up when you eat carbohydrates. So that's an issue, greater than 27. Alcohol. That is to say more than, strangely, two drinks a day for men is considered, if you stay under that, you're not at excess risk, and one drink a day for women is considered acceptable. But more than that, you're at a higher risk. Of course, smoking, and a very small amount of smoking is allowed in order for you to not have an excess risk. It's just what we call five-pack years. And, of course, the fourth is exercise. So exercise plays an important role. It's 120 minutes of moderate exercise a week. That's only two hours of moderate exercise, and walking is not exercise, by the way. Exercise is raising your heart rate, doing some sort of physical activity that raises your heart rate. And, finally, if it's intensive exercise, 90 minutes of intensive exercise a week is adequate. If it's at least that, you reduce your risk of developing cancer; and I encourage my patients to not only have proper nutrition, try to keep their Body Mass Index under 27, and also to exercise on a routine basis.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And our last question comes from Diane. Diane asks, "Why do we have to go through more toxic standard-of-care treatment before being eligible for less toxic new treatments?"

Fredrick Hagemeister, MD

Well that's a good question. First of all, the problem is that many of the treatments which we use today can cure patients with lymphoma. For indolent lymphomas, I understand, we've come up with bendamustine-rituximab, which is not as toxic as R-CHOP. There were more toxic regimens that we've also gotten away from, the fludarabine-based regimens that we've gotten away from. But keep in mind that about 40% of patients who have CLL, who have relative normal cytogenetics at the very beginning, are still free of disease if they take FCR. So that intensive regimen may actually cure some patients with CLL. At ten years, 40% of those patients who don't have bad cytogenetics are still in remission. So that's very important. We've got some treatments that can actually cure patients or put patients in remission; and that's why we look for these new agents, and new agents are usually studied in patients who have relapsed disease because we think there's a bigger risk for those patients.

We don't know all the side effects of many of these different agents. For example, venetoclax. When we first started studying that drug, it was an amazing drug. It worked quite well in patients with CLL, and it also works in other indolent lymphomas. But the problem was that some patients died of tumor lysis syndrome when they first received that agent, and we had to learn how to be able to give that drug more effectively and without getting into trouble as far as toxicity was concerned.

And sometimes when you start treating a patient, you do 40 patients, it's not enough to be able to see the toxicities that may exist from that particular drug. So that's why when patients go onto clinical trials with new agents, they are often studied very, very carefully; and they're looked at very, very frequently by research nurses. They're calling all the time trying to figure out what kind of side effects you have. And you're asked a lot about side effects because there may be a new side effect that we don't know about that shows up, not when you've done 40 patients, but more when you've done 100 patients. So that's why it's important to analyze responses as well as tolerabilities of agents before moving them into frontline therapy.

Lizette Figueroa-Rivera, MA

Thank you, again, Dr. Hagemeister, for volunteering your time to answer these presubmitted questions.