

**Speaker:** Stephen Ansell, MD, PhD

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## **Slide 1: Welcome & Introductions**

### **OPERATOR:**

Hello, everyone, and welcome to *Living with Slow-Growing Lymphoma*, a free telephone/web education program. It is my pleasure to introduce your moderator Lauren Berger of The Leukemia & Lymphoma Society.

### **LAUREN BERGER:**

Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Stephen Ansell for sharing his time and expertise with us today.

We have over 1,000 individuals participating from across the United States and from Australia, Canada, China, Italy, Peru and Sweden.

We'd like to acknowledge and thank Genentech/Biogen Idec and Spectrum Pharmaceuticals for their support of this program today.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who will share a few words. John?

### **JOHN WALTER:**

Thank you, Lauren. I'd like to add my welcome to the patients, caregivers and healthcare professionals on the program today.

All of us at The Leukemia & Lymphoma Society believe we are living in an extraordinary moment. Our mission is to cure blood cancers, including leukemia, lymphoma, myeloma, and to improve the quality of life for patients.

Since 1954 LLS has been a driving force behind almost every treatment breakthrough for patients with blood cancers. We have awarded more than \$875 million to fund blood cancer research.

Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with many different blood cancers. An important part of our mission is bringing you the latest information about advances in treatment in your blood cancer, so that you can work with your healthcare team to determine the best options for the best outcomes.

Until there is a cure, LLS will continue to invest in research, patient programs and services that improve the quality of life for patients and families.

We are fortunate to have as our presenter today Dr. Stephen Ansell, one of the nation's leading experts in lymphoma. We appreciate his dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and his care of patients living with blood cancer. I would like to thank him for providing us today with important information on living with slow-growing lymphoma.

Thank you and I'll turn the program back over to Lauren.

## **Slide 2: Follicular and Other Slow-Growing Lymphomas**

### **LAUREN BERGER:**

Thank you, John. I am now pleased to introduce Dr. Stephen Ansell, Professor of Medicine, Division of Hematology, Department of Internal Medicine at Mayo Clinic in Rochester, Minnesota. Dr. Ansell, we are so privileged to have you with us today. And I'll now turn the program over to you.

## **Slide 3: Learning Objectives**

### **DR. STEPHEN ANSELL:**

Lauren, thank you very much, and thank you to everybody who is on the line, appreciate your participation.

What I would like to do with today's presentation, and I trust everyone will be able to see the slides, those that are on the web, we're going to be talking about follicular lymphoma specifically, but also about other slow-growing B-cell lymphomas. And there'll be an opportunity, as mentioned earlier, for folks to ask questions at the end of this presentation.

Our learning objectives today are really to start off with an overview of low grade and slow-growing lymphomas, with a specific focus on follicular lymphoma. Specifically, then to talk about current and emerging therapies and treatments. We will talk also about stem cell transplantation. As I go through, I plan to discuss results of clinical trials or current ongoing clinical trials, really to highlight how this is moving the field forward and providing new and novel options for patients living with slow-growing lymphomas. And then as we also go through the presentations, I will be talking about some of the potential side effects associated with treatment, as it is very important, as one makes choices about treatment, to decide about the merits, on the one hand, of the treatment, the successes and the potential benefit of treatment, but balancing that on the other hand with potential side effects and complications, which can arise from treatment.

## **Slide 4: Patient with Enlarged Lymph Nodes, Abdominal Fullness and Fatigue**

So to start us off, I have put together a presentation here of a hypothetical patient, as I feel it's so important for us always to keep patients in our thinking and you as a listener, this may then help us as we have a discussion, really to know how this may apply specifically to you.

So this hypothetical person is a 43-year-old accountant, who presents to her doctor with lymph nodes that are in the neck, in the armpits, abdominal fullness and lymph nodes that she can feel in the groin. And as you can see in the picture on the right, the patient, when they have a CAT scan to assess this abdominal fullness, is found to have multiple lymph nodes that are enlarged inside the abdomen.

Additional blood testing is done. This includes a CBC, which includes the red cells, the hemoglobin, the white cells and the platelets, and of note, her hemoglobin is decreased at 10.5, when normal would be 13 or more.

An additional test is done, this is called an LDH test, or lactate dehydrogenase. This is a measure of cell growth and cell proliferation, not to be in any way confused with cholesterol measurement, and this has to do with how rapidly cells are growing and proliferating or dividing. And this shows a number that is above the normal range.

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The patient then undergoes a biopsy of one of the lymph nodes in the neck and the biopsy shows a B-cell lymphoma. And we'll talk in a minute about what is important about those biopsy results. Further testing is done, which includes a bone marrow test and this is negative for involvement by lymphoma and is a normal bone marrow test.

**Slide 5: Histology**

So the first question that is very important when one is diagnosed with lymphoma is exactly what kind of lymphoma does the patient have. So this is the histology of the disease. And the reason that's important is that each treatment can be tailored and should be tailored specifically for the kind of lymphoma the patient has. So treatment for slow-growing lymphomas, that we'll talk about, and follicular lymphoma specifically, is very different from more aggressive lymphomas.

And what you're seeing in these pictures, in the top left panel, is follicular lymphoma. And you can see lighter areas and darker areas and the lighter areas are nodules of lymph node cells and these are where the follicular lymphoma cells are located. The other diseases that you can see are different diseases. On the top right is a patient with large cell lymphoma and the treatment is very different for that type of disease. On the bottom left is a patient who has Burkitt lymphoma, which is a very aggressive lymphoma, and again treatment is very different for those patients. And on the bottom right is a patient who had nodular sclerosis Hodgkin lymphoma, and that again is very different and managed in a very different fashion.

So I really just want to emphasize as we start out that when one is talking to your doctor or getting information, being 100% sure of exactly what kind of lymphoma you have, is very important. And equally when obtaining information, either from the web or from others, ensuring that you get accurate information related to the slow-growing, low grade type of lymphoma you have, and not other diseases, is really important.

**Slide 6: WHO Classification for B-cell Malignancies**

And highlighted on this next slide is why further this is important. And you can see this is a classification by the World Health Organization of the different types of B-cell malignancies. And there are a variety of different kinds. Most of those highlighted in the darker bold print are those that are more low grade in nature, and that's really what we're going to be talking about today, the slow-growing varieties of lymphoma. But you can tell there are a variety of other types and there are other diseases which are not even on this slide and will be not addressed in today's presentation.

**Slide 7: The Patient has Questions**

So when all of that is done and the biopsy is obtained, the patient is informed that she has follicular B-cell non-Hodgkin lymphoma, and the patient, who is very informed, has multiple questions. And we're going to go through how each of these questions potentially could be answered, but maybe these are questions that would be pertinent to the situation of many patients.

The first question is does the patient actually need treatment at all? Would it be appropriate just to be watched and waited and no potential therapy given right away? The second question is well, maybe if one does need treatment, do you have to get chemotherapy plus, for instance, an antibody treatment like rituximab? Or wouldn't it just be sufficient to receive rituximab therapy alone?

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If it is necessary to receive chemotherapy in combination with rituximab treatment, what chemotherapy would be recommended? Is there a combination or is it a single drug or what is really the best choice?

A further question would be well, once initial treatment with chemotherapy or rituximab alone or the combination is completed, is maintenance therapy something that is necessary?

And finally, well, would it be necessary to consider a stem cell transplant, and as we'll touch on in a few minutes, this could either be an autologous stem cell transplant, where your own stem cells are used, or alternatively what's called an allogeneic stem cell transplant, where you would receive stem cells from a brother or sister or a matched, unrelated person from a bone marrow registry.

**Slide 8: Current Treatment Options**

But I just want to again stress that our focus today is talking specifically about low grade, slow-growing B-cell lymphomas and our focus is specifically going to be on follicular lymphoma. We're going to first go through some general information about follicular lymphoma and other slow-growing lymphomas, but then we'll focus our conversation on current treatment options.

**Slide 9: Follicular Lymphoma**

So important to know that follicular lymphoma is actually the most prevalent indolent or low grade or slow-growing kind of lymphoma. And in the United States it represents approximately a third of all of the adult patients diagnosed with lymphoma. And across the whole world, it's about a quarter of the patients.

Initially, as I'll show you in a minute, outcomes for patients really hadn't changed much, but in recent years with the introduction of rituximab, the overall survival is actually improving and has improved for patients with slow-growing and low grade lymphomas. And specifically the overall survival has really improved from only about 65% in low grade lymphoma patients at five years, to almost over 90% now. And the FFS is failure-free survival, in other words, patients remaining in remission, that's improved at five years from about only a third of patients to two-thirds of patients. Again, suggesting that patients are benefitting and particularly from the addition of rituximab treatment.

**Slide 10: Survival of Patients with Indolent Lymphoma**

The slide shown now is the outcome or survival of patients with low grade lymphoma and this was an analysis done at Stanford University over decades back from 1960 to 1996. And as one can tell, is that by a 15 year period, the outcome of patients had not really changed significantly and most patients were still having disease come back and unfortunately succumbing from the disease, regardless of which decade they were treated in.

**Slide 11: The Addition of Rituximab**

The addition of rituximab treatment and particularly when added to chemotherapy or when given as a single agent and potentially followed with maintenance therapy, that has made a big difference. And as you can see, the top line of patients that received CHOP chemotherapy with a monoclonal antibody, which in this case is rituximab, and that group of patients has done significantly better than previous groups of patients, CHOP chemotherapy or more intensive chemotherapy, such as the ProMACE chemotherapy that are shown in the bottom two lines.

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So with all of that said, the promise of living with low grade lymphomas and slow-growing lymphomas is encouraging in that patients are doing better and living longer. And what is important, going back to our patient, is as we think about future treatments for patients, the important thing to assess is how aggressive or how active does the disease appear to be.

**Slide 12: Follicular Lymphoma International Prognostic Index (FLIPI)**

So there are two indexes, and I'm going to highlight the first one and then discuss the second one, which is really from those tests that were done on our hypothetical patient. There is a Follicular Lymphoma International Prognostic Index, which uses these five different parameters: the age of the patient, the stage of the patient, whether or not the hemoglobin is normal, and how many different places the disease involves the patient's body, and whether that LDH test is abnormal or not. But as you can see on the right hand side of the slide, that actually allows us to stratify three different groups of patients, some of whom do extremely well, those in the low risk group, and some of those in the high risk group who do less well and obviously may need therapy sooner rather than later.

**Slide 13: The Follicular Lymphoma International Prognostic Index 2 (FLIPI2)**

This particular index is now being updated and modified and this is what most people would use at this point, called the FLIPI2 index. And what this is, is using very similar parameters, but including a new parameter, which is the beta-2 microglobulin, which again is a measure of cell activity. And including the bone marrow testing. But similarly, this can define three groups of patients: those that are very low risk with an extremely good long-term outcome and those that are far more high risk, for whom treatment might need to be initiated sooner and who are at risk for the disease causing significant problems in the future.

So armed with the information of exactly what kind of lymphoma the patient has, and in this case it's follicular B-cell non-Hodgkin lymphoma, and armed with the information about the FLIPI index, as to whether this is low grade, intermediate grade or high grade, that brings us to a decision regarding what treatment would be preferred.

And there's one additional piece of information that's important at this point and that's what's called the staging of the disease. In other words, where in the body the disease is present. And we use a staging measure called the Ann Arbor staging measure, where we would look for where the lymph nodes are distributed in the body, whether the disease is in the lymph nodes or outside of the lymph node system, and whether there is any evidence of bone marrow involvement.

**Slide 14: Indolent Lymphoma—Common Management Approach**

And that's important because highlighted on this slide is kind of the overarching kind of common management approach to slow-growing lymphomas. So after the staging evaluation is done, one can see that you can break patients, the groups of patients, into three big groups. The first is those that really just have very localized disease. In other words, just one place. The second group are those that have disease more kind of spread out, but there's not a lot of it. Actually lymph nodes are small or the amount of bone marrow involvement is very low. And then there's a third group of patients for whom there may be a much higher what we call tumor burden. Multiple sites of disease, large lymph nodes, significant bone marrow involvement.

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And as I'll show in the subsequent slide, when one has very localized disease, just one site of disease, it may be appropriate to treat those patients with radiation therapy, as there is a possibility that is truly the only site of disease, that patients may actually have their disease put into a durable remission.

For patients that have low tumor burden, but have more advanced disease, that may be an appropriate group of patients where just watching and waiting might be the right thing to do. Or treating patients with antibody therapy alone.

But those that have more advanced disease or a high tumor burden, those are people where a chemotherapy plus antibody approach is necessary.

**Slide 15: Therapies for Advanced Indolent Lymphoma**

Shown in this slide is most of the therapies that are available for slow-growing lymphomas, and they're kind of graded from those that are the mildest to those that are the most aggressive. So watchful waiting would be the mildest. Obviously you're not taking any treatment, so there's very little in the way of side effects. Right down to allogeneic transplantation, which is a much more aggressive approach. But it does show, as you go across the table, that the likelihood of benefitting, as far as getting the disease into remission is the lowest the least aggressive your therapy is, and the durability is the shortest. However, how aggressive or how much this affects the patient is obviously also the lowest. So those treatments that are the most aggressive are the ones that give the best results, but obviously have the greatest risk.

**Slide 16: Long-term Outcome of Stage I/II Follicular Lymphoma**

So specifically then going through various stages of disease and specifically talking about treatment options, I'd like to start off with saying that if a patient has a slow-growing lymphoma, like follicular lymphoma, and truly has only one site of disease after all of the scans and the bone marrow tests and everything has been done, this is a patient that should still be considered for some local radiation therapy, just to the lymph node site that's been diagnosed. And that's shown in this slide. The curve that you see, the percentage of patients over time that remain in remission without evidence of the cancer coming back. And you can see the top line is for those that have stage I disease. Those that have only one site of disease. And you can see that a sizable percentage, more than half of the patients in the study, even out 20 years on, were still in remission without the disease coming back.

Now I would stress this is a very unusual circumstance because many patients, most patients with low grade and indolent and slow-growing kinds of lymphoma like follicular lymphoma, will often present with disease more extended than just one place. But if it's truly only one site, that's a worthwhile consideration. The second group of patients are those that have low burden of disease, so it's more advanced, it's not just in one site, it's multiple sites of disease, but there's not a lot of disease present. These are patients for whom a watchful waiting approach is appropriate.

**Slide 17: Rituximab for "Low Burden" Untreated Indolent Lymphoma**

Or alternatively, as I highlight here, being treated with an antibody approach such as rituximab, is a very useful way to be treated. Rituximab, as most of you all know, targets the protein on the outside of the cell called CD20, and depletes or gets rid of all of the B-cells that express CD20. And initial studies, shown here, showed very high response rates, somewhere at least half to three-quarters of the patients,

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benefitting from treatment. In other words, at least a 50% reduction in the sites of disease. And as you can tell, even around a quarter of patients to a third of patients having the disease go to a state where there was no detectable remaining disease, a complete remission.

**Slide 18: Rituximab for “Low Burden” Untreated Indolent Lymphoma**

But the question that has come up since then is well, is it necessary to be treated just with four doses or should you actually receive ongoing maintenance therapy? In other words, should you receive a dose of treatment every two or three months for at least a two year period? Would that be a better strategy than, for instance, receiving a dose of Rituxan® only at the time when the disease reactivates?

So this is a recent study that was presented a year ago, which actually tried to answer that question. So these are patients that had low burden of disease, never received treatment before, with follicular lymphoma, and one group of patients received four doses of rituximab and then were given maintenance therapy, in other words, every two months they received another dose of treatment to keep the disease beaten down, as it were.

The second group of patients received four doses of rituximab, but then received no more treatment and were just watched. And at a time when it appeared the disease was reactivating, were retreated. So the comparison was between maintenance therapy and retreatment therapy.

And what you can see here is the two curves are superimposable. So there is, in these low burden of disease patients, in other words, more extensive, but still not a lot of disease, there is an equally reasonable approach, where one is treated with maintenance therapy versus retreated at a time your disease becomes active.

**Slide 19: Lenalidomide Plus Rituximab**

The next slide I wanted to show was to say that clearly we always want to build on these results. So here are some encouraging results and I think this is something that I would always encourage patients to participate in clinical trials, as there is such a clinical trial going on right now. And that is adding additional agents to rituximab in the hopes of obtaining a better result for the same patients with low burden of disease with indolent lymphoma.

And this is the addition of lenalidomide. Lenalidomide is also known as Revlimid®. It's an immune-modulator, it activates the immune system. And in this study of indolent low grade lymphomas, 50 of whom were follicular, the remainder were other kinds of lymphoma, you can see that the results were very impressive, with very high response rates of 90% and about two-thirds of patients having a complete response to treatment. And that was even higher when just the follicular lymphoma patients were assessed.

And with a follow-up of around two years, the patients still in remission was 83%.

Now obviously when you add additional therapies to rituximab, which is generally well tolerated, this does bring on additional side effects, so lower blood counts, some numbness in the fingers and toes, increased risk of blood clots, were problems that were seen in this study. But I think important to know as we move forward, that potentially additional agents may improve outcome.

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**Slide 20: Combination Therapy for Advanced Disease**

Obviously there is a further group of patients who have a more advanced disease, but also have a greater disease burden. So in other words, the lymph nodes are quite sizable and the patient is quite symptomatic. These are patients where the addition of chemotherapy to rituximab would be a good choice. But the question is just which chemotherapy would be the most appropriate treatment. And for those on the call who have received treatment, you know that some patients have been treated with the R-CVP regimen, some people have received R-CHOP, some people have received rituximab in combination with fludarabine-containing regimens, and others have received bendamustine in combination with rituximab.

**Slide 21: Bendamustine Plus Rituximab**

Important to know that comparisons and comparative trials have been performed to try and get to the bottom of which is the best therapy. And here is a result from a study called the STIL trial. This was a large study completed in Germany a few years ago and recently published, which took low grade, indolent, slow-growing kinds of lymphoma and compared patients who received six cycles of R-bendamustine, bendamustine being a new chemotherapy drug, and compared it to the standard treatment, which was felt to be R-CHOP chemotherapy.

And interestingly, the response rates were very similar in both groups, except the complete response rate was higher for the bendamustine group. And the time that it took for the disease to become active and progress was significantly longer in the patients that received R-bendamustine.

And overall, actually R-bendamustine was better tolerated with fewer side effects.

**Slide 22: Bendamustine Plus Rituximab**

This has now been published and you can see these are the curves that show that. So again, the line represents the time and the number of patients who remain in remission. And as you can tell, the red line, the bendamustine plus rituximab arm, those patients remained in remission longer than the patients who received R-CHOP chemotherapy.

**Slide 23: Bendamustine Plus Rituximab**

To further confirm these results, a trial done in the U.S. was recently presented at one of the national meetings about six months ago. This compared the R-bendamustine regimen to either R-CHOP or R-CVP. So you could choose in the one arm whether you received R-CHOP or R-CVP, but in the other arm the patients received bendamustine plus rituximab.

And so in comparison between the two arms, the patients receiving R-bendamustine had a higher complete response rate and the patients' side effects or adverse effects were actually quite similar in frequency, but generally better tolerated in the R-bendamustine treated patients. Again, supporting the information from the German study.

So this has led to R-bendamustine being one of the standard treatments given for patients with slow-growing lymphomas.



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**Slide 24: Ofatumumab Added to CHOP**

But obviously one would always like to improve on these results, so I want to highlight one or two additional studies or clinical trials that have been done. Ofatumumab is a different anti-CD20 antibody, different to rituximab in that it binds or grabs onto the cell in a slightly different way. So there have been studies using CHOP chemotherapy but not with R, but with O, or ofatumumab, and again was shown to be an effective regimen. You can see the overall response rates and the complete response rates, were very high. And it didn't appear to have any greater degree of side effects than one would have expected with R-CHOP chemotherapy. So a comparison obviously against R-CHOP or R-bendamustine would need to be done in the future.

**Slide 25: Bortezomib Added to R-CVP**

Bortezomib is a further new drug. This is a proteasome inhibitor. Its job is to stop the cell from being able to process proteins and, as it were, get rid of its trash, so the trash heats up in the cell and causes the cell to die off. This was combined with standard R-CVP in patients with follicular lymphoma and recently published. This again shows a very high response rate with a high percentage of patients having a complete response. And about half the patients went on to receive maintenance rituximab. Mostly this was well tolerated, but as one adds new drugs, you also add additional toxicities. And an additional toxicity of bortezomib is potential neuropathy.

**Slide 26: Rituximab Maintenance**

For patients treated with R-CHOP chemotherapy, a question that commonly comes up is is there merit after R-CHOP chemotherapy to then receive maintenance treatment. So you heard me say a little earlier that in patients who receive rituximab as their first and only treatment, maintenance therapy may have a similar role to retreatment in those patients with a low burden of disease. In patients that have more disease and who receive R-CHOP chemotherapy as their initial treatment, this study compared R-CHOP and stop, no further therapy, to R-CHOP chemotherapy followed by maintenance therapy. And you can see that the patients receiving maintenance therapy actually did significantly better than patients who just had R-CHOP and no further treatment.

So there's a strong case to be made for maintaining patients with rituximab, especially when they have a greater burden of disease.

**Slide 27: Recurrent Follicular Lymphoma**

Changing gears now to talk a little bit about well, what happens if you've received initial treatment and may have benefitted, may have been in remission for an extended period of time, but then the disease comes back. What are the options and what could one do at that point?

And really at this time there are two overall strategies. There's a conventional strategy and there are novel new drugs that one could consider.

So the conventional strategies, I'll talk about them in a few minutes, are to receive additional antibody treatment like rituximab with further maintenance therapy, to receive additional chemotherapy plus rituximab with additional maintenance therapy, to receive radioimmunotherapy, so this is an antibody with radioactivity attached to it, or alternatively to just receive radiation therapy to various sites that are

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problematic. And as I'll touch on in a minute, autologous, using your own stem cells, transplant, or allogeneic, using someone else's stem cells, are an option at this point.

A number of new strategies are also being tested in these patients. And I always encourage patients to consider being on clinical trials, because this allows us to move the field forward and to learn about what's the best therapy for patients with slow-growing lymphomas.

But there are new antibodies which could be considered, and I'll touch on them in a few minutes. Additional treatments with bendamustine, lenalidomide or bortezomib, and other therapies.

**Slide 28: Autologous Transplant for Relapsed Follicular Lymphoma**

So the first thing that I wanted to talk about in patients with relapsed follicular lymphoma is what is the benefit of considering an autologous stem cell transplant. So again, important to differentiate autologous and allogeneic. Autologous is the use of your own stem cells.

And this was a comparison in this study of patients that had either a purged bone marrow or an unpurged bone marrow, in other words they cleaned the bone marrow up or they didn't, compared to chemotherapy alone. And seen on the right, you can see that whether you purged the bone marrow or you didn't purge the bone marrow, the results were very similar, but the results appeared significantly better than the patients who received chemotherapy alone.

So an autologous stem cell transplant in patients where the disease has come back is a very reasonable approach for patients with follicular lymphoma and other slow-growing lymphomas.

Important, though, to know, is that autologous transplant, to the best of our knowledge, is not curative, but provides longer disease control.

**Slide 29: Indolent Lymphoma—Autologous vs. Allogeneic Transplant**

In the next slide here is a comparison of going through an autologous stem cell transplant versus an allogeneic stem cell transplant. And as you can see, the top line is when you use your own bone marrow. And you can see that the bone marrow transplant using your own bone marrow, that line slowly continues to slide down, suggesting that over time patients' disease does come back. The advantage of an autologous transplant is that it's well tolerated because it's your own stem cells and the risks are not that high.

In contrast, the allogeneic transplant, using bone marrow from a brother or a sister or a matched donor from a registry, it has a significant risk right away in the beginning, and you can see the bottom curve drop straight down right in the beginning, where a high percentage of patients can get very sick and even potentially die from the transplant. But then the graph flattens off, suggesting that if one gets past that period, you may actually have a very good outcome and a subset of patients are cured with this approach. High risk, but higher yield, versus the autologous transplant, which is much lower risk, but lower yield.

**Slide 30: GA101 (Obinutumumab)**

Changing gears a little to talk about new antibodies that could be used in patients with relapsed disease. New antibodies targeting CD20 are being developed. You heard me mention earlier the ofatumumab.

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That binds to a different site on the B-cell. GA101, which is this antibody here, it's designed to actually activate the immune system to a greater degree. So this therapy has actually been compared between GA101 and rituximab, it's been shown to be very safe, it's been shown to be highly effective, and the responses between the two have been very similar, with a little bit of promise to suggest that the GA101 antibody may actually have a greater degree of activity. But larger randomized studies are going to be necessary to really confirm that. But I think again, encouraging folks to consider clinical trials, this allows us to develop new antibodies with greater degree of activity and better results.

**Slide 31: Other Antibody Approaches**

Other antibody approaches: there are antibodies targeting different proteins on the cell and there are antibodies that are active in different ways, by bringing complement or other immune mechanisms into play with a greater degree of good results. So these two antibodies, the ocaratuzumab is actually a different way in which the CD20 is targeted and again showed a high response of a quarter of patients that had received rituximab in the past and had not benefitted. They went on and benefitted from this particular antibody. The second one is an anti-CD74 antibody, which is trying to activate the immune system in combination with a CD20 antibody. And again this is showing promise. So I think that different antibody approaches may well be beneficial for patients in the future.

**Slide 32: Bendamustine in Rituximab-Refractory Indolent B-cell NHL**

You heard me present some information about bendamustine with rituximab in patients that had not been treated before, but had a lot of disease and the fact that it might have a better result than R-CHOP chemotherapy. Here you can see the results for patients that had had previous treatment including rituximab and had had their disease come back.

And in this study bendamustine was used at a reasonably high dose every three weeks and it was effective and patients who had not benefitted much from previous treatment, significantly benefitted from this therapy. Clearly there's still work to be done because the duration of response was only about nine months, but the hope is that if one builds additional treatment in combination with bendamustine, one may actually get a better result in the long term.

**Slide 33: GA101 (Obinutumumab) Plus CHOP or FC**

The GA101 that we discussed just a few minutes ago, which can be used on its own, there are also trials now comparing this new anti-CD20 antibody with other standard chemotherapy. So this trial presented a year ago was combining GA101 with CHOP chemotherapy or with fludarabine-based chemotherapy, and again showed a high response rate. The main thing obviously that will need to be tested is whether this combination is better than R-bendamustine treatment or R-CHOP chemotherapy and more studies are clearly going to be necessary.

**Slide 34: Lenalidomide in Relapsed/Refractory Indolent NHL**

You also heard me mention lenalidomide, which is the immune activator given with rituximab to new patients with a very high response rate. This was a study done with lenalidomide on its own in patients with slow-growing lymphomas, where the disease had reactivated and they needed additional treatment. And you can see that even though they'd had multiple previous therapies and had the disease come

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back, there were still patients that would benefit with treatment with lenalidomide. Unfortunately, when patients are treated with many different therapies and then receive these kind of agents, the duration of the responses can be quite short. But in these patients, those that benefitted from treatment and had a good response, the results were promising in that the duration of response was over a year, with many patients still in remission.

**Slide 35: BTK Inhibitor in Relapsed Lymphoma**

As a final note, the BTK inhibitor is a new drug that's also in clinical trials with a lot of promise. BTK is actually a protein that is part of the signaling cascade inside of cells. Cells are stimulated through a protein on the outside of the cell called the B-cell receptor. That's what keeps them activated and growing. So messing with that particular ability to be activated and encouraged to grow by using a BTK inhibitor can actually benefit patients by suppressing the growth of the cancer cells.

And this therapy is a pill. As you can see from the top slide, that's what's called a waterfall plot, so any patients who benefitted from treatment, the bar goes below the line. Any patient who didn't benefit from treatment and the tumor actually grew, that goes above the line. And you can see very clearly that the majority of patients benefitted from the treatment. Each of the bars in different colors represents different types of diseases, but most of the patients in this trial had indolent or slow-growing kind of lymphomas and clearly benefitted. And the lower figure shows how long the patients have continued on treatment. And you can see that there are many patients that are a year out and remain on treatment and continue to do well. This drug is very well tolerated with not a lot of side effects and so I would anticipate this to be a very promising drug, either on its own or in combination with other drugs, in patients that have slow-growing and low grade lymphomas.

**Slide 36: Summary**

So in summary, what do I hope have been some of the messages that you might have heard. First, I hope that you clearly heard that it's very important to make sure that the type of lymphoma that you have is clearly delineated and the histology is well interpreted, so that the right choice of treatment is made right from the beginning.

Secondly, it's important that there's a good staging evaluation, to know whether there's more extensive disease or more localized disease. And if the disease is kind of more bulky with a lot of it, versus a lot less of it. And also that one utilizes the follicular lymphoma or other prognostic scores to determine whether the disease is going to be more aggressive versus not.

But as highlighted on this slide, if one really has a single or only one area where the disease is noted, it may be reasonable to consider being treated with radiation therapy. If the disease is clearly more extensive, but the patient feels quite well and you feel well without much in the way of symptoms or problems and the amount of disease in the body is actually very low, it may be very reasonable just to watch and wait and not initiate any treatment until more symptoms develop. If symptoms are more of a problem, then receiving a rituximab alone approach, either with maintenance therapy or retreated as necessary, may be the way to go. Additionally, this may be a group of patients who may consider participating in a clinical trial.

**Speaker:** Stephen Ansell, MD, PhD

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**DR. STEPHEN ANSELL:**

And finally, for patients who have more extensive disease, greater burden of disease and clearly are much more symptomatic or have poor prognostic features by the FLIPI index, typically chemotherapy in combination with rituximab is the most appropriate treatment. Many patients will receive R-bendamustine treatment and then many will receive additional maintenance therapy thereafter. Again, participating in a clinical trial is encouraged.

You also heard me talk a little bit about transplantation and new antibodies and other new drugs. These are all options and may well be considered if the disease reactivates at a future time.

So with that I'll thank you for your time and I'm going to turn the podium back to Lauren for the question and answer time.

**Slide 37: Question and Answer Session**

**LAUREN BERGER:**

Thank you so much, Dr. Ansell, for a very clear and informative presentation.

**LAUREN BERGER:**

We'll take the first question from the web audience and this question is from Mimi and Mimi asks, "What does grade 3 follicular lymphoma mean? Is it like grade 3 cancer? And how are follicular lymphomas graded?" And we know you talked a little bit about that, but these are specific questions regarding grading.

**DR. STEPHEN ANSELL:**

Yeah, that's a very good question. All follicular lymphomas are graded either as grade 1, grade 2 or grade 3. And generally grade 1 and grade 2 are grouped together and are felt to be much more slow-growing, and grade 3 is felt to be a little bit more aggressive. Typically the way in which the grading is done is to look to see whether there are large cells present in the biopsy specimen. Most follicular lymphoma cells are small cells, but the larger cells tend to be more rapidly growing and that's why follicular grade 3 lymphoma can often be more badly behaved and more aggressive in its growth pattern. Often that would encourage one to receive chemotherapy with an antibody, something like R-CHOP chemotherapy or R-bendamustine chemotherapy, for patients with follicular grade 3 type of lymphoma.

**LAUREN BERGER:**

Thank you and thank you for your question, Mimi. We'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Patricia in Maryland. Your line is now open.

**PATRICIA:**

Hello, thank you for a great conference. I was wondering if you could speak a little bit more about the maintenance rituximab therapy. You mentioned that there's evidence that a two year maintenance period would be useful. You mentioned that it could go longer than two years. And I wondered about your thoughts on that.

Speaker: Stephen Ansell, MD, PhD

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**DR. STEPHEN ANSELL:**

Thank you very much, good question. So I think all of the studies that have looked at the role of maintenance therapy compared to no additional therapy have shown benefit for maintenance therapy. All of the studies, however, there are some studies now ongoing which will take things further, but all of the studies so far have been for two years of treatment. And typically there's been different schedules that patients have received it, either once every two months, once every three months, or four doses every six months. But all of them have really given the treatment predominantly for two years. So I think at this point the most standard approach is to receive maintenance therapy every two or three months, one dose, for about a two year period.

In the trial that I mentioned about comparing retreatment versus maintenance therapy, in that study patients were receiving rituximab until their disease came back, so there'll be more information as data matures as to how much longer one can continue to go with maintenance therapy. But I think at this point the evidence would suggest that one would go with two years maintenance therapy.

**LAUREN BERGER:**

Thank you for your question, Patricia. We'll take the next question from the web and this is from Nanette. "Are six rounds of R-bendamustine necessary or can one get by on less rounds if the therapy is working?"

**DR. STEPHEN ANSELL:**

That's again a very good question. Generally speaking, the studies that have been done, that have shown a significant benefit for R-bendamustine, did give six rounds of treatment. However, patients being treated with R-bendamustine will know that as you get to round number four, five and six, it begins to wear on the bone marrow quite substantially. So I would say that in practice it depends on how well one is tolerating the treatment. If you've had a fantastic result, all disease has melted away, and you've completed four rounds of treatment, it may be reasonable to stop or to just go to the maintenance rituximab approach at that point. But if you really wanted to be a purist and stick with where the data is, that would be the six rounds of treatment. However, as I say, the side effects do tend to mount up as you get more and more rounds of treatment.

**LAUREN BERGER:**

Thank you for your question, Nanette. We'll take the next question from the telephone audience, please.

**OPERATOR:**

Our next question comes from Carol in Iowa. Your line is now open.

**CAROL:**

Hello. My husband was diagnosed with follicular lymphoma ten years ago. He's right now in his second relapse. And we were wondering whether rituximab maintenance would be a good idea or to do nothing.

**DR. STEPHEN ANSELL:**

Again, very good question. A few things to comment on. The fact that one has had follicular lymphoma and had it for ten years would suggest that the disease has moved quite slowly and that's a good sign that would make one optimistic, that you'd have a good result with whatever your next therapy option is.

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**DR. STEPHEN ANSELL:**

I would say as regards the maintenance Rituxan treatment, the data generally would suggest that maintenance rituximab is a good approach, particularly if you've given chemotherapy plus rituximab as your initial treatment. If, however, one wants to watch and wait, it's also reasonable to give four doses of rituximab and then each time the disease looks like it wants to reactivate again, to give four more doses at that point. The retreatment strategy. And the reason is that the retreatment strategy and the maintenance strategy seem to have very similar outcome.

**LAUREN BERGER:**

Thank you for your question, Carol. We'll take the next question from the web and Jane asks, "Please talk about the role and outcomes of radioimmunotherapy as an option for slow-growing lymphomas."

**DR. STEPHEN ANSELL:**

Again, a fine question. Radioimmunotherapy has been a highly effective treatment. We didn't address that much in the presentation. But radioimmunotherapy delivers radiation because it's attached to an antibody that will attach itself to the lymphoma cells. And the evidence would say that it is a very effective strategy, particularly in consolidating benefit from the initial treatment. So typically if one received R-CHOP chemotherapy or some standard induction treatment, to then receive a dose of radioimmunotherapy, one can have a very durable long term benefit from that.

What hasn't really been done really has been to compare head-to-head the rituximab approach versus the radioimmunotherapy approach. So both of them are very reasonable. And I would also add that in a group of patients with relatively low burden of disease, in other words not a lot of disease, who received radioimmunotherapy as their first treatment, these patients also had a very durable long term benefit from treatment. So at this time, this is a very reasonable, very effective therapy. What's not clear, though, is it better or is it similar to some of the other strategies. So I think one can use it if that's something that your physician or you would like to do.

**LAUREN BERGER:**

Thank you for your question, Jane. We'll take the next question from the telephone audience, please.

**OPERATOR:**

Our next question comes from Stella in California. Your line is now open.

**STELLA:**

Doctor, I've had small B-cell lymphocytic lymphoma for ten years. I did go on the rituximab and after the first two sets of treatment, I went in remission. I went on a maintenance program after my two years. Now when I relapse, what would be the best sort of chemical combination to use? I'm sold on rituximab.

**DR. STEPHEN ANSELL:**

Let me ask you a quick question before your line goes off. How long ago did you complete your rituximab treatment?

**STELLA:**

I'm still on it. I'm on a maintenance program.

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**DR. STEPHEN ANSELL:**

Right. So if you're on the maintenance program and your disease comes back, that would suggest that actually your disease is now becoming increasingly resistant to the rituximab therapy. So continuing just with rituximab alone may not be your best choice. But many patients actually might receive the rituximab, finish out maybe a two year period, go into a period of no treatment, and then have their disease come back a few years down the line. In that group of patients, it may be very appropriate to be retreated at that point with rituximab, because again the evidence would suggest that the patients can benefit all over again in a similar fashion to what they've benefitted initially. If you're on the treatment, however, and the disease comes back, it would be very reasonable at that point to be considered for other treatment and often that's in combination with chemotherapy, or also be considered for some of the clinical trials. The drug I mentioned, ibrutinib, the BTK inhibitor, has actually been very promising in patients with small lymphocytic lymphoma and CLL. And so that may be a very reasonable consideration.

**LAUREN BERGER:**

Thank you for your question, Stella. We'll take the next question from the web audience and this one is from Erin. Erin asks, "Does age at diagnosis change the prognosis or the course of the disease? That is if you were diagnosed in your 30s is your treatment different than for someone who's diagnosed in their 60s?"

**DR. STEPHEN ANSELL:**

Yeah, that's a very good question. It does affect your outcome and your management to some degree. I think generally speaking, people are always or should always be treated on their biological age and not chronological age. But if you're a 30 year old patient, the information would actually suggest that your outcome may be better than patients who are older. And that might be for a variety of reasons. One, not least of which might be that you actually tolerate treatment and treatment options to a greater degree. The only downside or a major downside of being younger is that there's a much longer period of time that one needs to live with this lymphoma and hence their need for a variety of different treatments to be considered. I think I'd also add that younger patients are more commonly thought of as good candidates for allogeneic stem cell transplantation. So that may also affect your results and may also affect your outcome because it may be a very good result, because it gets the disease in a long term remission, but it also increases the risk because you might actually have a lot of side effects from the transplant approach. But all told, younger patients do tend to do somewhat better than older patients and as you can see from the FLIPI score, age is actually one of the factors to determine outcome, so it plays a significant role.

**LAUREN BERGER:**

Thank you for your question. We'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Rafael from Texas. Your line is now open.



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**RAFAEL:**

Yes, Doctor. If it's been determined that you're refractory to Rituxan because you've progressed within six months of the last treatment, is it possible to become resistant again to Rituxan over time, if you don't have it for a while? And also if you are refractory, are you likely to be refractory to ofatumumab as well as the other CD20 antibodies?

**DR. STEPHEN ANSELL:**

Yeah, very good questions. I'll take the second one first and that is that a number of the CD20 antibodies are being targeted to try and improve the outcome, particularly in those patients who have proved refractory or have had little benefit from rituximab. So maybe some of these newer antibodies may actually be better for patients that are refractory to rituximab.

The second issue is just to say that rituximab refractory does suggest that you might want to add other agents to the combination, in combination with rituximab, or on their own, to try and get a greater, better benefit from treatment. Patients that progress within six months or who actually don't benefit at all, you could always retreat with rituximab, but the likelihood of benefit is small. So that's where I think it's a better strategy, to bring combinations to the table and potentially consider clinical trials.

**LAUREN BERGER:**

Thank you for your question, Rafael. We'll take the next question from the web audience and this question is "Is follicular non-Hodgkin lymphoma inherited? I have a sister with CLL. If it's not inherited, how did we turn this gene on or how did we get a blood cancer?"

**DR. STEPHEN ANSELL:**

Again, a very good question. As best we know, different to diseases like breast cancer where there is a clear-cut genetic or gene that predisposes patients to the disease, we don't have that particular gene in follicular lymphoma and in other kinds of lymphoma. However, there may well be some genetic changes, which make people more susceptible. So it doesn't guarantee that they get lymphoma, it just puts them in a greater risk to get lymphoma. And it might require a second event, either an exposure to something or an additional genetic change in their cells or something else to happen, for there to be a trigger that then generates lymphoma. Because if one does studies of families, there's definitely an increased likelihood of getting lymphoma in certain families, but not in all. And there's no guarantee that you, as a child, are going to get lymphoma if your parent had lymphoma. So this is still an area of active investigation. So although there are some family predispositions, there's not a clear genetic link.

**LAUREN BERGER:**

Thank you for your question, Nan. We'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Laurie in California. Your line is now open.

**LAURIE:**

Yes, Hi, Dr. Ansell. Great presentation. My question relates to the two slides you had about Revlimid. The one slide appeared to be published in 2009 and showed that the response rates, while significant, weren't all that appealing. And then the response rates overall and complete remissions on the ones that

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**LAURIE:**

were dated 2012, where Rituxan was incorporated in the treatment, appeared to be far superior. And I was just wondering is that because of the use of Rituxan in that particular study or is it because the dosing of Revlimid was changed? And if you could comment on that.

**DR. STEPHEN ANSELL:**

Thank you very much. That's a great question. I think very important to recognize, that the two groups of patients that are treated in those two studies are very different from each other. The group of patients that were treated in the first study were treated after they'd received a lot of other treatment and they may have had quite a lot of disease, big bulky lymph nodes, and somewhat resistant to a variety of other chemotherapies administered prior to this. And that resulted in a response rate in about a quarter of patients, but clearly not the majority.

The study that was done in combination with rituximab, all those patients in that trial were treated as their very first therapy, plus they were only included in the study if they had a low amount of disease, not a lot of disease. So clearly that's a very different patient: first treatment, low burden of disease, compared to multiple previous therapies, high burden of disease.

I think it also speaks to the fact that lenalidomide-Revlimid provides an immune activation and if you've had a lot of previous chemotherapy, your ability to activate your immune system may be limited and that's where the benefit might be greatest, earlier on in the disease, hence the good results from the first study.

But I think it's also important, and this is where there's a comparative study, comparing rituximab alone to rituximab plus Revlimid. There have been studies of just using rituximab alone, with a response rate of 80% when you pick patients that had a very small amount of disease. So patient selection plays a big role here.

**LAUREN BERGER:**

Thank you for your question. We'll take the next question from the web audience and this is from Dorothy and Dorothy asks, "Can Rituxan increase LDH levels months after chemo treatment? My LDH was 197 at the beginning of chemo. Three months later it is 284. Should this be a concern?"

**DR. STEPHEN ANSELL:**

That's a very good question. The LDH is not a very specific test. It really just tells you that cells are active and growing. Now those could be normal cells. They could be lymphoma cells. They could be bone marrow cells in response to growth factor injections. That number on its own is not that helpful and it's much more important to put that in the context of the whole patient. But rituximab itself, to the best of our knowledge, does not increase the LDH. But chemotherapy and sometimes recovery after chemotherapy and growth factor injections such as Neupogen and Neulasta, those can all increase the LDH. So it could be entirely unrelated to rituximab therapy, but related to something else.

I'd also just add that occasionally in some patients, when the LDH goes up, but usually in conjunction with enlarging lymph nodes or heavy drenching sweats or high fevers or losing a lot of weight, there is the risk of a transformation to a more aggressive lymphoma. So if the LDH is increasing and particularly if other symptoms, or lymph nodes are present, they always need to be evaluated.

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**LAUREN BERGER:**

Thank you for your question. We'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Christine in New York. Your line is now open.

**CHRISTINE:**

Hi, Doctor, thank you for the presentation. My question is what is considered a relapse after Rituxan maintenance for two years? Say after R-CHOP, six cycles of R-CHOP. And from what I understood, you're saying that Rituxan, if you are in remission after the maintenance, another course of treatment with Rituxan could be considered after recurrence or relapse.

**DR. STEPHEN ANSELL:**

Right. If I understood your question correctly, if you've received R-CHOP chemotherapy and then been on maintenance therapy, if you actually progress while on maintenance therapy or very shortly after completing maintenance therapy, I would not recommend that you immediately were treated with rituximab alone. Because I think your likelihood of benefit is extremely small. If in contrast you either did not receive maintenance rituximab, or you received maintenance rituximab for two years and then were off treatment for two or three years and then have your disease come back, then that's very appropriate to be considered for rituximab treatment again. And the reason is there was actually a comparative study done where patients received rituximab, had a response, and then were retreated at a time of disease activity again, with rituximab, and it showed the responses were similar. So patients who responded tended to respond again. So those who didn't respond tended not to respond again. So I think how you did with your initial treatment is often a suggestion of how you're going to do when you get retreated. So in those who don't benefit much, I think additional treatment should be added. And those who clearly benefitted substantially, retreatment with Rituxan is very appropriate.

**LAUREN BERGER:**

Thank you for your question, Christine. We'll take the next question from the web audience and Lynne asks, "Can one have an allogeneic transplant if their bone marrow is involved with the lymphoma?"

**DR. STEPHEN ANSELL:**

And that again is a good question. The answer is yes, you can. So when you have an allogeneic stem cell transplant you in essence are replacing your entire immune system with the immune system of somebody else. So the treatment can either be what we call myeloablative, which means all bone marrow and all immune system is totally wiped out and then the new immune system is put in. Or you can have a reduced intensity or non-myeloablative transplant, where your old immune system, the patient's immune system is suppressed substantially, but not necessarily wiped out, and the new immune system is put in and given free rein. So the new immune system will actually force out the old immune system. The problem is that if there's actually a lot of cancer activity still, then neither approach is particularly successful. So you can have the transplant, an allogeneic transplant, even if there still is disease in the bone marrow, but it's not a good strategy if there's a lot of disease in the bone marrow, suggesting that the patient has not really benefitted from previous treatment and it may be very difficult for either the immune system or the chemotherapy treatment to eradicate the cells in the bone marrow.

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**LAUREN BERGER:**

Thank you for your question, Lynne. We'll take the next question from the telephone audience, please.

**OPERATOR:**

Our next question comes from Jody in Florida. Your line is now open.

**JODY:**

Thank you. Hi, Dr. Ansell, thank you so much for such an informative presentation. I was diagnosed with subcutaneous panniculitis-like T-cell lymphoma in October of 2009. The treatment plan that we went with was cyclosporine with a combination of prednisone. I was weaned off the cyclosporine as of October, 2011 and I'm still on a maintenance of prednisone, 5 milligrams per day. I guess what I'm wondering is, what would happen, would I be able to go back on the cyclosporine if it's so far worked so well. I haven't developed any more lumps or anything since then, so I'm just wondering.

**DR. STEPHEN ANSELL:**

Yeah, very good question and I think for those on the call important to know that subcutaneous panniculitis-like T-cell lymphoma is a little different. It's actually a T-cell lymphoma and behaves in a different fashion. But to answer your question, you've had a very nice result with the cyclosporine and the prednisone and so I would put to you that if your disease reactivates, restarting the cyclosporine may be a very reasonable approach and hopefully you'll get a similar benefit like you did before. I also would encourage you to say that there are other new drugs that are available that may really benefit this particular disease and these include drugs such as romidepsin or pralatrexate and other standard chemotherapy options, too. But I would keep those in reserve and retry the cyclosporine, as you suggest.

**LAUREN BERGER:**

Thank you for your question, Jody. We'll take the next question from the web audience and this one is from Brian. Brian asks, "Besides the BTK inhibitor, are there any other new tyrosine kinase inhibitors that show promise?"

**DR. STEPHEN ANSELL:**

Yeah, that again is a very good question. There are a number of pathway-specific therapies, therapies that are targeting further downstream, everything from PKC-delta to mTOR to the PI3 kinase pathway. So there are multiple tyrosine kinases or activated phosphorylated proteins that are part of that pathway, all of which are being specifically targeted. However, the other tyrosine kinase inhibitors that have proved very successful for leukemias and other diseases are very specific for the tyrosine kinases that are active in those diseases. And to date they haven't really been very specific for lymphoma. So we're in the era now of highly targeted, focused therapies that are specific by disease and even by patient. So although there are some of them that are active, most of the activity right now is focusing on pathway-specific. And some of them are a little further down the pathway, if you like, than the tyrosine kinase part of the pathway.

**LAUREN BERGER:**

Thank you for your question, Brian. We'll take the next question from the telephone audience, please.

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**OPERATOR:**

The next question comes from Teresa in Colorado. Your line is now open.

**TERESA:**

Yes, my question is how do these treatments affect the bone marrow if the lymphoma is in your bone marrow? We talked about how it affects the nodes and so forth, but how do the treatments affect the bone marrow?

**DR. STEPHEN ANSELL:**

Yeah, great question. Generally speaking, the goal of all treatment is to get at the disease no matter where it is. And that includes the bone marrow and includes the blood, includes the lymph nodes, includes the spleen, other sites of disease. So many of the agents will be able to get to all of those sites and whether it be chemotherapy, whether it be rituximab therapy, all of these will have an effect, not just on the lymph nodes, but on the bone marrow as well. And that's the reason for giving most of these treatment intravenously, or have you take a pill that gets absorbed and subsequently goes around intravenously, so that it has an effect on all of these sites to suppress the cancer, be it in the bone marrow, be it in the lymph nodes. I would put to you, though, that some of the chemotherapies do have an effect on the bone marrow from a perspective of decreasing the blood counts, so it has both a good effect and a bad effect, and that sometimes requires us to make some modifications to the treatment, either to how frequently you give it or the dose that's given, because it has some negative effects as well. But as far as treating the cancer is concerned, it will have effects both in the bone marrow and in the blood and in the lymph nodes or the spleen.

**LAUREN BERGER:**

Thank you for your question, Teresa. We'll take the next question from the web audience and this is from Scott. Scott asks, "When will some of these novel treatments and drugs in clinical trials be available more widely? Do you have to be near a clinical trial site to participate, since most patients otherwise would not have access to these drugs, even if they could benefit now?"

**DR. STEPHEN ANSELL:**

Again, a very good question. Generally speaking, many drugs these days are being fast-tracked to approval, particularly when they're highly effective. I would use bendamustine as an example, that three or four years ago, that was a drug that was in clinical trials, now it is a drug that is commercially available. The drug ibrutinib, the BTK inhibitor, that is currently on fast track, that if the results prove as good as they currently have proved so far, that may be a drug that may already be approved, particularly for small lymphocytic lymphoma, within the next year to 18 months. So I think many of them are being made available to patients generally in a much quicker process than might have been before. However, if the drug is not yet commercially available, that does require you to participate in the trial and that's where it can be a little challenging if where you live is not close to a center that may have access to those studies.

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**LAUREN BERGER:**

And I'd like to just add to that, to Scott and anyone else who's interested in more information about a clinical trial, there may be something that is closer to home than you might know about. But at least to get information, call The Leukemia & Lymphoma Society Resource Center at 800-955-4572 and they will do an individual search for you, to get more information about a clinical trial that might be available to you.

So we'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Sarah in Michigan. Your line is now open.

**SARAH:**

Hi, I just had a question regarding the, is it the CDK?

**DR. STEPHEN ANSELL:**

Yes. So CDK inhibitors or CDK, variety of different CDKs, are proteins that regulate the growth of a cell. And many times if they are not doing their job and may allow the cell to continue to grow, even when it's not appropriate, using an inhibitor that controls the growth of the cell, may actually be quite beneficial. So there are particularly CDK5 and 6. There are a number of inhibitors that have been very specific for that and actually have proven very promising in clinical trials. Certain lymphomas, particularly like mantle cell lymphoma, seem to be CDK – variety of CDKs appear very important in those diseases. And so inhibiting that with a CDK inhibitor is a very appropriate way to go. If one's interested in that, again, I would be talking to my doctors about participating in those clinical trials because that may be very beneficial, particularly if other more standard therapies have been exhausted.

**LAUREN BERGER:**

Thank you for your question, Sarah. We'll take the next question from the web and this one is from Michele and Michele asks, "Should I be concerned about radiation from the scans that I need to have in terms of being monitored?"

**DR. STEPHEN ANSELL:**

Yeah, again a good question. I would say that scans these days have become much, much better with far less radiation than previously. And I think the risk of developing a further problem from the exposure to radiation is extremely low. I also try and stress to patients that for most patients with lymphoma, the greatest risk they have is from the lymphoma they currently have. Far, far greater than the risk they might get from a second or another problem that could develop from the radiation. And I would also say it's really important to really know whether disease is benefitting from treatment or progressing or something like that. So all told, when you weigh out the risks and the benefits, the benefits of having the scan done very much outweigh the risks of any side effects from the scan. And I would encourage people not to be overly concerned about scans. The only caveat is if you have done very well with treatment and have been in remission for years, then it's very appropriate to cut back on the scans because the idea then is hopefully you're not going to have any further problems from the lymphoma and then you want to minimize any risks. But while you're on treatment or early in your disease course, the scan is critical and I would encourage people not to shy away from it.

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**LAUREN BERGER:**

Thank you for your question, Michele. We'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Martha in Maryland. Your line is now open.

**MARTHA:**

Hello, and thank you very much. I have a lot of leg cramps, severe leg cramps, and I figure it's low potassium. I don't know if it's related to my treatment. I find eating a banana seems to help. But I was wondering if cancer treatment does have that side effect of severe leg cramps.

**DR. STEPHEN ANSELL:**

If I could just ask, are you on treatment right now and if so, what treatment are you receiving?

**MARTHA:**

I have received rituximab, wait and watch, and I have received bendamustine, but I will be in a clinical trial very soon for ibrutinib. And I'm not in treatment right now. I'm waiting to go I think in June or July. They'll start a new clinical trial with that drug.

**DR. STEPHEN ANSELL:**

Right. Well, just to say that certainly some leg cramps can be associated with some of the chemotherapies that are given for lymphoma. Also just being generally ill, if you have a lot of active lymphoma, can also bring about leg cramps. And then also there are some patients who might have leg cramps that are almost entirely unrelated to their treatment and would benefit, as you said, from correction of various minerals in the blood or from a walking exercise program or from stretching. There are a variety of different things that can be tested. I would say that again that's an important thing to discuss with your doctors and particularly as treatments are being chosen, to choose drugs that wouldn't make your leg cramps worse. So it's a little hard to know exactly whether the treatment you're on is specifically causing that. The fact that you're not on treatment might suggest that that's not the case. But certainly moving forward, selecting therapies that would not worsen that would be an appropriate thing to do.

**LAUREN BERGER:**

Thank you for your question, Martha. We'll take the next question from the web and Lisa asks, "Can you go back a stage? For instance, if you're in stage III, can you go back to stage II if you have lymph node removed?"

**DR. STEPHEN ANSELL:**

That's again a good question. Generally speaking, what you want to do is to say what is the most extensive the disease is and use that as the staging. Removing a lymph node doesn't really make your stage go down because microscopic cells that were right next to where that lymph node was, might persist. And the point of doing the staging is really to get a sense of where the cells might have spread to. You use the cells that are detectable, but you assume that there may well be some others that are not detectable that are in the same region. So removing it doesn't really change the stage, and certainly in

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**DR. STEPHEN ANSELL:**

my practice I wouldn't change my treatment just because a lymph node was removed. I would assume that lymph node was still there, as it were, in making a treatment decision.

**LAUREN BERGER:**

Thank you for your question, Lisa. We'll take the next question from the telephone audience, please.

**OPERATOR:**

Our next question comes from Tina in California. Your line is now open.

**TINA:**

Dr. Ansell, I am so pleased. I have Waldenstrom's and I wasn't able to make the foundation's educational forum this last weekend, so here you are. Can you tell me specifically, as far as you know, with the fast-tracking of ibrutinib, in the year to 18 months that it should be approved, would it be, I mean, for our little rare orphan disease—Waldenstrom's macroglobulinemia? Or just the CLL it's been pretty much trialed for? And would Medicare pay for it if it is approved or only for the specific lymphomas it's been approved for?

**DR. STEPHEN ANSELL:**

Very good questions. So again I think for the audience, just so that they know, Waldenstrom's macroglobulinemia is also a slow-growing, low grade kind of lymphoma, but is associated also with a protein, an antibody protein in the bloodstream. So it often affects the bone marrow and the protein can cause a number of symptoms. So to answer the question about ibrutinib, generally speaking, most strategies for getting drugs approved are very focused in the beginning and my prediction is that the folks developing ibrutinib will get it approved initially for just the CLL and maybe for mantle cell lymphoma. But very commonly, as with rituximab and other drugs, right on its heels then there is a broadening out of the indication to other diseases. So I would be hopeful that in the not too distant future there will be access for other diseases, too. But I think at this point, to answer the question also about what will Medicare pay for, initially that they will probably most likely pay for where it would be approved, the approved indication, but obviously as that indication expands, the hope is that that would be available then to more diseases that are similar and all the low grade type of lymphomas.

**LAUREN BERGER:**

Thank you for your question. We'll take the next question from the web audience and Chloe asks, "I am 46 years old with grade 2, stage I follicular lymphoma. I have minimal symptoms and occasional night sweats. I'm tired and I'm having itching. I'm being treated with R-CVP. Is it possible that I'm being over-treated and am I harming myself?"

**DR. STEPHEN ANSELL:**

Very good question. When you have a small amount of disease, R-CVP is a very appropriate treatment. It's, in the grand scheme of things, is not a very intensive therapy. It's clearly a more intensive therapy than rituximab alone or just watching and waiting, but it's still not an extremely intensive treatment. The recommendation, however, would be to receive the treatment for a period of time, maybe six months. If you've had a good result, in other words, all measurable disease is now not detectable any more, it



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**DR. STEPHEN ANSELL:**

would be very appropriate at that point to stop the chemotherapy and maybe just continue with the rituximab therapy or no therapy. The idea is not to just keep going with chemotherapy for a very long period of time because then there is a risk that you could hurt the bone marrow or cause other problems. So long term chemotherapy is not a great strategy. It's a better strategy to get disease control and retreat but not continuously treat.

**LAUREN BERGER:**

Thank you for your question, Chloe. We'll take the next question from the telephone audience, please.

**OPERATOR:**

Our next question comes from Lisa in Florida. Your line is now open.

**LISA:**

Hi. I have a question. It was a great conference you did. I had low grade follicular lymphoma, which was also a small trace in my bone marrow. I just finished with my maintenance treatment last Thursday. I had eight rounds of Rituxan to cure me. And then 16 maintenance treatments. So it was four treatments every six months. My doctor said that would, you know, it's been proven, not guaranteed, to keep it away for 10 to 15 to 20 years. My second question is if that's true, what percentage of people that are in remission, like I am, that it's never come back, and has lymphoma ever spread to other areas in the body? And I really didn't have any symptoms, even though I was loaded down, I wasn't fatigued, I did have the sweats and I was in menopause and I am currently 49. So I don't know if mine was graded. He just said it was low grade, I mean stage. He did say in the beginning he would have treated it as if it was stage IV for treatment, but it's not that I had stage IV.

**DR. STEPHEN ANSELL:**

Good questions. Firstly just to say, it would sound from the statement of low grade lymphoma, that it's most likely a follicular grade 1 or 2. The fact that you had a small amount of bone marrow involvement would make your disease stage IV. So I would say that the treatment that was given was very appropriate and your physician is quite correct in that you've received a very standard approach of treatment that has a proven track record and many patients may benefit substantially and have a very durable long term remission. And I really trust you're going to be one of them. I would caution, though, to say in those studies, and experience with treating patients, there is a significant spectrum of disease. In other words, some patients who go many years without the disease coming back, some people who are 10, 15, 20 years out and the disease is still not giving any trouble. But equally there are a number of other patients where the disease has reactivated and require further treatment. There clearly is a role that your immune system needs to play to keep the disease in check. We don't always know to what degree the rituximab has cleared out every single cell or not. So what I'm saying in all of that is it sounds like you've done wonderfully well and I trust that it continues to go well, but I would still recommend ongoing long term follow-up with your doctor and regular routine checkups because, unfortunately, there's not a guarantee that the disease will stay gone. But certainly there's a high likelihood of a durable remission and that's really what we're hoping for.

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**LAUREN BERGER:**

Thank you for your question, Lisa. We'll take the next question from the web and this is from Scott. "Dr. Ansell, you talked about high disease burden and low disease burden. I know that for some patients that isn't so cut and dry. What if a patient is diagnosed with grade 1, stage IV follicular non-Hodgkin lymphoma with three sites of tumors, but otherwise no symptoms, no elevated LDH, and normal blood tests? Would you suggest watchful waiting?"

**DR. STEPHEN ANSELL:**

Yeah, very informed, good question. The most important part of all of your disease management is always patient symptoms. If the patient feels really well with no real problems going on, it's not appropriate always just to dive in with treatment just because you can. Even with patients with more disease, it may be relevant and reasonable to continue to observe and monitor patients without initiating treatment. I often joke and say our goal is to initiate treatment the day before you get symptoms, but that's often obviously hard to know. But the idea is that if you have disease symptoms that can be benefitted from treatment, that's exactly when you would consider treatment. If a patient is in good health and no symptoms at all, treatment is likely to bring on symptoms rather than alleviate symptoms. So that's the reason for a watchful waiting approach being very reasonable in many patients.

The point you also made, which is really good, is that it's very difficult to know sometimes exactly where the low burden of disease or high burden of disease, where it starts and where it ends. But in what was described, I would say that this sounds like a relatively low burden of disease in an asymptomatic patient. And so because of that, that would be a very appropriate course of strategy and that is to be observed with a vigilant eye, with a plan to initiate treatment at any point if the disease becomes active and causes symptoms.

**LAUREN BERGER:**

Thank you for your question, Scott. We'll take the next question from the telephone audience, please.

**OPERATOR:**

The next question comes from Carol in New York. Your line is now open.

**CAROL:**

I've had lymphoma for seven years and just low grade, very low grade, and all of a sudden I've had ITP within the last year, where I'm losing platelets and have to go in once a month for an infusion. And I'm wondering if this is related, is this related to the low grade lymphoma or is it something totally different?

**DR. STEPHEN ANSELL:**

Very good question. So for those on the call and are not sure what ITP is, it's immune-mediated thrombocytopenia and what that means is there are antibodies being produced that are binding to platelets and depleting platelets out of the system, so patients have very low platelet counts, may be at risk for bleeding or something like that. Whether or not it's associated, it's hard to know in your specific case, but in general there can be an association with various types of low grade lymphoma and patients then getting ITP. So sometimes the treatment actually might be for both at the same time, where rituximab can be used because it targets the cells that make the antibodies, but it also targets the

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**DR. STEPHEN ANSELL:**

lymphoma cells. So that's something I would best refer back to your doctor to say could they more specifically answer the question as to whether they are directly related, but I would certainly say that's possible.

**Slide 38: LLS Resources**

**LAUREN BERGER:**

Thank you for your question, Carol, and thank you all for your questions. Our program has come to an end and we hope this information will assist you and your family in your next steps. We received so many questions that I know we were not able to get to all of them on the call today, but I do want to let you know that we will do a follow-up Q&A with Dr. Ansell. He has so graciously agreed to volunteer his time for 30 more minutes of questions and answers, so we will take the questions that you submitted and Dr. Ansell will respond to them and we will put that up onto the web with the rest of this program as an archive program. And as a follow-up, you will be able to get that information at [www.LLS.org/lymphomaeducation](http://www.LLS.org/lymphomaeducation). So you can look forward to that, too.

Also if you have additional questions, please feel free to call The Leukemia & Lymphoma Society's Information Specialists toll-free at 800-955-4572 or reach us by email at [infocenter@lls.org](mailto:infocenter@lls.org). Our specialists can provide you with information about lymphoma research, clinical trials, and other questions that you may have about disease treatment and questions about financial assistance for treatment.

Also if you're interested in participating in another upcoming program on peripheral T-cell lymphoma or other blood cancer topics, please go to [www.LLS.org/programs](http://www.LLS.org/programs).

Please help me thank Dr. Ansell. We are so grateful he has volunteered his time with us today. And on behalf of The Leukemia & Lymphoma Society, Dr. Ansell and I would like to thank you for sharing your time with us today. Good-bye and we wish you well.