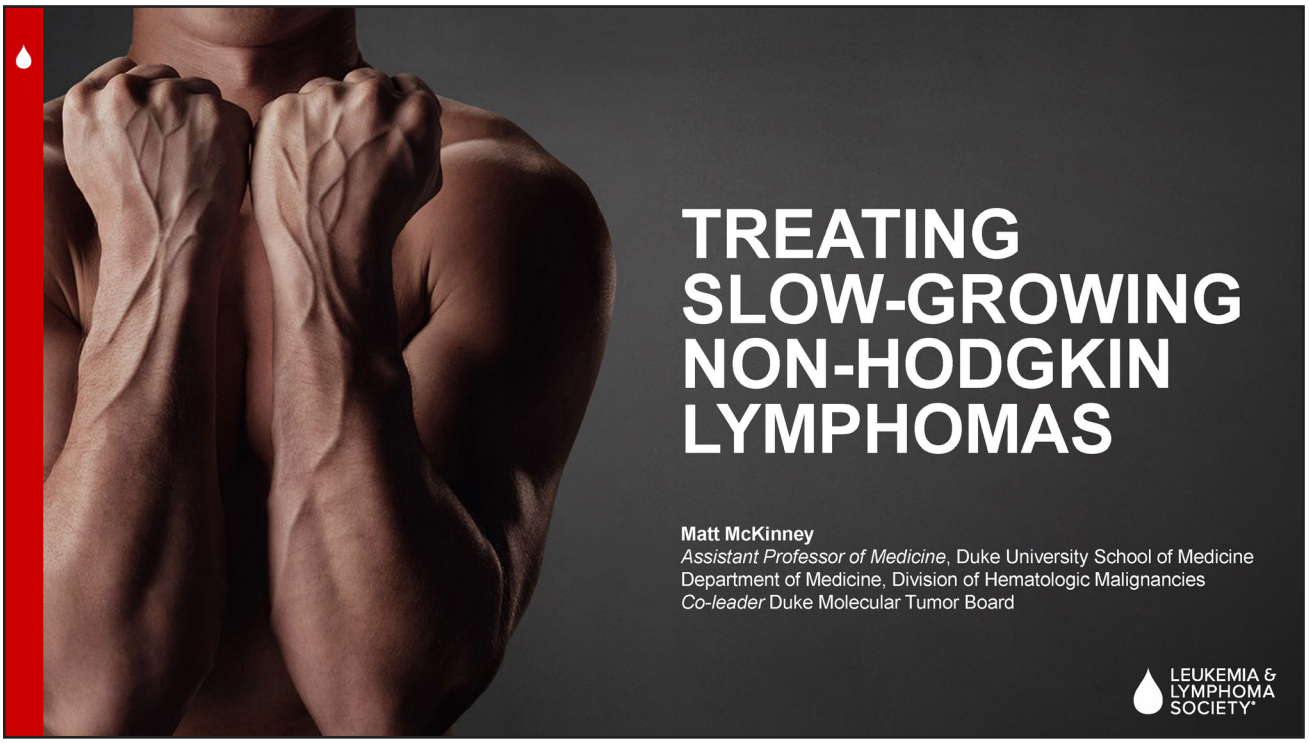


Slide 1: TREATING SLOW-GROWNG NON-HODGKIN LYMPHOMAS

Greetings and welcome to ***Treating Slow-Growing Non-Hodgkin Lymphomas*** telephone and web education program. It is now my pleasure to introduce your moderator Lizette Figueroa-Rivera.

Slide 2: INTRODUCTION

Hello, everyone. On behalf of The Leukemia & Lymphoma Society I would like to welcome all of you.

Special thanks to Dr. Matthew McKinney for volunteering his time and expertise with us today.

We have seen and experienced changes to cancer care due to the COVID-19 pandemic, and we want to ensure that we provide you, our blood cancer patients and caregivers with the latest information on how COVID-19 may impact you. You may find current information about COVID-19, as well as the COVID vaccines, on our website at LLS.org/Coronavirus.

For this program, we would like to acknowledge and thank Bristol-Myers Squibb, Epizyme, Genentech and Biogen, and Pharmacyclics, an AbbVie Company, and Janssen Biotech for support of this program.

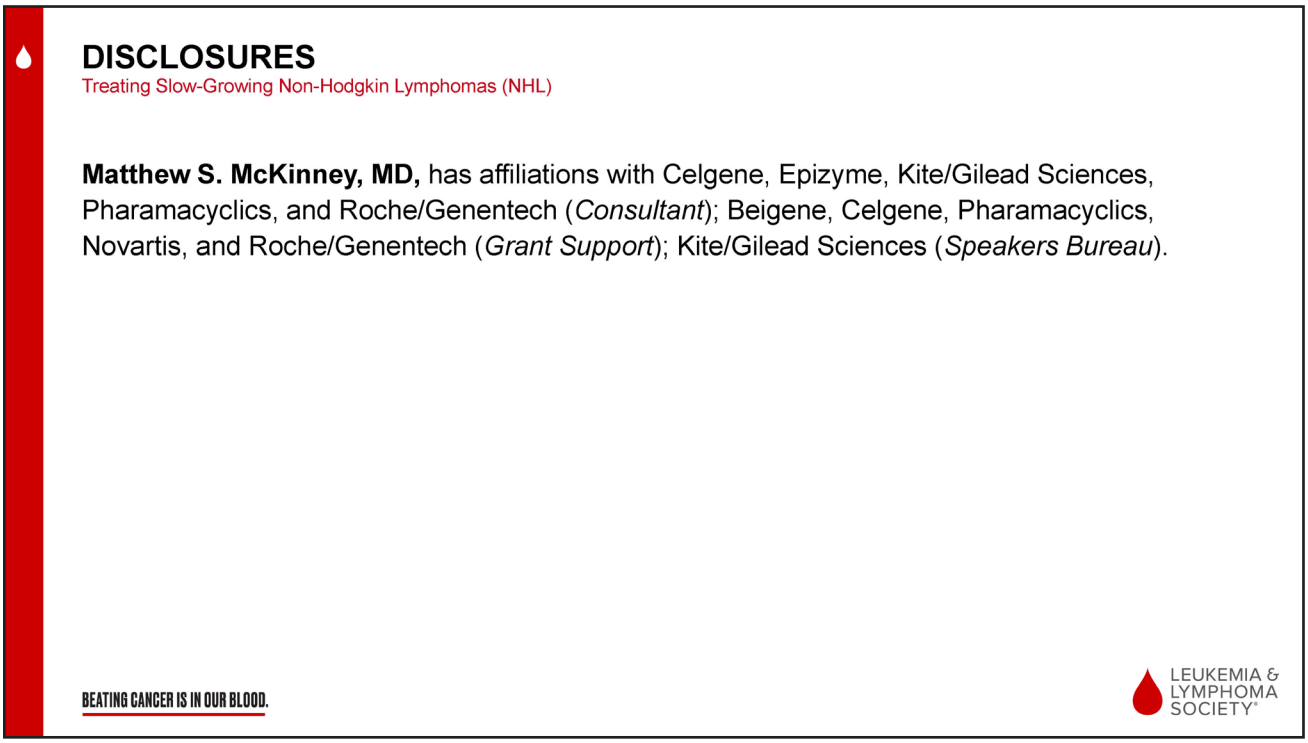
If you are participating today by computer, Dr. McKinney's slides will display as you see him via video and hear his audio through your computer. You can also view or print the slides from our website at www.LLS.org/Programs.

Following the presentation, we will take questions from the audience.

I am now pleased to introduce Dr. Matthew McKinney, Assistant Professor of Medicine at the Duke University School of Medicine, Division of Hematologic Malignancies, in Durham, North Carolina. Dr. McKinney, I am privileged to turn the program over to you.

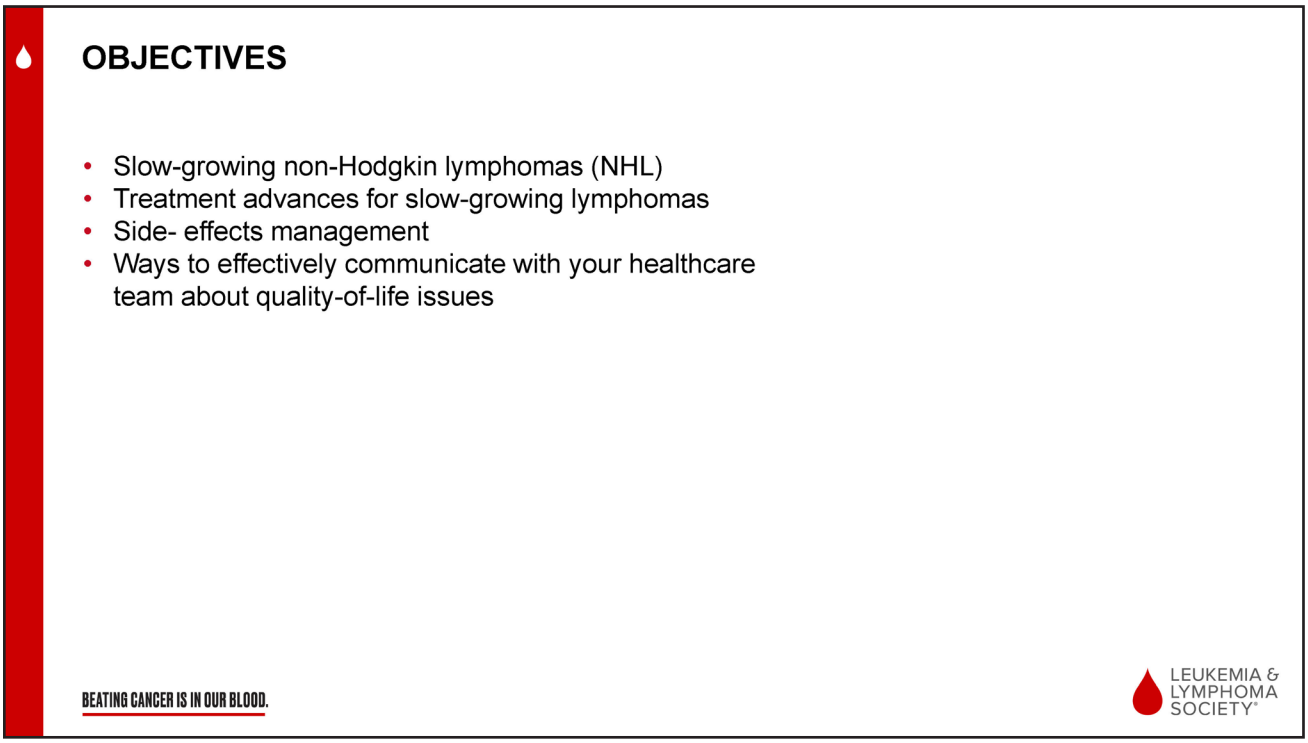
Dr. Matthew McKinney:

Thank you, Lizette. I'm certainly honored to be able to be here today to present to you all. LLS is just a fantastic organization I think both for our patients, in terms of communication, as well as support getting on medicines. They've also supported our research work at Duke in many, many ways, and I think the number of folks on is very much reflective of that strength of LLS.



Slide 3: DISCLOSURES

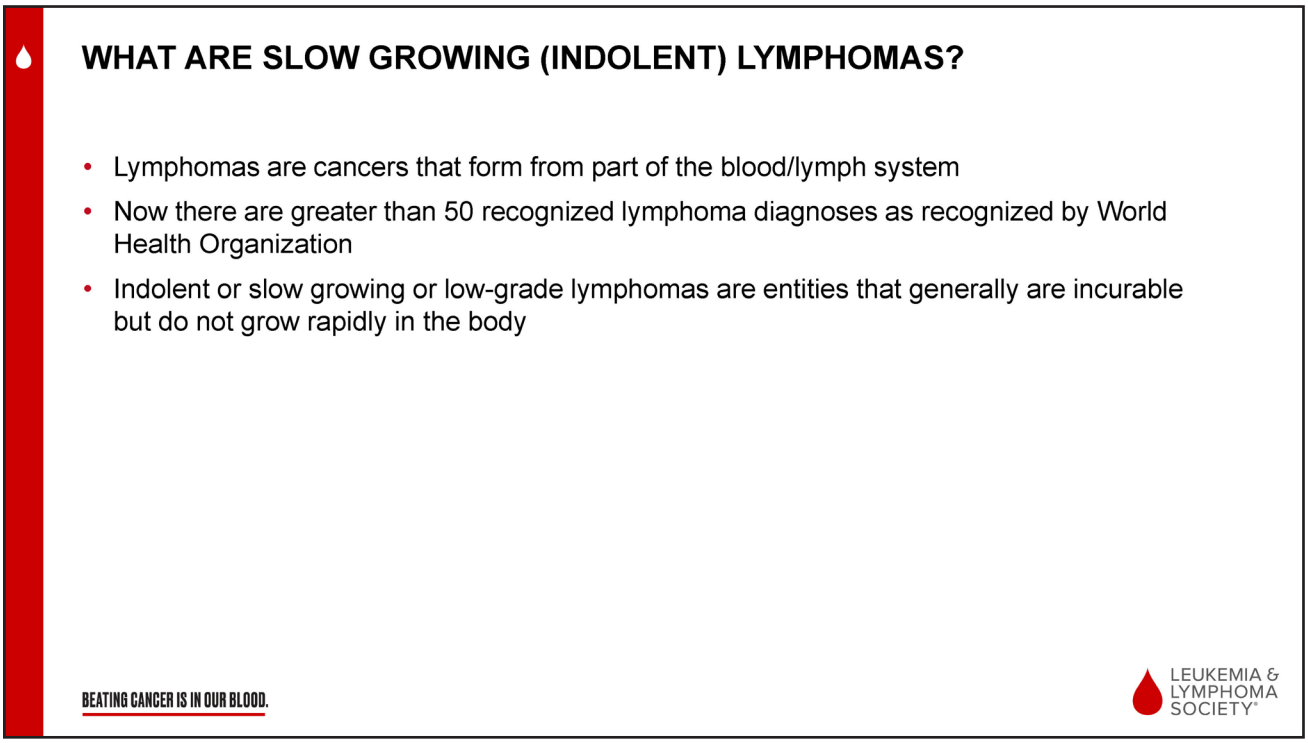
I will point out I do have a few disclosures to make, which is mostly around research funding for some of the clinical work that we do, as well as some educational things around CAR-T cells, which is listed here.



Slide 4: OBJECTIVES

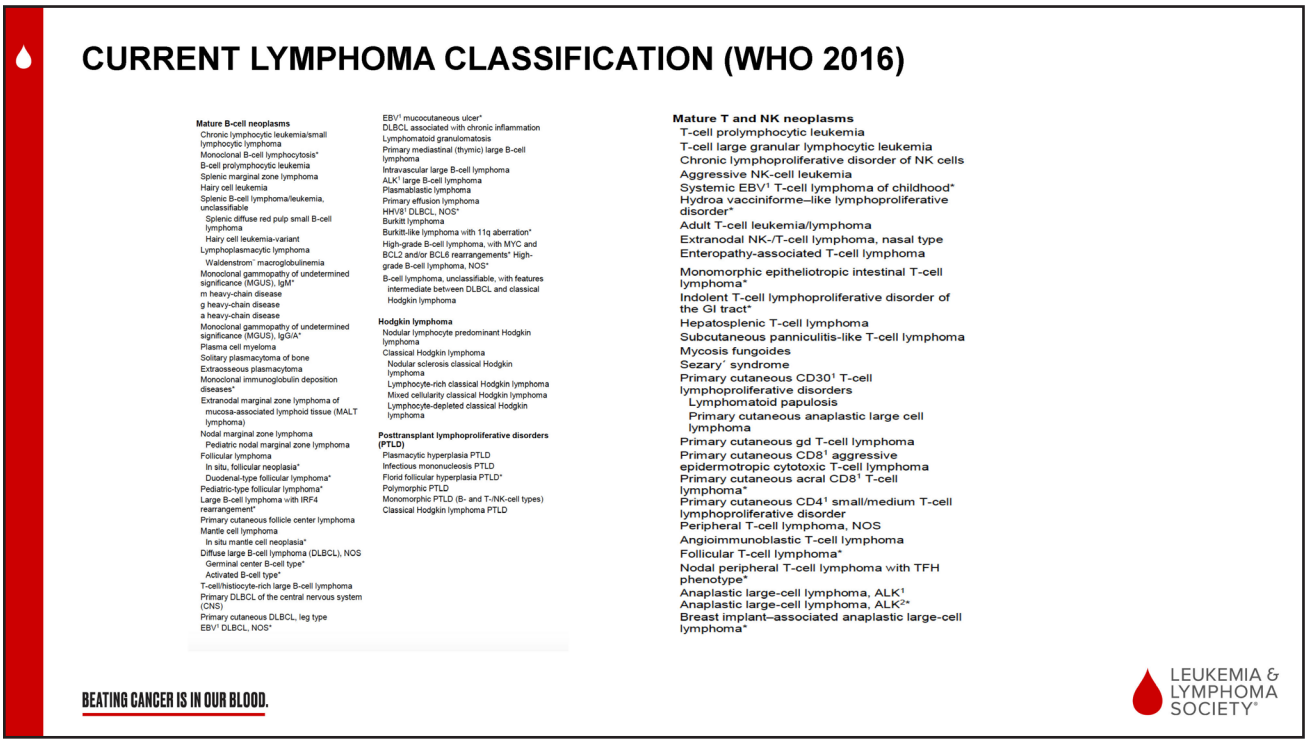
With that, I'll go ahead with the program. I think this is a very informational set of slides we've put together and good information, particularly around treatments and ways to communicate, mainly around side effects and decision making.

So, I'll go through 4 things. One will be to introduce you to the spectrum of slow-growing or indolent or low-grade non-Hodgkin lymphomas that we think about. And then, talk about some of the most recent treatment advances for some of the slow-growing lymphomas. A lot of this will be around follicular lymphoma, which is probably the most common lymphoma suffered by people on this call. And then, we'll discuss ways to think about how you consider side effects and decision making and ways to approach managing those. And then, some tips for communicating with your healthcare team about many of those issues. At the very end, I'll have some very specific kinds of hints and tips and things that are sort of up to date with how we're thinking about COVID-19 in lymphoma patients and also coronavirus vaccination, which I think may be very important issues for you all to consider.



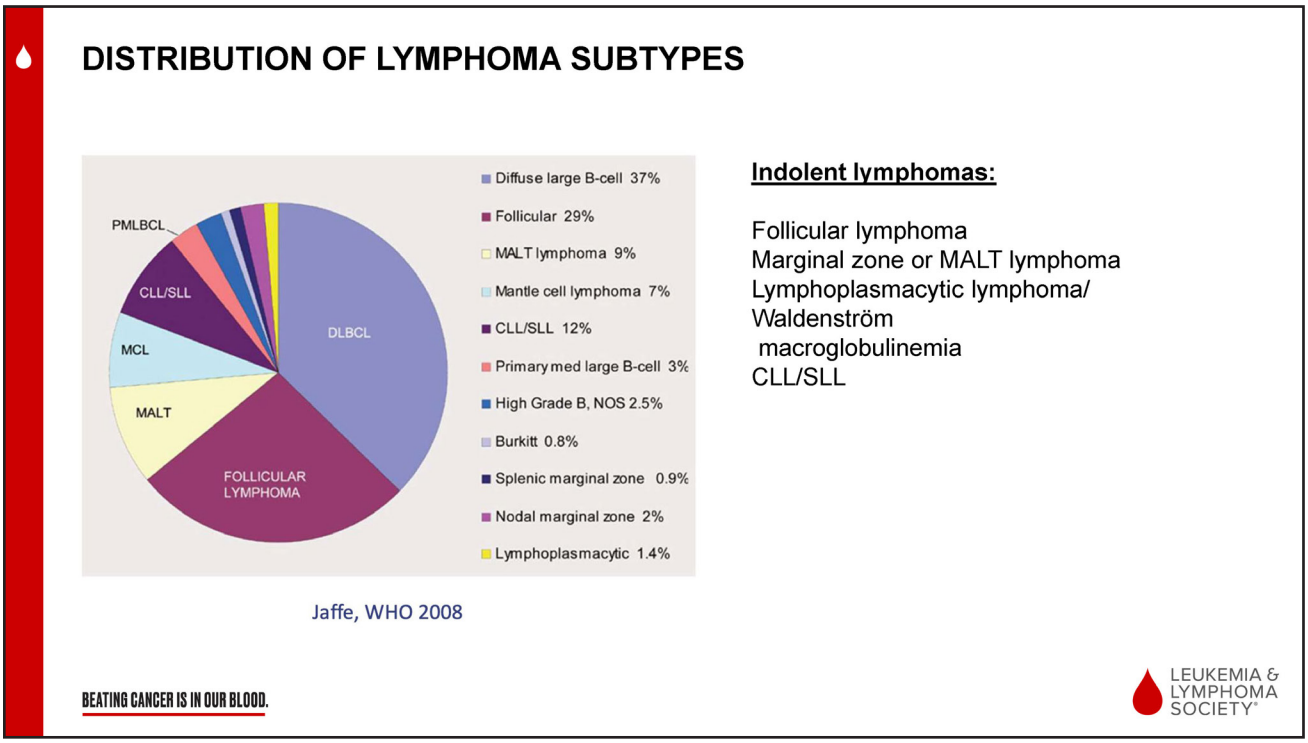
Slide 5: WHAT ARE SLOW GROWING (INDOLENT) LYMPHOMAS?

So, the first question is what are slow-growing or indolent lymphomas, what do those terms mean? So, I think we should step back and understand that lymphomas are generally blood cancers, so they're cancers that form from your blood cells or lymph system, which is part of the complicated human immune system. And, I think it's important to understand that we now recognize more than 50 different lymphoma entities, so I think a lot of patients get very confused with understanding the non-Hodgkin lymphomas, a very generalized term with literally many dozens of different illnesses that all have their own behavior. And, I think we're also learning more and more that, 2 lymphomas that look the same under the microscope, can behave very differently in the clinic and so we have to kind of take a personalized approach.



Slide 6: CURRENT LYMPHOMA CLASSIFICATION (WHO 2016)

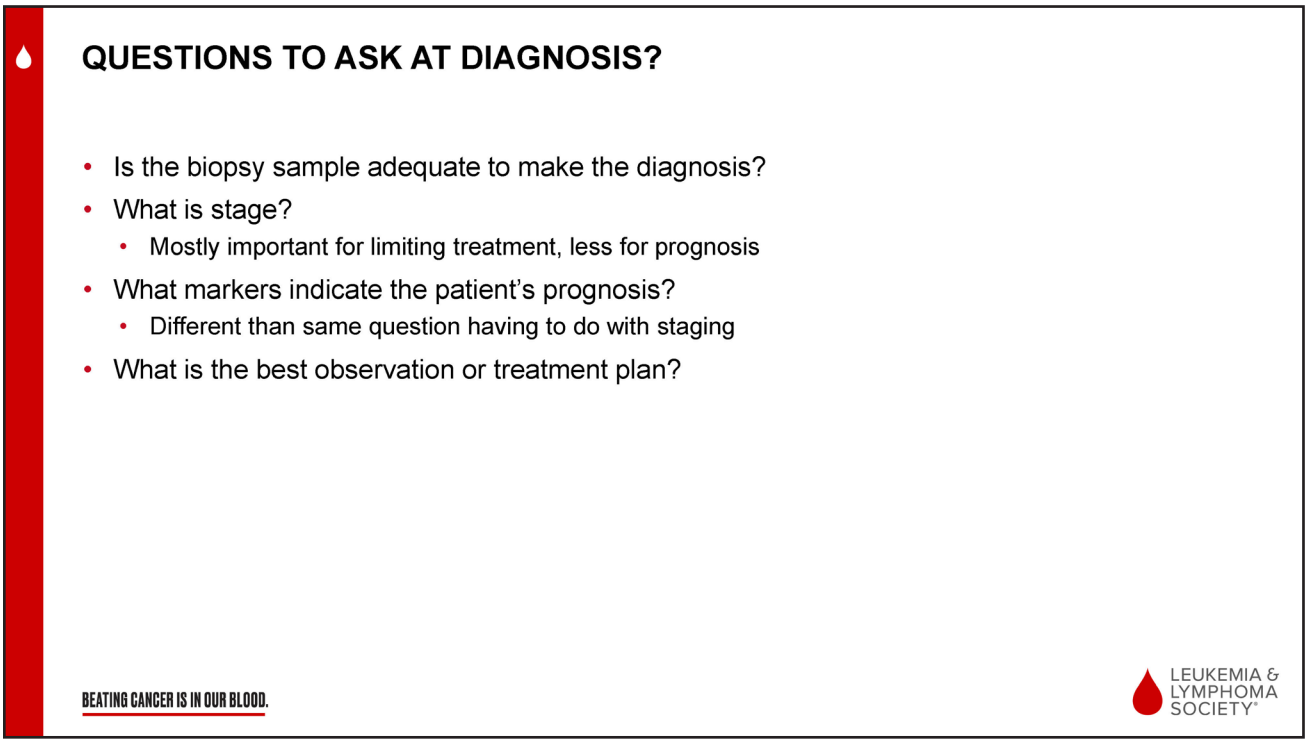
And, the other generalized thing is there's no necessary definition of the indolent or slow-growing lymphomas in terms of their behavior or some sort of objective criteria, but in general they are entities that we think of as being incurable forms of blood cancer that, in general do not grow rapidly in the body, but often do have important health implications and need sometimes complicated treatments that have a lot of side effects for the patient.



Slide 7: DISTRIBUTION OF LYMPHOMA SUBTYPES

Again, this slide sort of reiterates the fact that there's a lot of complicated decision making around the individual diagnoses, but the main point that I will make to simplify things is that you can think of indolent lymphomas as being 3 or 4 main kinds of subtypes. And, this kind of pie chart here depicts the kind of breakdown of different lymphomas. So, in the U.S., diffuse large B-cell lymphoma is the most common form of non-Hodgkin lymphoma. It is an aggressive yet curable lymphoma. And then, other kinds of common non-Hodgkin lymohomas that we see are follicular lymphomas, MALT or marginal zone lymphomas and then some of the other indolent things like CLL or SLL, some of the kind of more indolent leukemias.

And so, when I think of indolent or slow-growing lymphomas, I use those terms interchangeably, I think of entities, such as follicular lymphoma, marginal zone or MALT lymphomas, or lymphoplasmacytic lymphoma, which also relates to Waldenström macroglobulinemia, which I'll explain, and then also CLL and SLL. And mainly, I'll focus on the first 3 of these entities just as being sort of interrelated, lymphomas that we often treat, very similar to one another. I would encourage you if you're further interested in learning more about CLL/SLL, mantle cell or aggressive lymphomas, there's additional resources at the LLS that can be used for more information about the treatment and diagnosis of those illnesses.



Slide 8: QUESTIONS TO ASK AT DIAGNOSIS?

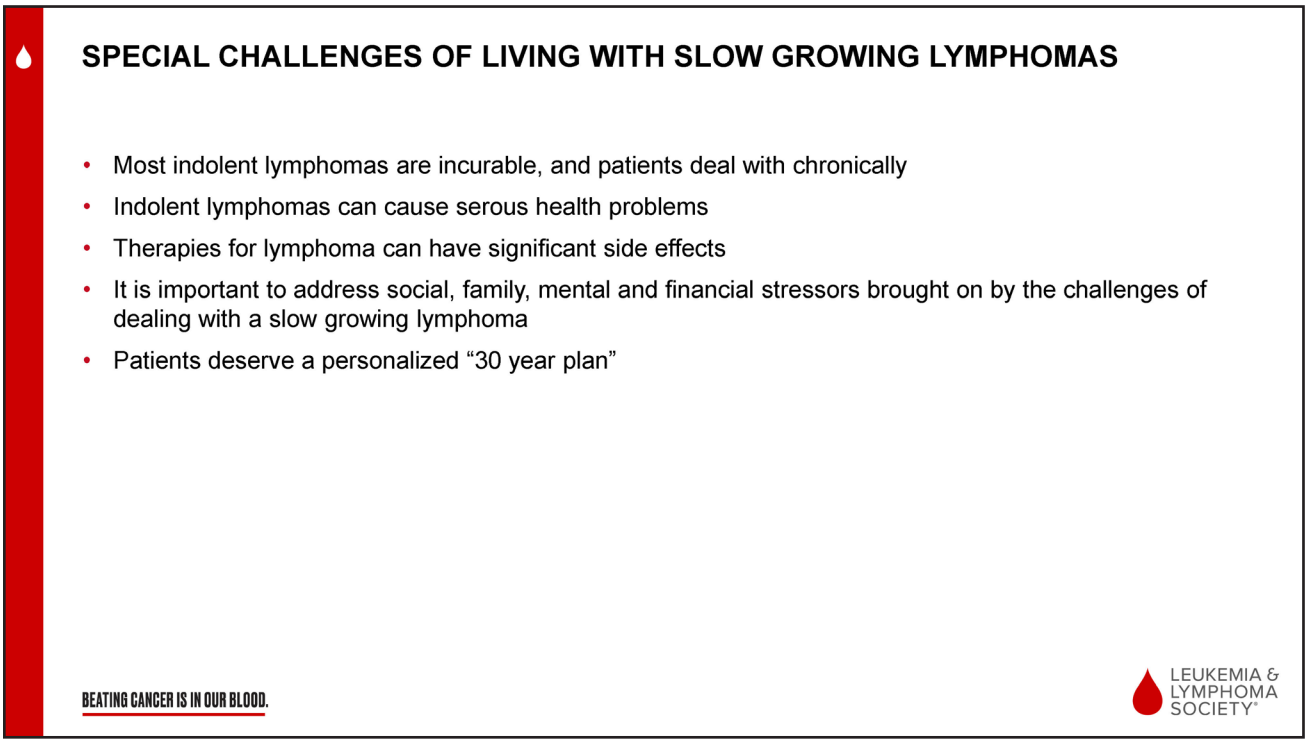
The other thing that I usually start with when meeting a new low-grade lymphoma patient is some questions to go through at diagnosis. And, I think this is important for any patient, both at diagnosis and then at different treatment or checkpoints as you go through therapy.

I think the first is, do you have the right diagnosis? And, I think that harkens back to the WHO slide with all the dozens of different types of lymphomas, sometimes it can be really hard for pathologists to make a good diagnosis, depending upon how a biopsy or how things were done. So, I think that's important to consider, because there's a lot of variation in our treatments across the different diagnoses.

The second question is, what stage of lymphoma or what is the burden of disease? And, this is perhaps less important for prognosis because many low-grade lymphomas are extensive stage and so we have to use other tools for prognosis, but I'll show you it is important to understand in some patients, if they're early stage, that they may be curable with different interventions, and so I think that's also important.

And then, there's other questions about markers can be prognostic. Sometimes that really requires expert skill, skill to sort of integrate all the different kinds of molecular tests and things that we have.

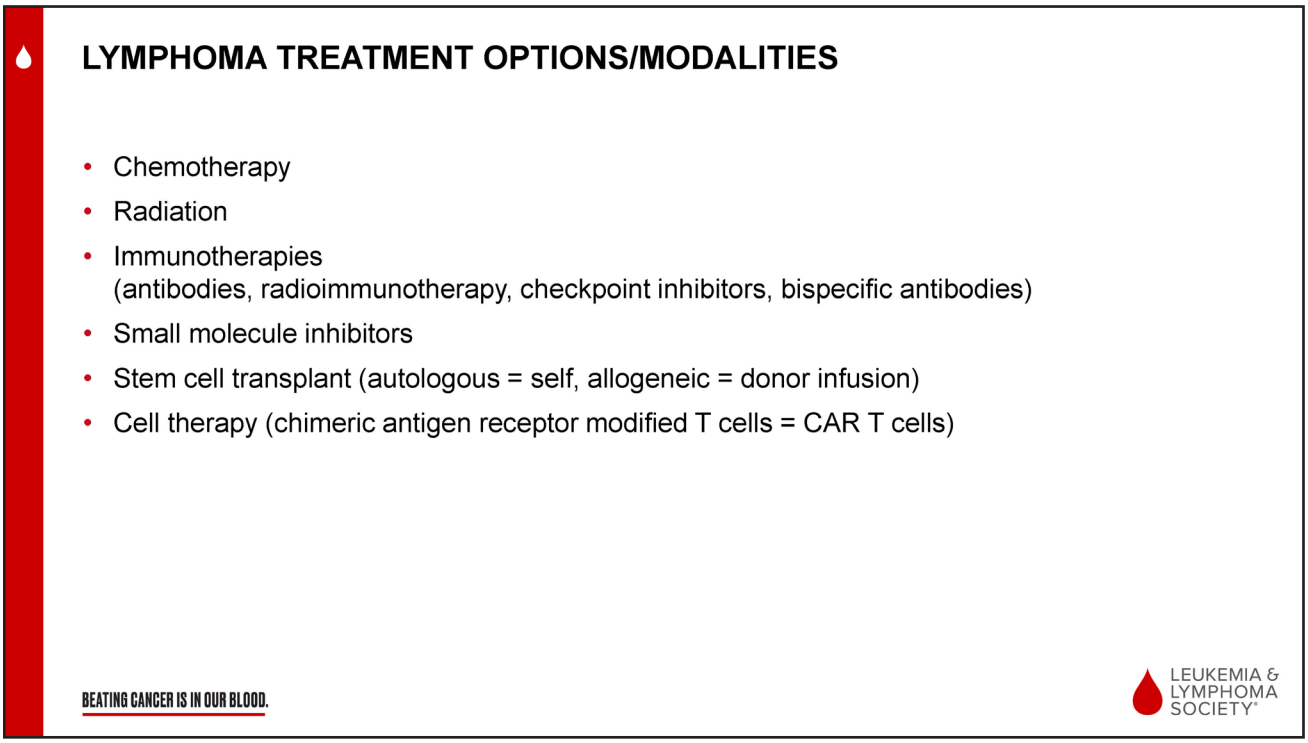
And then, the final question is, what is the best kind of observation or treatment plan? And I think this is when I see referrals in the clinic, probably one of the biggest examples where my recommendation differs vastly from that of a referring physician, because I think there's a lot of differences in practice for treating some of the indolent lymphomas and a lot of nuances that we don't want to under- or over-treat our patients and we really want the best outcome for them.



Slide 9: SPECIAL CHALLENGES OF LIVING WITH SLOW GROWING LYMPHOMAS

With that being said, I do think there are a number of special challenges living with slow-growing or indolent lymphomas. I'm sort of speaking to this from the clinician's end and what I've seen. I think one of the biggest challenges is that most of these lymphomas are incurable, so the patients are going to deal with them generally for the rest of their lives, and so that becomes another chronic condition that they have to deal with and, can cause very serious or even life-threatening health problems.

The other thought around that is many of our therapies, while we're trying to get to the most non-toxic and appealing therapy and chemotherapy-free treatment plans, many of the therapies still have significant side effects. And, kind of the downstream problem with that is that you often get into very complicated implications around people's social lives, their family, their work lives, a lot of the mental and financial stressors that someone, even me the clinician, I may not be thinking about as much, but are very important to patients. And so, the way I was taught to deal with thinking about follicular lymphomas, you really have to be careful and develop a 30-year personalized game plan for the treatment of these kind of patients. And similarly, I think it's helpful for patients to understand as much information as they can and start to develop a game plan around how does this sort of treatment follow-up for the lymphoma to fit in their life.



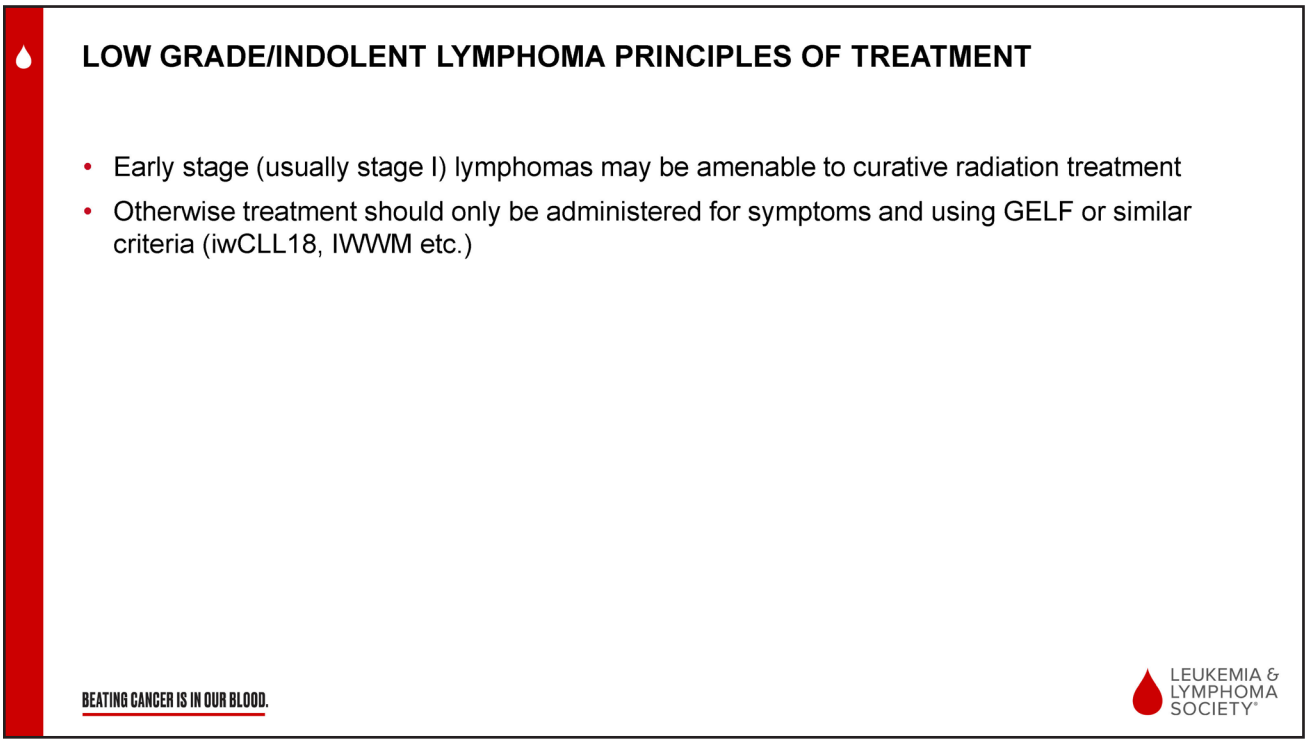
Slide 10: LYMPHOMA TREATMENT OPTIONS/MODALITIES

So, most of this talk is going to be around different treatment options and information around that and some considerations, I think, largely for follicular lymphoma and then somewhat for, marginal zone lymphomas and MALT lymphomas and Waldenström.

So, I'll just point out that there's a number of important treatment modalities. There's chemotherapy, which has sort of been the traditional way that we treat lymphomas. There's radiation, which I think, as I'll point out, has a lot of very important roles in treating some of the low-grade patients and can be very useful when we're worried about patients on intensive chemotherapy around the COVID-19 pandemic. There's also immunotherapies, which really have revolutionized, and I think will continue to revolutionize, the treatment for indolent lymphomas, those range from monoclonal antibodies like rituximab to radio immunotherapies, to other checkpoint inhibitors, and now the things like bispecific antibodies that also relates to CAR-T therapy.

There are also now small molecule inhibitors, as I'll show toward the end of the talk, approved chimeric antigen receptor modified T-cells or CAR-T therapy.

And so, we're sort of leaning away from things like stem cell transplant and intensive chemotherapy due to those things, because we're getting better and better at providing therapy that's both effective and non-toxic for our patients.



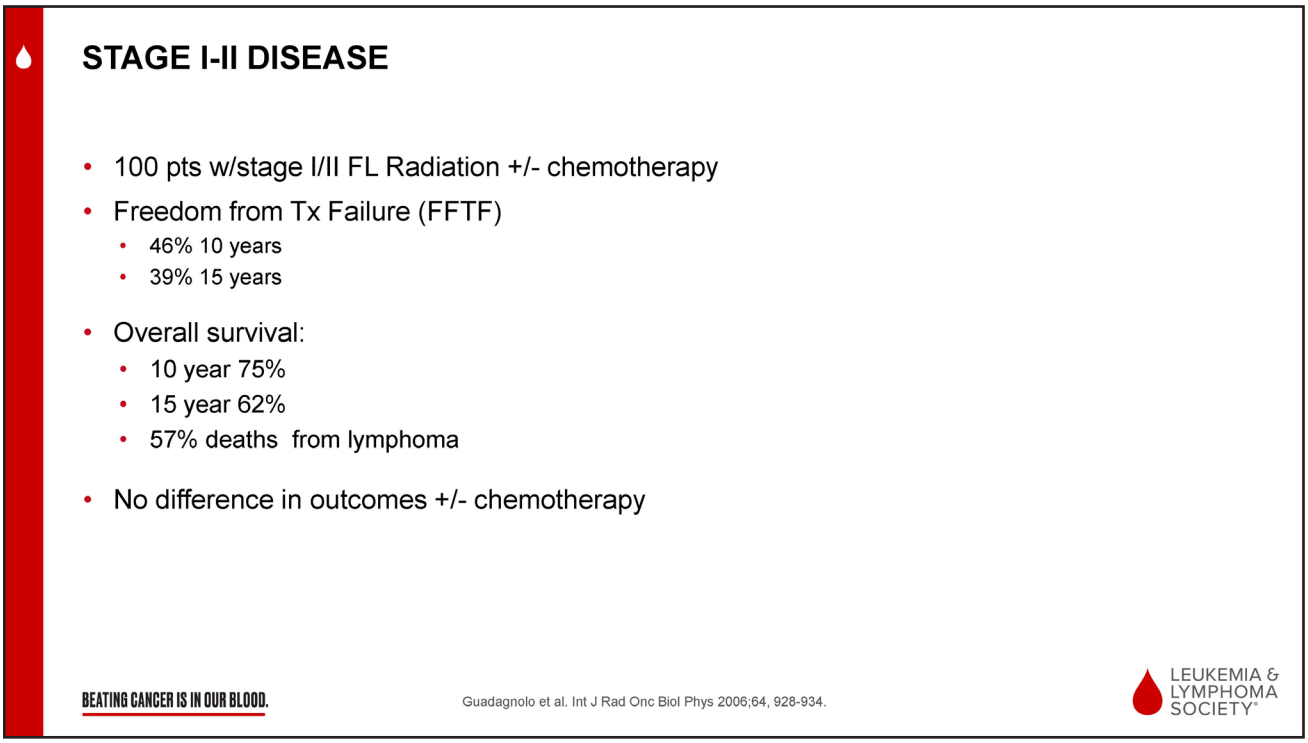
Slide 11: LOW GRADE/INDOLENT LYMPHOMA PRINCIPLES OF TREATMENT

So, what are the principles of therapy? I think of 2 main things, and I think it's important to think of these, especially at diagnosis, and then we'll talk a little bit about, initial treatment versus observation and then relapse therapy.

The first question is, in an indolent lymphoma, is this a situation that may be curable? Often this is a situation where you have a stage 1 localized lymph node involved at diagnosis, no evidence of disease elsewhere or elsewhere in the body, or specific situations such as gastric MALT lymphoma which sometimes can be cured with therapy for a chronic infection. And so, that's the first question. And, if the patient does have a potentially curable lymphoma, I think you don't want them to lose out on that potential therapy, so that's an important consideration.

And then beyond that, I generally have a conversation as to the goal following and treating these lymphomas to make the patient live as long and do as well as possible. And so, there's a lot of information that treatment should only be administered for really high burden of lymphoma disease and symptoms. There's criteria and kind of personalized things that we can look at to guide that therapy.

I'll show a little bit of information about why I think about those 2 options as the main considerations first.

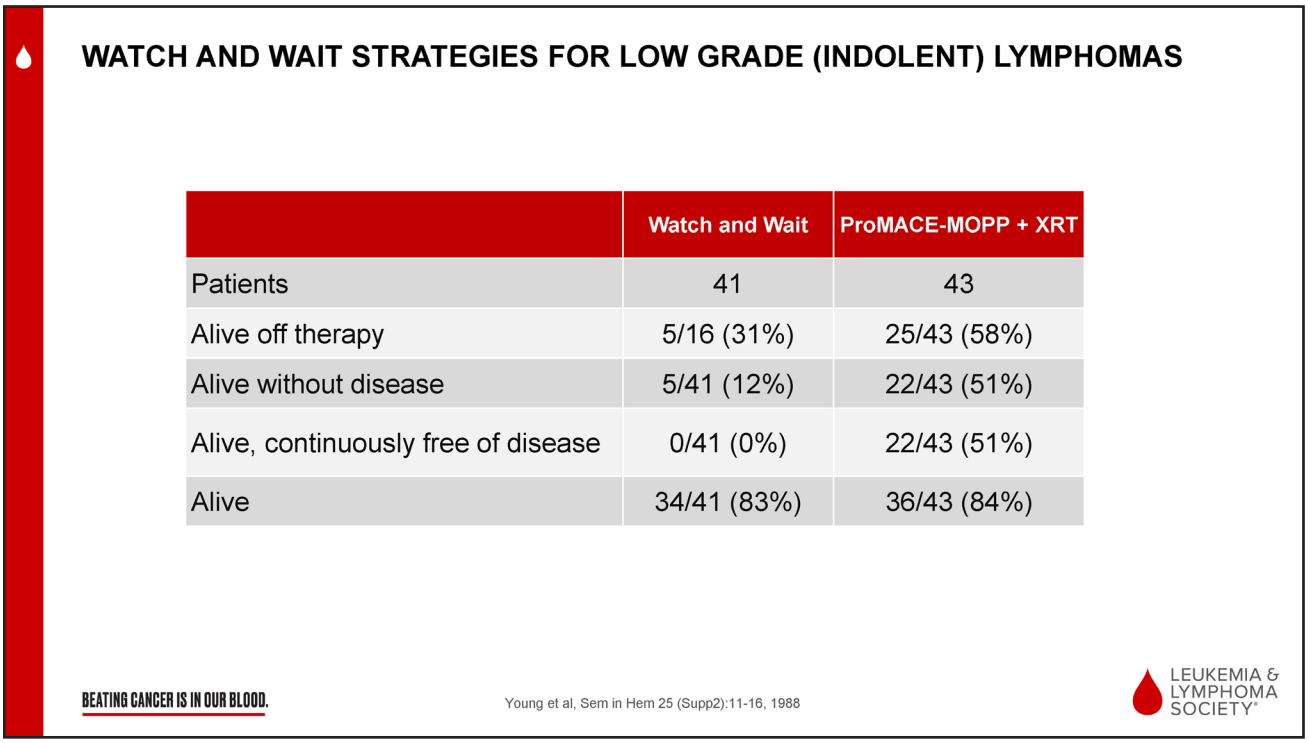


Slide 12: STAGE I-II DISEASE

This is an example of some of the older studies around radiation therapy. So, this was a study that took 100 patients, and basically, with a course of radiation, some of these patients got chemotherapy, it didn't seem that the chemotherapy helped much. In low, early-stage follicular lymphoma and other low-grade lymphomas, if you do definitive radiation therapy, you'll cure around half of those patients long-term, where the disease will not come back within their body. And so, I'll often talk about this if I see a patient where this is potentially something that can benefit the patient.

Similarly, outcomes are good with things like gastric MALT lymphomas with antibiotics, eradication of infection, or with localized radiation therapy. So, I think this is very important to think about.

The other question I think a lot of times comes up is earlier therapy better and does it, can you kind of eradicate the lymphoma, someone live longer or be without lymphoma for some longer period of time? And so, there's a lot of information around this.



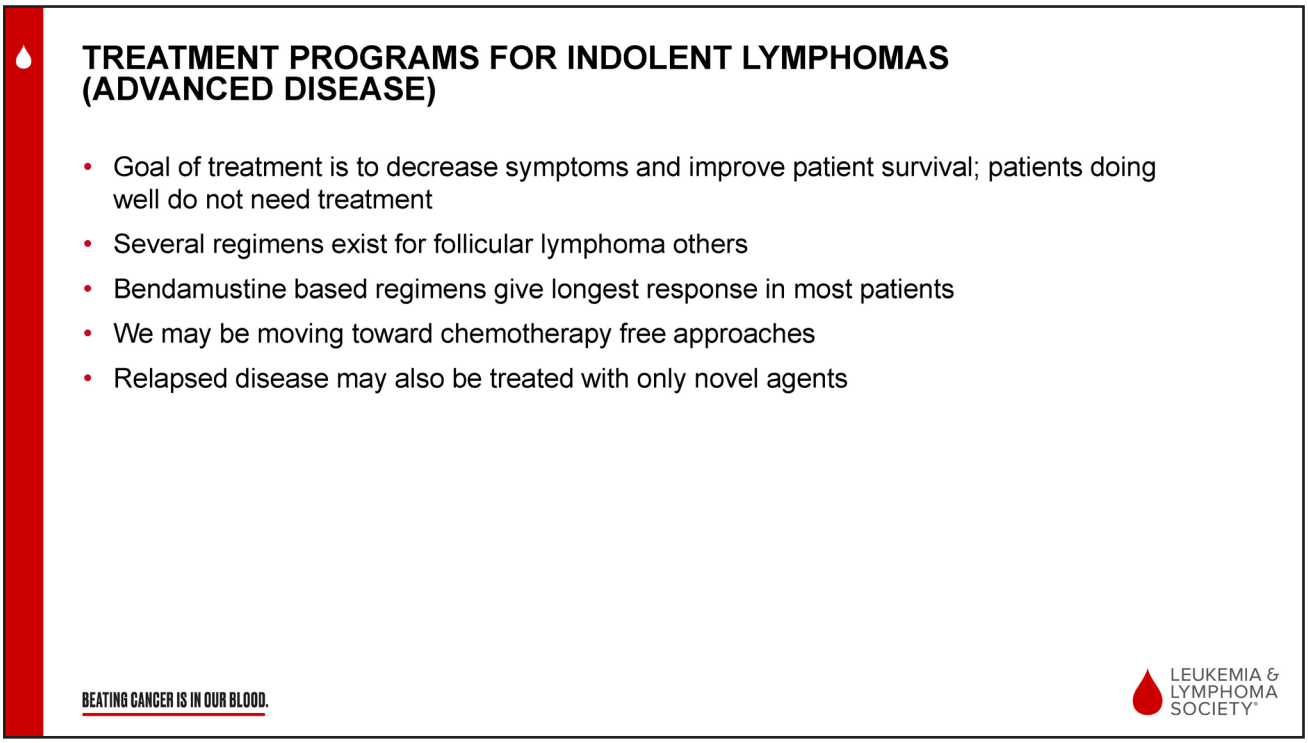
	Watch and Wait	ProMACE-MOPP + XRT
Patients	41	43
Alive off therapy	5/16 (31%)	25/43 (58%)
Alive without disease	5/41 (12%)	22/43 (51%)
Alive, continuously free of disease	0/41 (0%)	22/43 (51%)
Alive	34/41 (83%)	36/43 (84%)

Slide 13: WATCH AND WAIT STRATEGIES FOR LOW GRADE (INDOLENT) LYMPHOMAS

This is an older study. Basically, this study took, again around 100 patients. And basically, randomized patients to whether you would just observe them and only treat, if a patient has specific symptoms or some sort of medical problem that you needed to address versus giving them very aggressive chemotherapy and sometimes radiation therapy to areas of lymph nodes, with the goal of eradicating the lymphoma earlier and maybe making people live longer.

And so, this and a number of other studies has really failed to demonstrate that earlier treatment in low-grade lymphoma patients for systemic-type treatments really affects, especially over survival. So, the other thing that I think is important with this and other studies is, in this study look, about a third of patients were able to be observed for a pretty long period of time with no active therapy and were otherwise doing well. And so, my first sort of inclination with patients that I don't think were going to have a local strategy that may be curative, is to sort of come up with a plan for observation and just make sure that the patient is understanding of those issues.

The other thing that I'll show at the end of the talk is that I think there's a lot of hope out there that our therapies, that not only are we getting better with better therapies, but our ability to make better less toxic and more effective therapies for indolent lymphomas is accelerating. So, I think you have to accommodate that, when going through potential treatment regimens for patients.

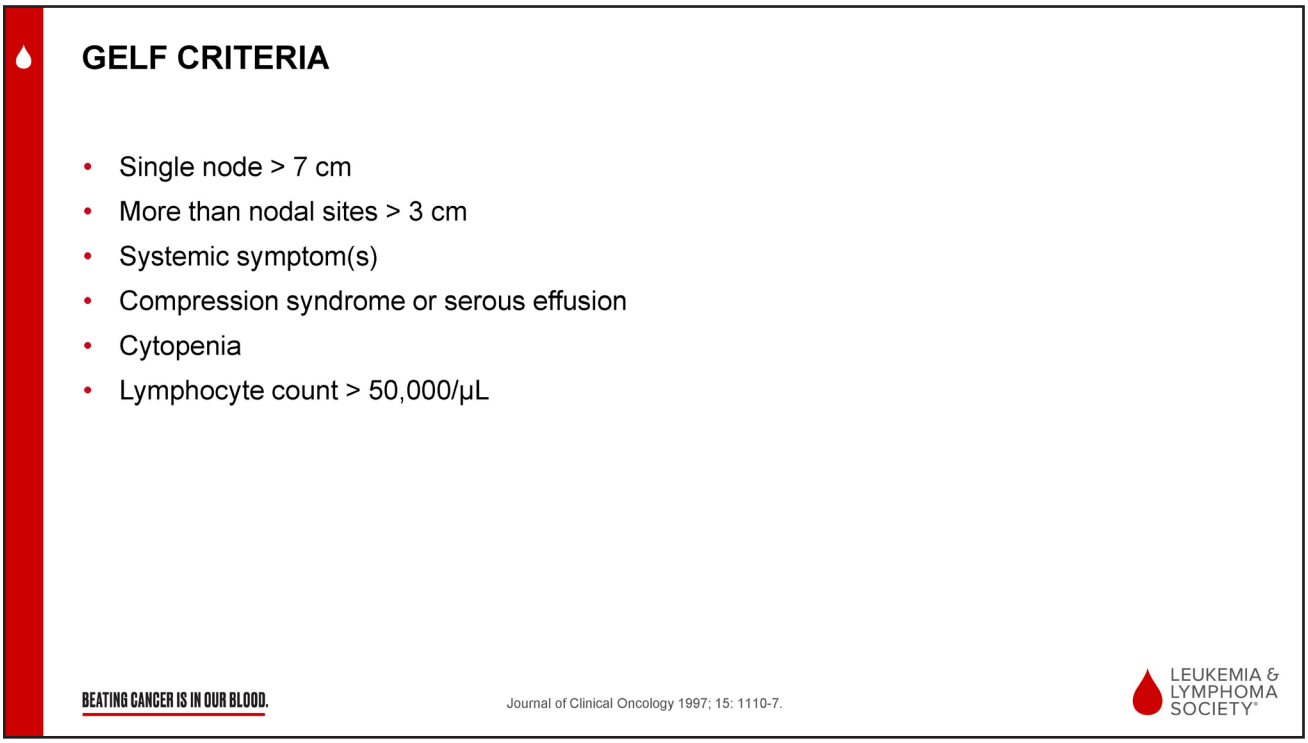


Slide 14: TREATMENT PROGRAMS FOR INDOLENT LYMPHOMAS (ADVANCED DISEASE)

So, a little bit about designing treatment programs for advanced stage indolent lymphomas or – really these are pretty much systemic immunotherapy or immuno-chemotherapy strategies.

Again, the goal of these is to decrease symptoms and alleviate burden of disease and ideally to improve patient survival. My general philosophy is if a patient is doing well and I'm not concerned about the location of their lymphoma or disease progression, is really try hard to watch them off of treatment.

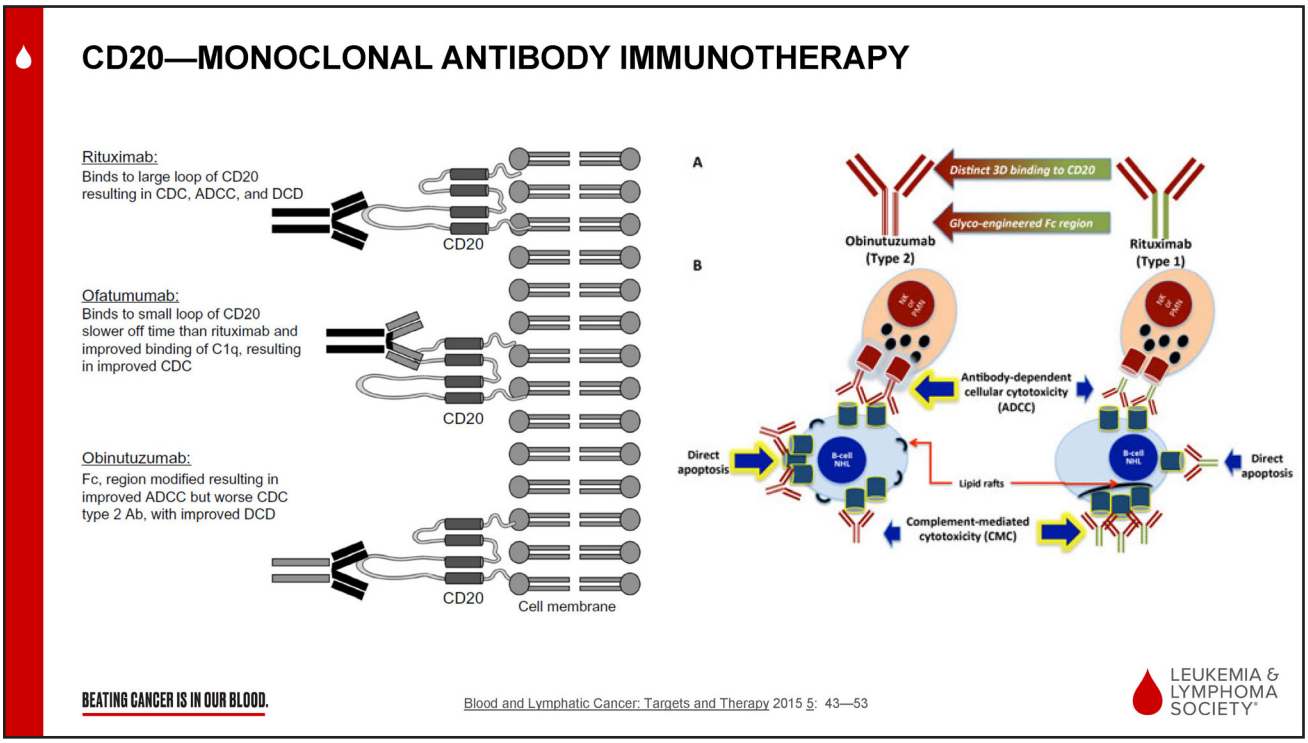
There's a lot of different regimens out there. I'll kind of go through some of the key studies that we look at in terms of information about how we do certain therapies in certain situations. We'll talk a little bit about the chemotherapies and then, how we may be moving toward chemotherapy-free approaches, particularly in relapsed disease setting.



Slide 15: GELF CRITERIA

Sometimes, I think it is helpful to give patients some very definitive criteria about when I would consider starting therapy, and so one of the ones that we frequently use is the GELF Criteria which is used mainly in follicular lymphoma, so GELF is the acronym for the French lymphoma study group. And basically, as you can see there's a number of things, things like, real large bulky lymph nodes, a lot of bulky sites of lymph nodes, whether the patient has either pain or some sort of systemic symptom. I also get really concerned if patients have low blood counts as part of the progression of their lymphoma, or a lot of, lymphoma cells in the blood and that's something we can look at. Or, there're things like, does the patient have, a mass in their lung, liver, or important organ or fluid around that organ. Those may all be things that would make me as a clinician interested in thinking about some sort of treatment plan.

So, what are some of the examples of initial treatment for follicular lymphoma? And then, I'll kind of move to the other subtypes after that.

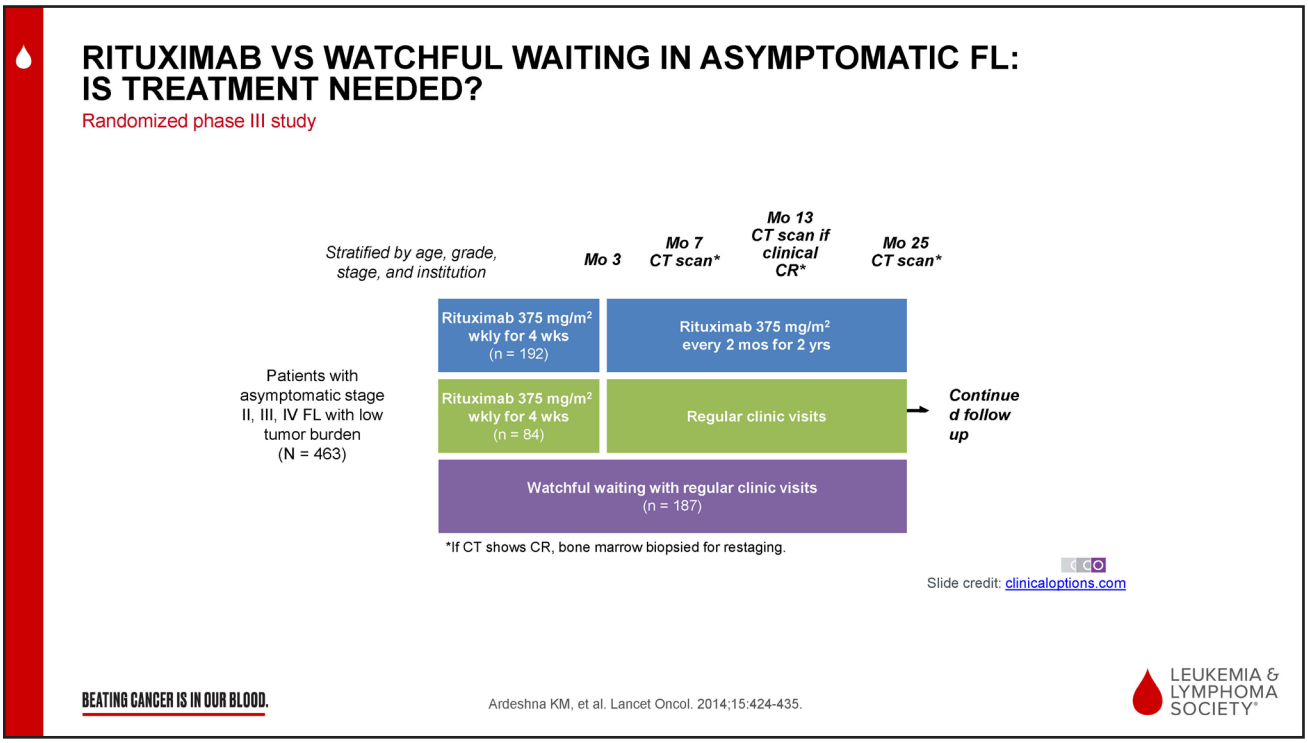


Slide 16: CD20—MONOCLONAL ANTIBODY IMMUNOTHERAPY

So, the first thing I think about is CD20–based immunotherapy with monoclonal antibodies. And, this is a kind of complicated cartoon, but this explains a little bit about what these are doing, hopefully in a little bit more detail.

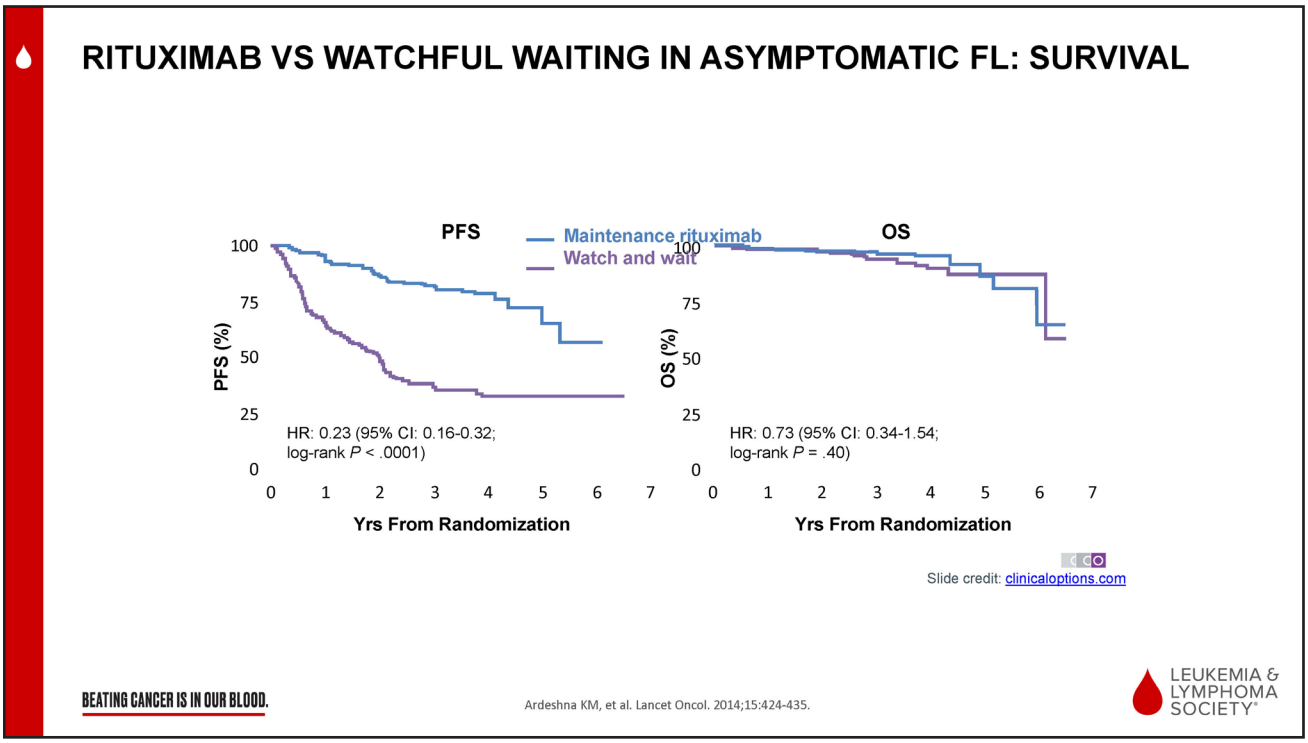
So, the first monoclonal antibody that was out there was rituximab, so rituximab, it's basically a protein and it has this kind of Y shape. It's an antibody and so on lymphoma cells, which is this sort of line, cell membrane kind of cartoon in the middle, is that there's proteins that kind of stick out, almost like little fingers from the surface of the lymphoma. And, one of my former colleagues, Joe Moore said, talk about these as hood ornaments on a car so you could look at what hood ornament and kind of tell which lymphoma cell it is.

These monoclonal antibodies basically can reach out and grab these fingers and then they basically direct an immune attack against the lymphoma cell, which is supposed to be depicted in the right cartoon. And basically, what this leads to is, death of the lymphoma and the lymphoma shrinks. And so, now there's 3 of these different medicines. There's rituximab, there's ofatumumab, and obinutuzumab. And, as you can see, the way that these differ is they hit different areas of the CD20 fingers that kind of stick out there, and they also have some different engineered immune response.



Slide 17: RITUXIMAB VS WATCHFUL WAITING IN ASYMPTOMATIC FL: IS TREATMENT NEEDED?

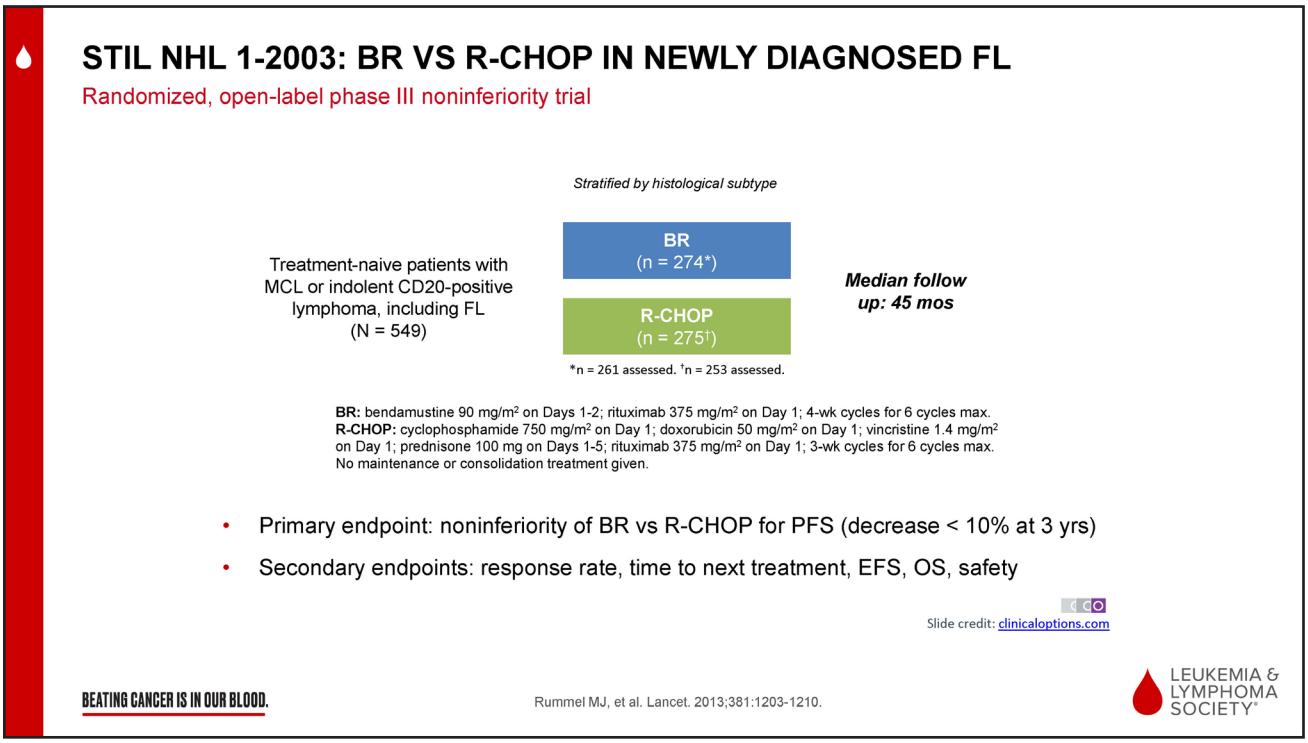
So, there's been a number of studies looking at these. This is one of the oldest experiences. This was a study that asked the question is early rituximab versus watchful waiting beneficial to patients, how does it affect the care of their lymphomas? And then also, the kind of secondary question is can maintenance rituximab for a longer period of time further that response?



Slide 18: RITUXIMAB VS WATCHFUL WAITING IN ASYMPTOMATIC FL: SURVIVAL

Here was the results of this study, there's 2 different Kaplan-Meier curves, so what I'll point out is that these curves go out left to right over time. And then, it's the percentage of patients that went without either lymphoma progression versus the percentage that was still alive with that therapy.

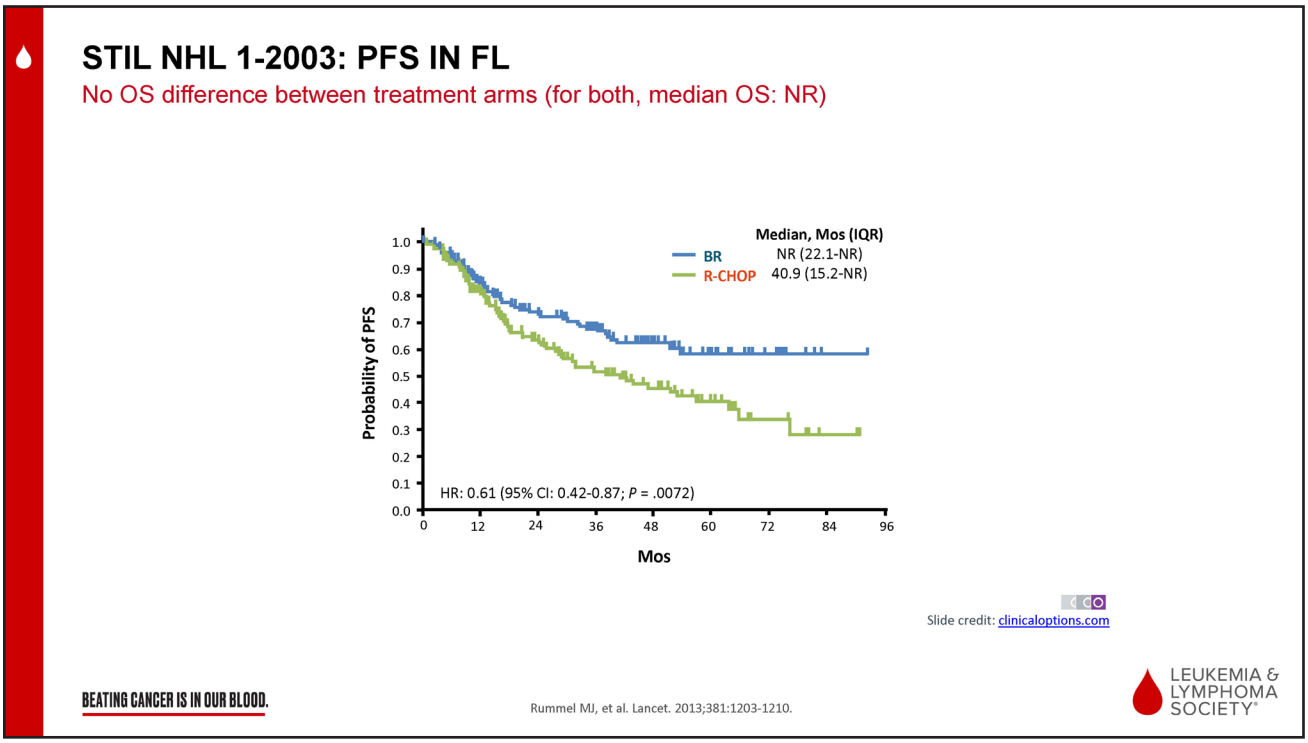
So, you can see there's a big difference with rituximab treatment in terms of slowing lymphoma growth, these patients did have lymphoma response, but actually no difference in the overall survival of those patients. And so, I'm very careful with selecting up-front therapy because, if you're not making the patient live any longer and there's not a clear indication that you're alleviating some symptoms, you know, again I'm really careful with even rituximab, because in the study there's a percentage of patients who will have very severe either reactions to rituximab or infections. And I think, those are not trivial to think about in terms of long-term side effects for patients. So even something maybe as innocuous sounding as rituximab, I'm still a little bit resistant to use, although, you are controlling lymphoma for a longer period of time and interestingly on this study, there seemed to be less anxiety among the patients who were getting active treatment with Rituxan® as compared to not. And so, some patients I think, benefit just mentally from being on a therapy, doing something about their disease, kind of with warning that there are toxicities, associated with any therapy.



Slide 19: STIL NHL 1-2003: BR VS R-CHOP IN NEWLY DIAGNOSED FL

So then, what about chemotherapy? Which chemotherapy do we prefer to use, how do we prefer to do that? This is an older study that's now been around almost 2 decades, the STIL study. So, there's 2 main studies basically studying, bendamustine-based chemotherapy versus other regimens like CHOP or CVP. CVP basically being very similar to CHOP, but you take out 1 of the medicines, the doxorubicin that has a lot of side effects and cardiotoxicity.

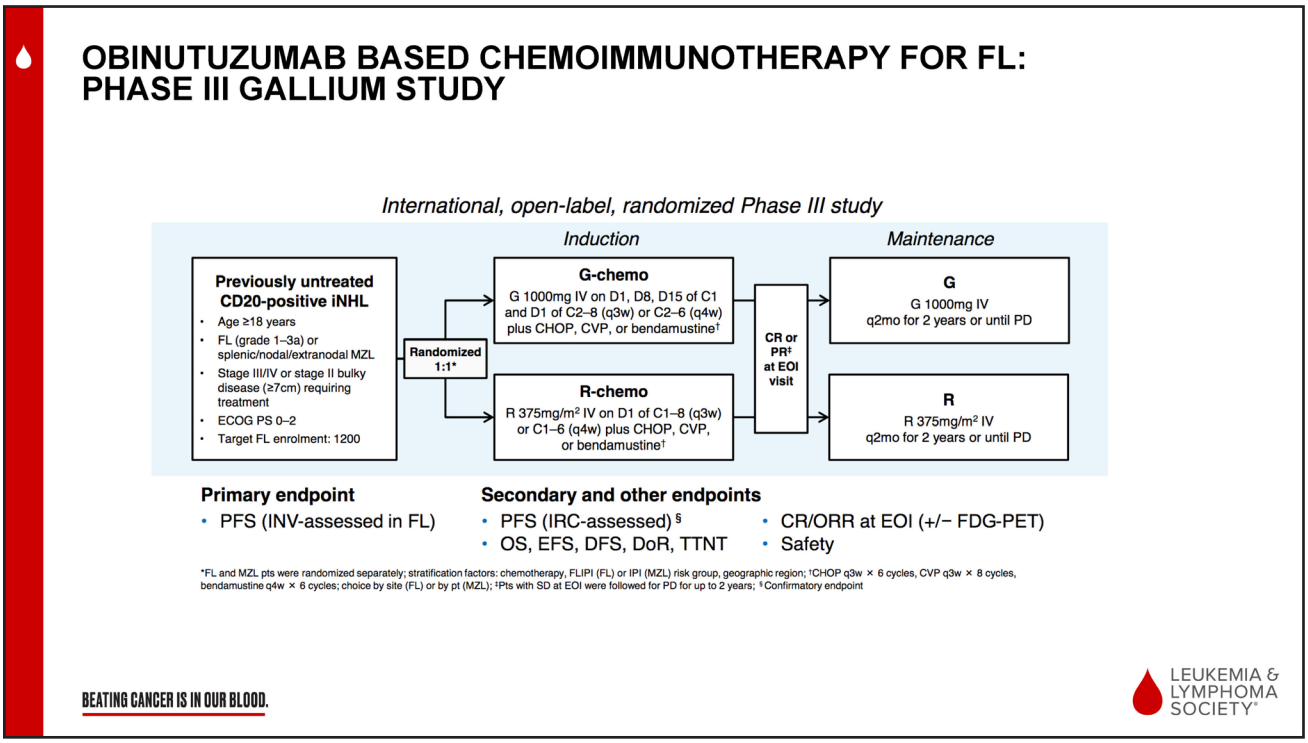
So, this study was a randomized trial that they took indolent lymphoma patients, mostly follicular lymphoma patients and randomized them to either bendamustine-Rituxan or to Rituxan with CHOP. This study also included mantle cell lymphoma patients, which kind of led to more bendamustine use also in those entities as well.



Slide 20: STIL NHL 1-2003: PFS IN FL

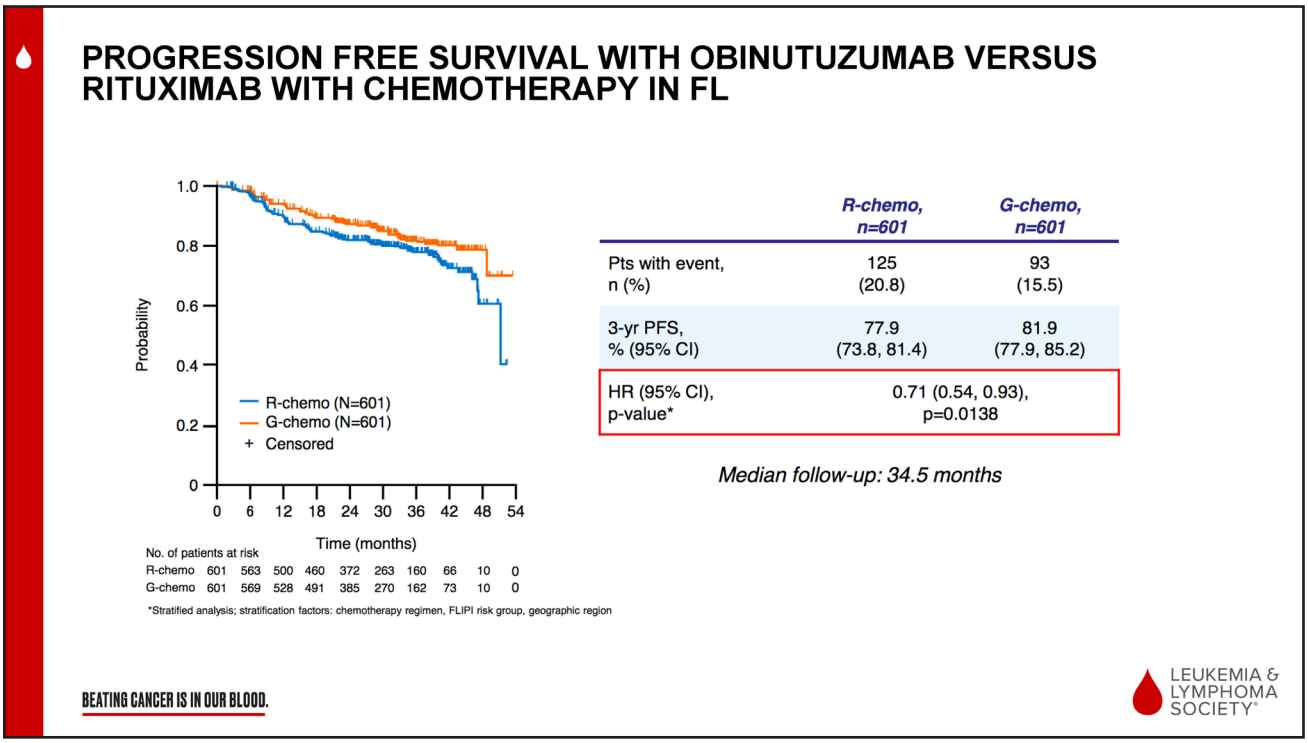
Here are the main results from that study. So, as you can see there's a difference. There's less lymphoma progression over time with the patients that got bendamustine and rituximab. And, this basically led to the use of more bendamustine in this patient population.

The other thing that is not on this slide and I'm not going to show here, but bendamustine I think is a much easier regimen to tolerate, even at the level of just patients, don't lose their hair on bendamustine, and they have less low blood counts, less infections. So, even if these curves were the same, it would probably be a superior regimen for patients that needed, effective chemo-immunotherapy for their indolent lymphoma.



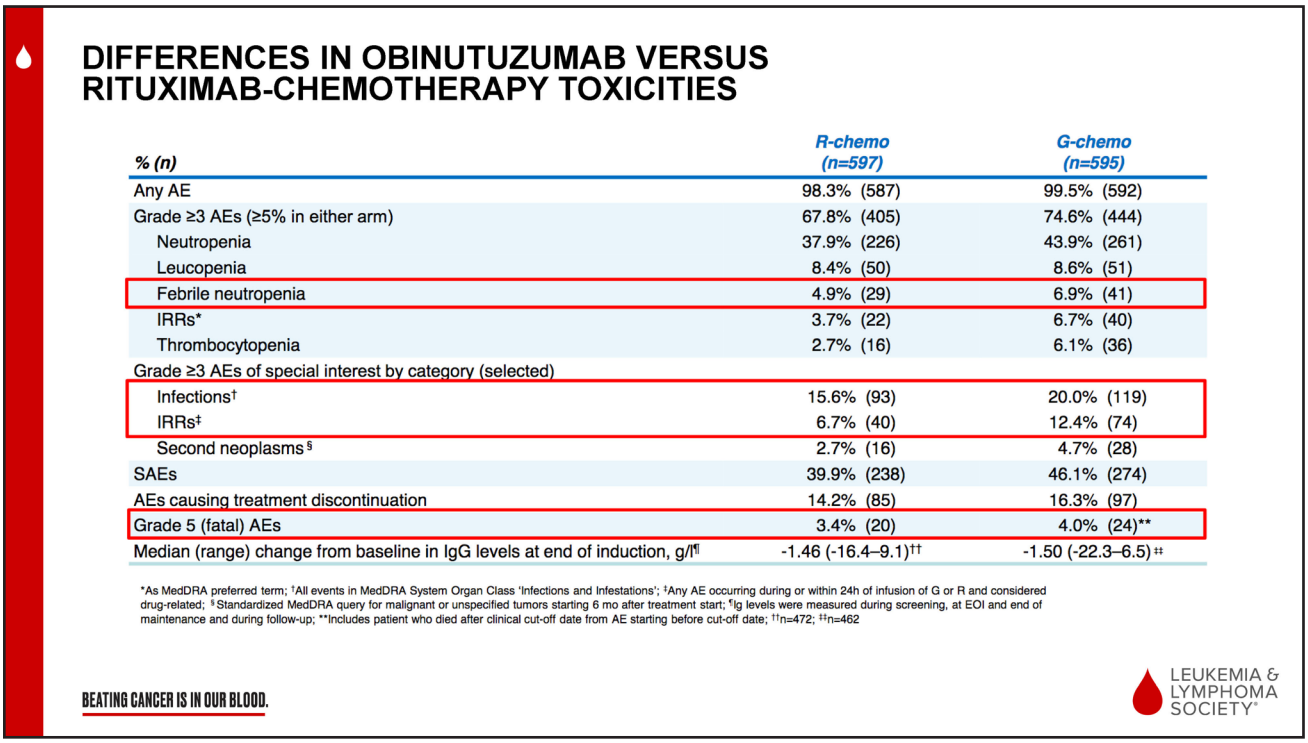
Slide 21: OBINUTUZUMAB BASED CHEMOIMMUNOTHERAPY FOR FL: PHASE III GALLIUM STUDY

The next question that has been asked in the field, especially for front-line therapy and also in the relapsed setting now, can you optimize the CD20-based antibody? And so, this is the GALLIUM Study, which was a Phase III study, it was randomized between 2 different approaches, one using obinutuzumab with chemotherapy compared to rituximab with very much matched chemotherapy, either bendamustine, R-CHOP – or CHOP or CVP. And, in this study they also gave maintenance therapy with either agent, sort of the goal, you'd prolong progression-free survival as much as possible.



Slide 22: PROGRESSION FREE SURVIVAL WITH OBINUTUZUMAB VERSUS RITUXIMAB WITH CHEMOTHERAPY IN FL

This slide has the results of the GALLIUM Study. As you can see there was a little benefit of the obinutuzumab arm, that's this orange line here in the graph. The trade name for obinutuzumab is Gazyva®, so its G-chemo versus R-Rituxan chemo. And so, many people have sort of expounded that, maybe we should be optimizing our therapy with obinutuzumab and rituximab in this population, just given the higher kind of lymphoma effects.



DIFFERENCES IN OBINUTUZUMAB VERSUS RITUXIMAB-CHEMOTHERAPY TOXICITIES

% (n)	R-chemo (n=597)	G-chemo (n=595)
Any AE	98.3% (587)	99.5% (592)
Grade ≥3 AEs (≥5% in either arm)	67.8% (405)	74.6% (444)
Neutropenia	37.9% (226)	43.9% (261)
Leucopenia	8.4% (50)	8.6% (51)
Febrile neutropenia	4.9% (29)	6.9% (41)
IRRs*	3.7% (22)	6.7% (40)
Thrombocytopenia	2.7% (16)	6.1% (36)
Grade ≥3 AEs of special interest by category (selected)		
Infections†	15.6% (93)	20.0% (119)
IRRs‡	6.7% (40)	12.4% (74)
Second neoplasms§	2.7% (16)	4.7% (28)
SAEs	39.9% (238)	46.1% (274)
AEs causing treatment discontinuation	14.2% (85)	16.3% (97)
Grade 5 (fatal) AEs	3.4% (20)	4.0% (24)**
Median (range) change from baseline in IgG levels at end of induction, g/l¶	-1.46 (-16.4–9.1)††	-1.50 (-22.3–6.5)‡‡

*As MedDRA preferred term; †All events in MedDRA System Organ Class 'Infections and Infestations'; ‡Any AE occurring during or within 24h of infusion of G or R and considered drug-related; §Standardized MedDRA query for malignant or unspecified tumors starting 6 mo after treatment start; ¶Ig levels were measured during screening, at EOI and end of maintenance and during follow-up; **Includes patient who died after clinical cut-off date from AE starting before cut-off date; ††n=472; ‡‡n=462

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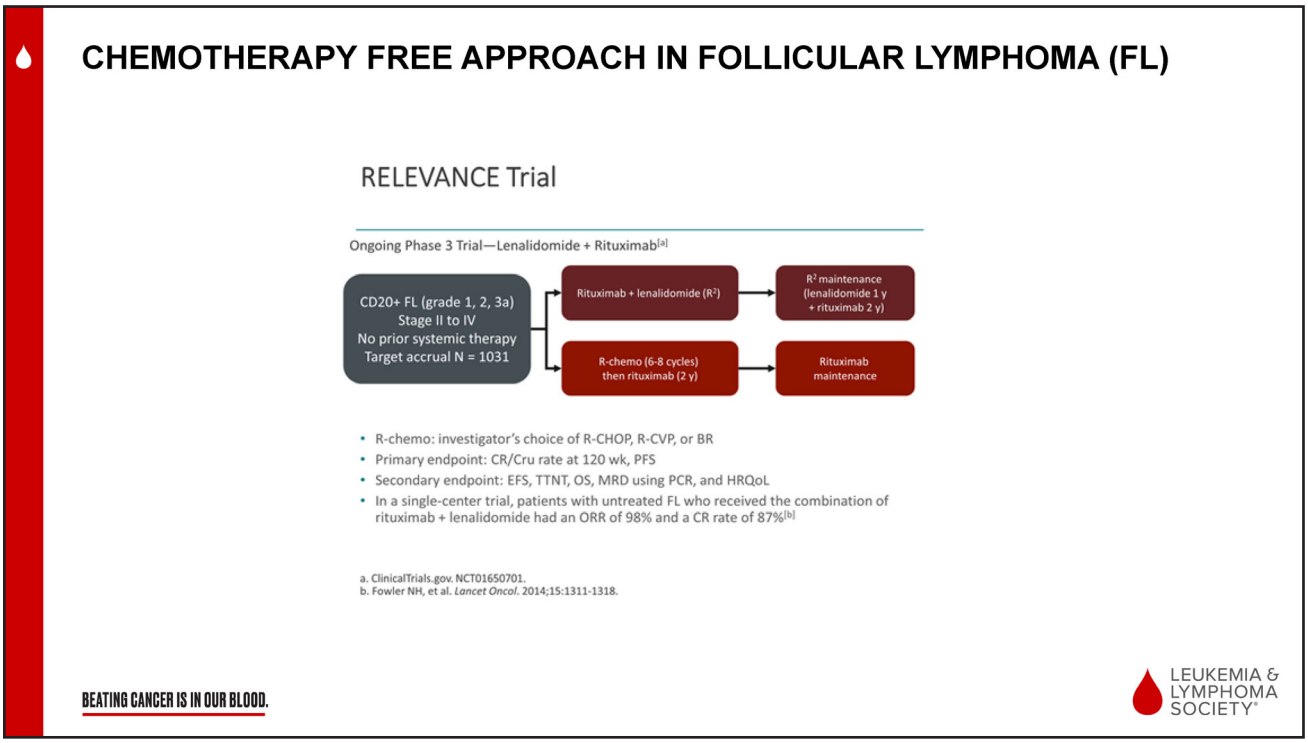
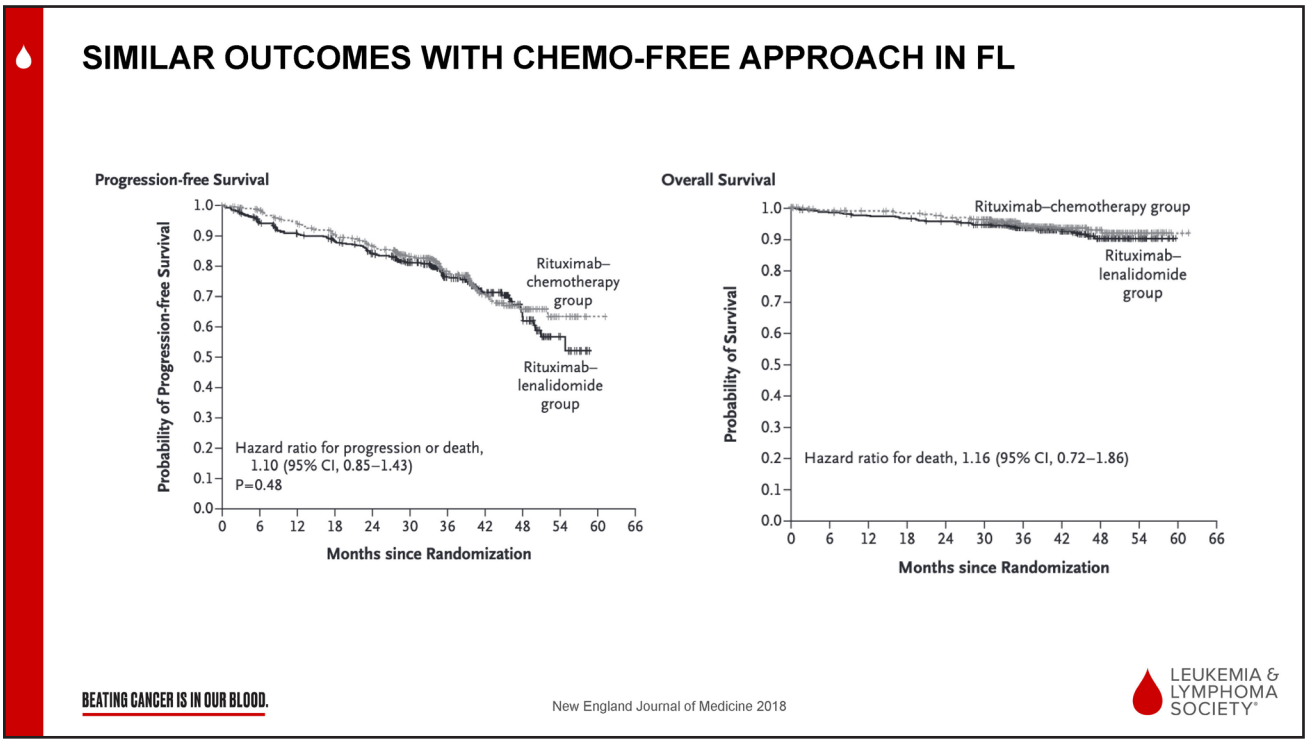
Slide 23: DIFFERENCES IN OBINUTUZUMAB VERSUS RITUXIMAB CHEMOTHERAPY TOXICITIES

The one drawback I think to obinutuzumab in that strategy is there are more side effects, so I've highlighted a few things that are important. Obinutuzumab added to chemotherapy does seem to cause more side effects, mainly around things with infections, and I will say in this trial there was a few older patients that had very, unusual infections. A few patients had died from those in the obinutuzumab arm, which is very unusual with rituximab-bendamustine. So, I think, you know, we're very careful with adding that therapy, especially in individuals over 60, 65, although it may be readily applicable in someone who's younger that really wants to push out the amount of time that they're free of lymphoma, prior to needing another potential therapy and going about their lives.



Slide 24: CHEMOTHERAPY FREE APPROACH IN FOLLICULAR LYMPHOMA (FL)

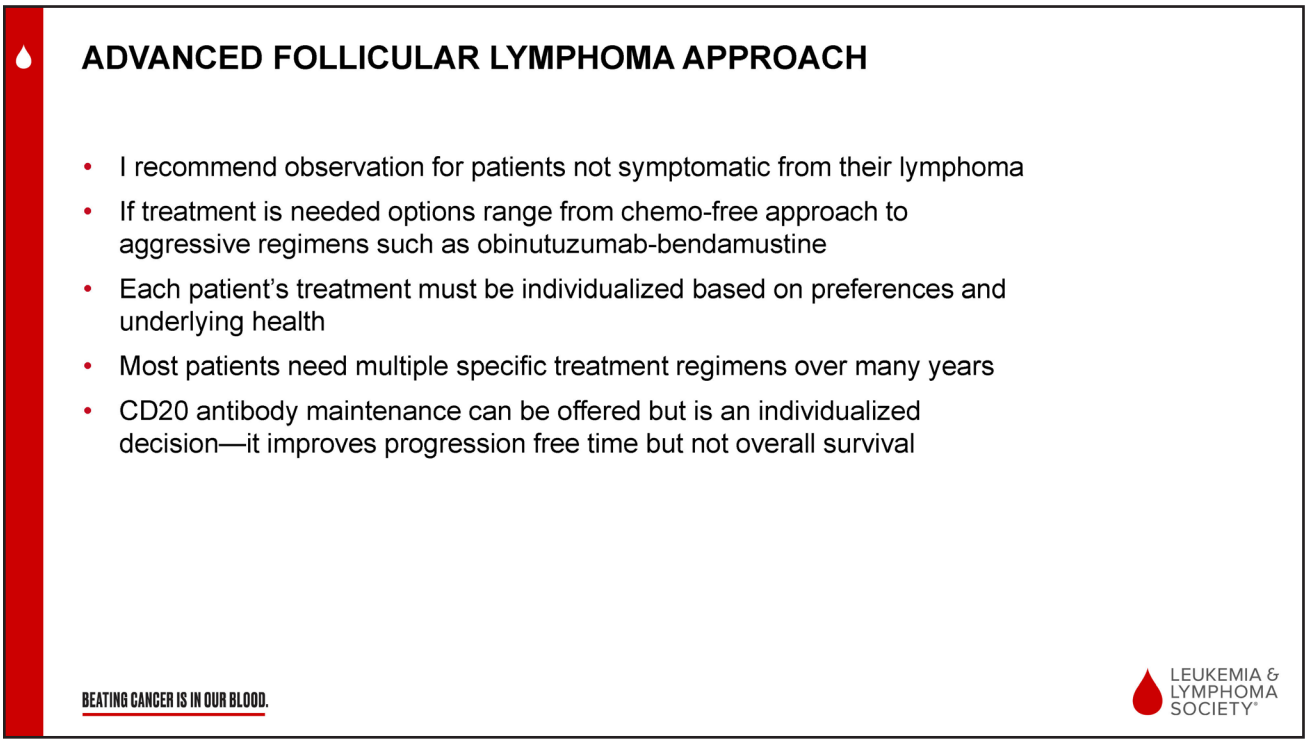
The next question that has been answered in large clinical trials, is whether or not we can get to a chemotherapy-free approach. I'll show this in a lot more detail, this is now more applicable in the relapsed kind of setting, basically across all of the different indolent lymphoma or slow-growing lymphoma entities. But the RELEVANCE trial actually did this in the front-line and studied initial treatment of follicular lymphoma patients, and basically randomized them to rituximab with chemotherapy versus rituximab with lenalidomide. Lenalidomide is an oral medicine which is taken on a daily schedule, usually 3 weeks on and 1 week off for rest purposes. It has a lot of effects on both the lymphoma cells in terms of shutting down some of the molecules that drive the lymphoma progression, as well as on the immune system.



Slide 25: SIMILAR OUTCOMES WITH CHEMO-FREE APPROACH IN FL

And so interestingly in this trial, if you look at the lymphoma-specific effects and also survival, the Rituxan with lenalidomide group actually did almost exactly the same as the rituximab and chemotherapy group, both in terms of response rates and time of response and how long people were in remission and those kinds of things, as well as survival.

Unfortunately, the lenalidomide has not yet gained FDA approval for this front-line indication, because at least on paper, there are more side effects, especially things like rash and diarrhea, as compared to the chemotherapy arm. The other downside of the chemotherapy approach in the lenalidomide-based approach is, it was 18 months of therapy with lenalidomide as opposed to 3 and a half months of chemotherapy. So, it's also a longer period of time that patients are exposed to those side effects, and I think that drove the inability of us to move this further ahead in the front-line situation.

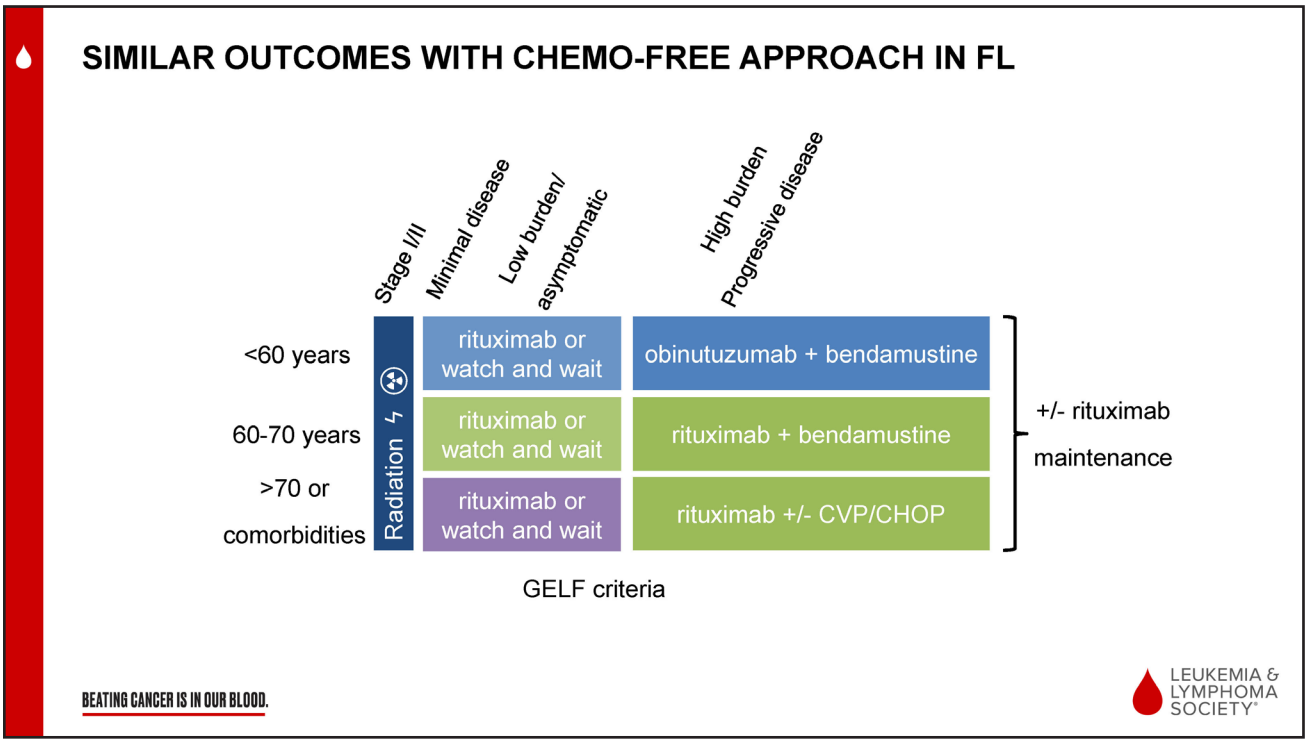


Slide 26: ADVANCED FOLLICULAR LYMPHOMA APPROACH

So, as a summary for thinking about observation and then moving patients to potential therapy for slow-growing advanced follicular lymphoma, I think of these points.

Again, I already told you that I very much favor observation for as long as possible in patients that are not symptomatic for their lymphoma and don't fit things like the GELF and other criteria. And then, if patients appear to approach needing therapy, therapy can range from things like rituximab maintenance to a little bit more aggressive therapy, such as obinutuzumab and bendamustine. And, that's all a very patient-centered, individualized discussion with the patient and the oncologist, around all kinds of preferences and things related to the patient's underlying health and age and other factors.

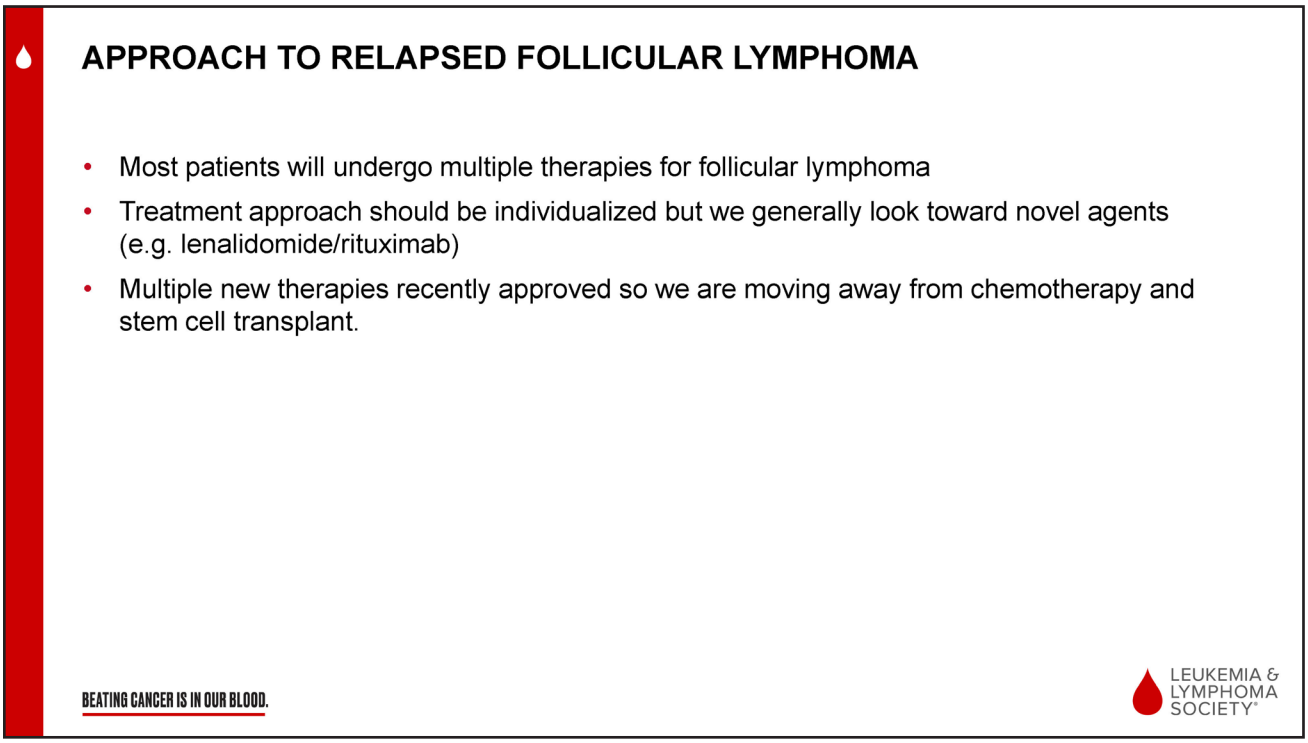
The other thing to remember in choosing therapy and discussing with patients, and choosing from the patient's side, choosing what therapy you're going to go on, is to remember that these are generally incurable, but very manageable illnesses, that often patients will need multiple different treatments over time. So, thinking about what may be available in the future is also important and that can also even drive observation or different strategies.



Slide 27: SIMILAR OUTCOMES WITH CHEMO-FREE APPROACH IN FL

The other thing that will come up often in discussion is rituximab or obinutuzumab maintenance after response to initial treatment. The main thing I can say about that is I think it's a very individualized discussion. Hopefully, you got a feel from the slides that I showed here just now, that those maintenance strategies sort of prolong the duration of time that people get responses, but they don't improve overall survival or cures for lymphoma. And, I think again that's an individualized discussion with the patient and their provider.

So, if you were to look at our most common treatment pathways for patients across the spectrum of their initial diagnosis and initial treatment, this is how I often think of things. So, top to bottom is patient age and health features. And then, left to right is early stage versus progressive disease. And then, getting them through initial therapy, so we may actually individualize and try to do less intensive therapy in patients that are older or have more health problems. But again, that's a very individualized discussion.

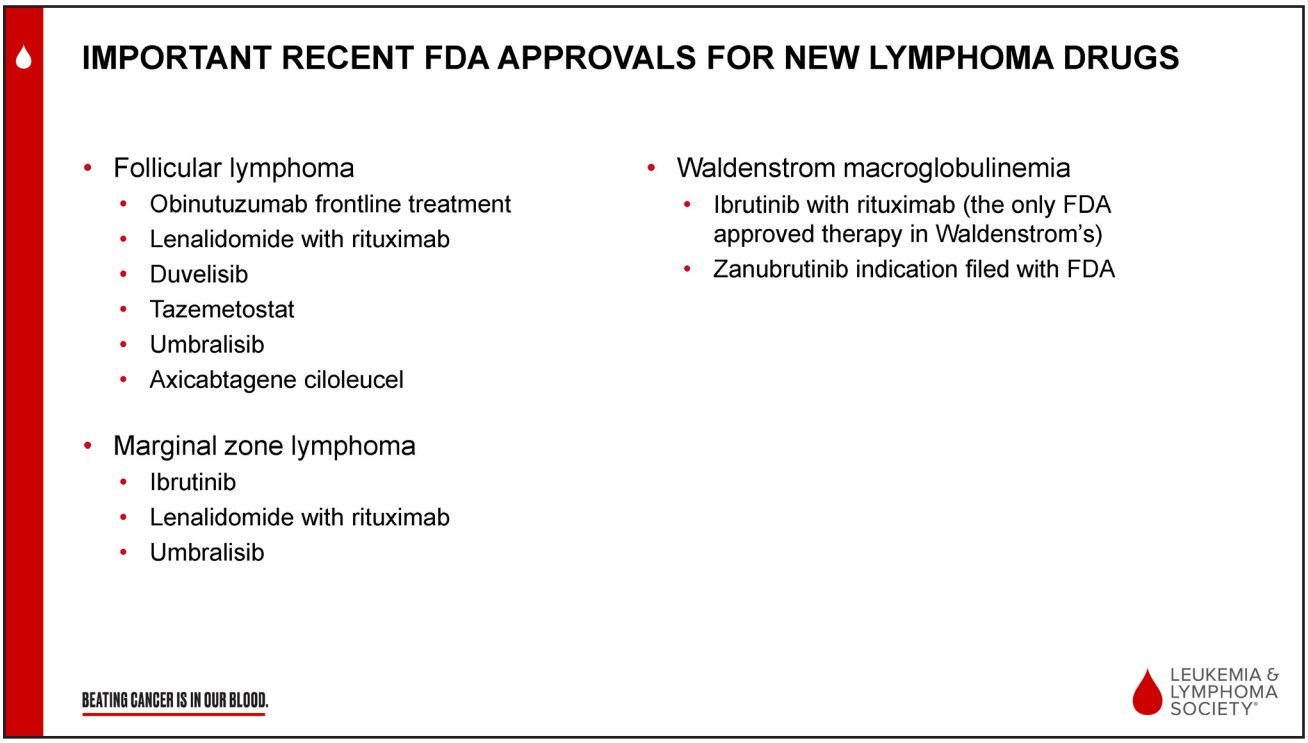


Slide 28: APPROACH TO RELAPSED FOLLICULAR LYMPHOMA

So, what about relapsed disease? We'll talk a little bit about relapsed follicular lymphoma and many of the agents are the same across marginal zone lymphomas and other things like mantle cell lymphomas or CLL/SLL. Again, remember most patients are going to need multiple different therapies for follicular lymphoma. We always individualize treatment, but for the most part we lean very much to novel, sort of small molecule agents, as well as immunotherapies.

I put lenalidomide and rituximab here. That seems to be the most common kind of second-line therapy that we look at. Again, results very similar to the front-line chemotherapy with bendamustine and things. And so, often that's kind of a standard second-line approach.

There are multiple newer therapies out there that I'm going to talk a little bit about, explain some of my thoughts and give some more information that may help patients decide and think about those things. So, we're fortunately moving away from higher dose chemotherapy and things like stem cell transplant, even to the point where, if I refer one of my patients to our bone marrow transplant program, often they say, there's so much stuff out here, especially in follicular lymphomas, that's new and improved, let's do some of those things first and not put the patient through a really intense chemotherapy program or transplant.



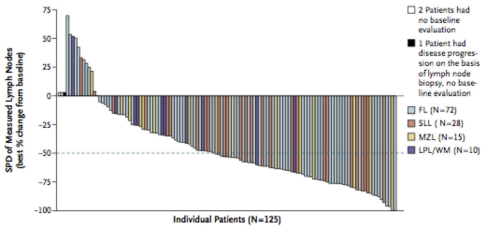
Slide 29: IMPORTANT RECENT FDA APPROVALS FOR NEW LYMPHOMA DRUGS

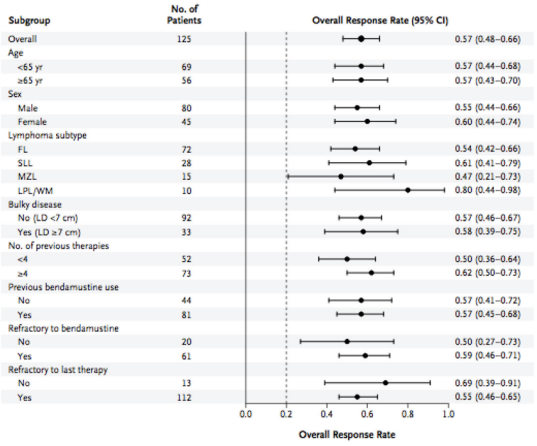
So, I'll talk a little bit about these agents. Again, this slide depicts some of the landscape we have for really recent FDA approvals in the past 3 to 4 years. Again, in follicular lymphoma, there's more than half a dozen things that we now put on this slide. I'm sure I forgot several different things that are out there, just because there's been so much development of newer agents. Also, in the past 3 or 4 years, we've seen multiple new FDA approvals for diseases like marginal zone lymphoma with ibrutinib, now lenalidomide, now PI3 kinase inhibitors, such that many of these patients don't need multiple lines of chemotherapy, they can often be managed with novel, targeted agents or immunotherapies.

We're also now seeing this in even rare diseases like Waldenström, where you have ibrutinib. We're probably going to see another BTK inhibitor and some other novel combinations approved in that space.

PI-3 KINASE INHIBITORS FOR FL

- Phosphatidylinositol-3-kinase delta (PI3Kδ) inhibitor
- 57% response rate, 1.9 months to response, durability 12.5 months
- Phase II protocol
  - 125 patients
  - Refractory/relapsed within 6 months of rituximab/alkylator





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Gopal, et. al. NEJM (2014)

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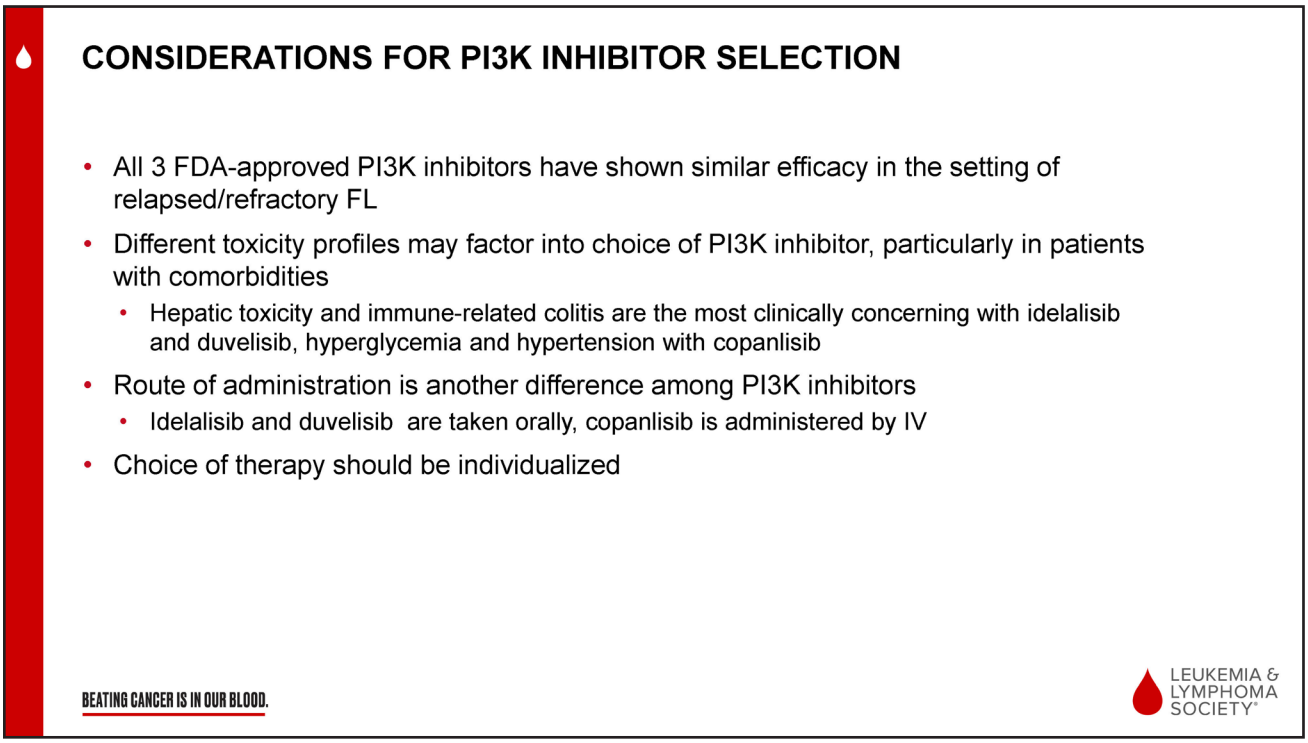
Slide 30: PI-3 KINASE INHIBITORS FOR FL

I'll talk a little bit now about the individual drug classes that are newer in follicular lymphoma. First, I'll talk a little bit about PI3 kinase inhibitors, so PI3 kinase is an enzyme that basically works on some protein in the cancer cells, allowing them to divide and grow. And so, there are medications that can very effectively shut that down in the lymphoma cells that we can effectively treat patients with.

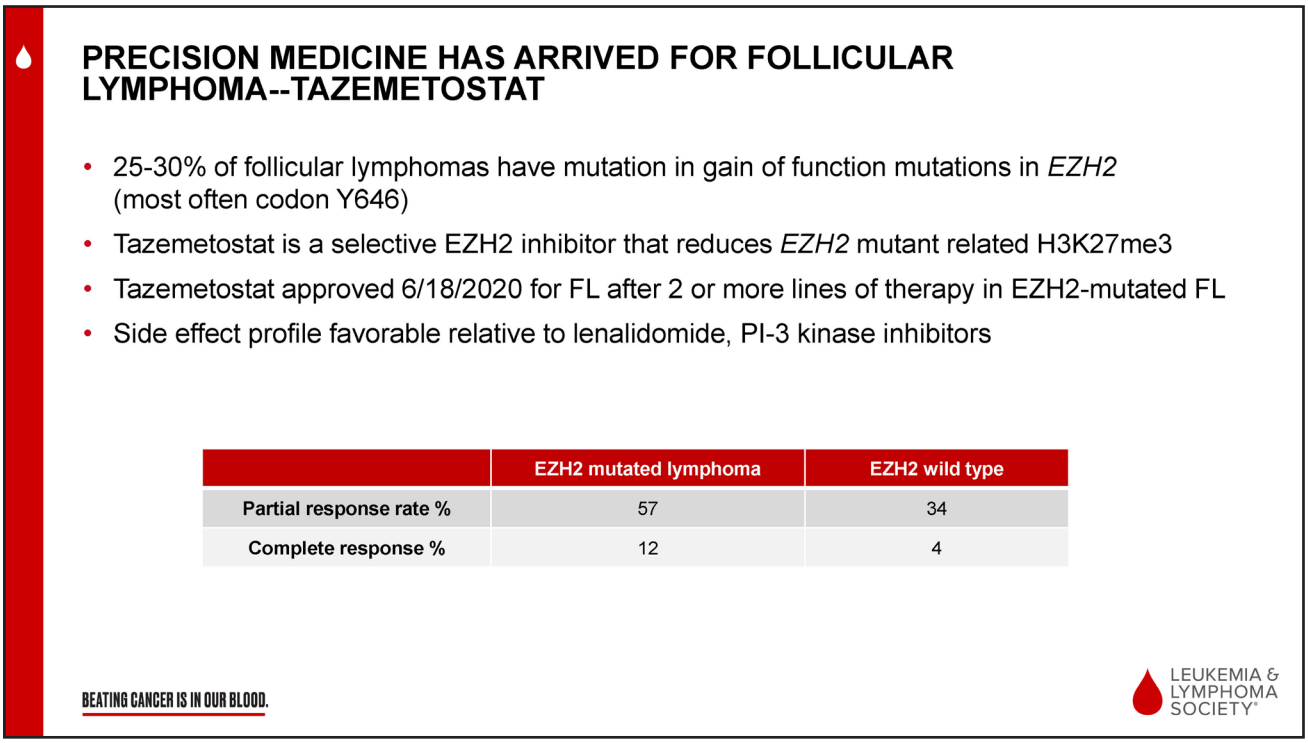
The first PI3 kinase out there was idelalisib. The data I'm showing here is from the original idelalisib paper. This graph is what we call a waterfall plot, so it depicts the amount of shrinkage of lymph nodes as a percentage. So, you can see most patients, their lymph nodes go down somewhere between 100, a little bit less than that percent. And, for any of the PI3 kinase inhibitors out there, copanlisib now, duvelisib, umbralisib. We've actually studied a couple more in recent clinical studies, basically I could superimpose any of the data from those agents on this curve, and it would all look the same. So, they're rather effective. Some patients that you put on PI3 kinase inhibitors, they go home for a couple of weeks, come back, generally feel fairly well with some of the newer agents and have pretty good lymph node shrinkage.



Slide 31: CONSIDERATIONS FOR PI3K INHIBITOR SELECTION

The one thing to consider with PI3 kinase inhibitors is some of the side effects. So, the toxicity profiles do differ pretty radically. Idelalisib, which was the first agent, I would say does have a very unfavorable kind of side effect profile. It can cause a lot of pretty severe liver, lung damage. It can also cause a diarrhea syndrome that can be life-threatening and often has to be managed with things like steroids. Some of the newer agents I think are a little bit safer in that respect, but we will have to watch for many of those side effects.

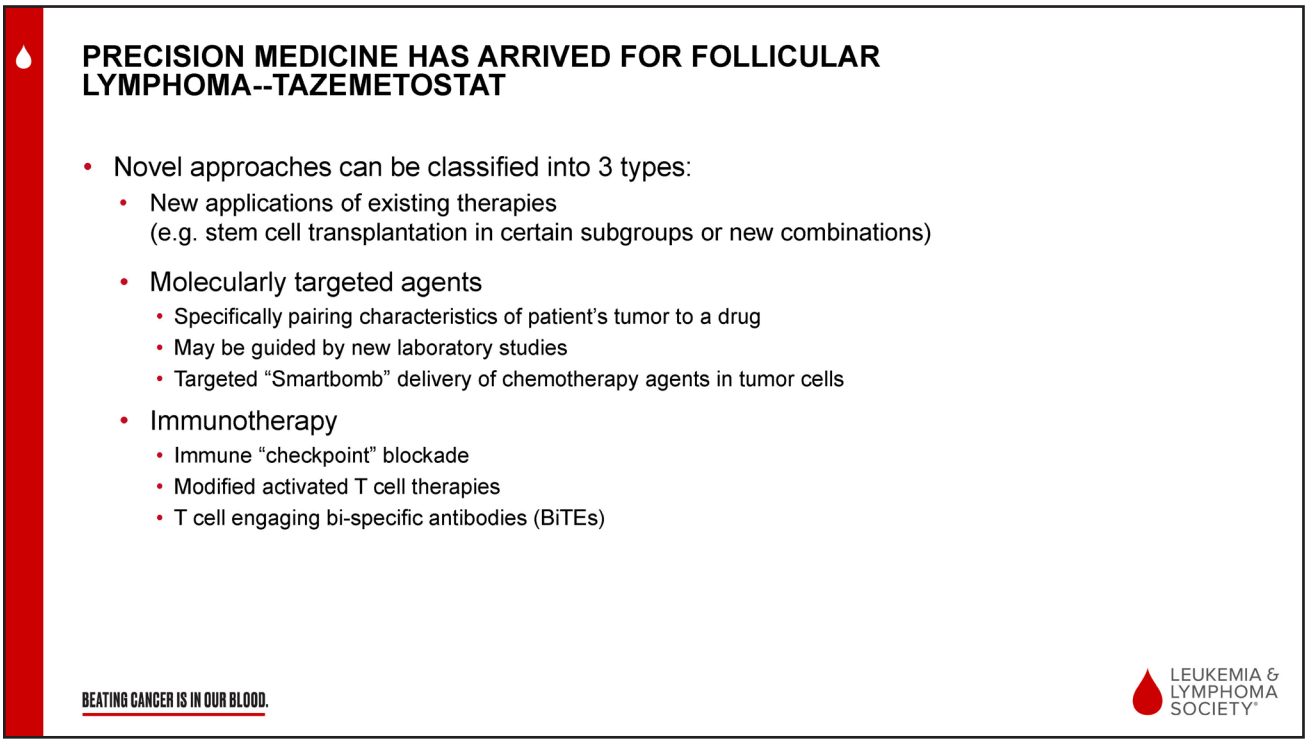
The other medication that is out there is, copanlisib. Copanlisib is an IV-based PI3 kinase inhibitor, whereas the others are an oral medication. The difference with copanlisib is about a half of patients actually will develop new diabetes, requiring insulin, and so that's a conversation that you have to have in terms of what are the risk factors for those kind of side effects, how does the patient prefer their treatment to be administered. And, all of that again should be individualized.



Slide 32: PRECISION MEDICINE HAS ARRIVED FOR FOLLICULAR LYMPHOMA–TAZEMETOSTAT

The next thing that I'll talk about is very exciting. It's a medication called tazemetostat. So, one of the things I've been involved with at Duke is what we call precision medicine. And so, the idea of precision medicine is that we can take an underlying tumor and basically sequence the DNA mutations within that tumor and then match therapy to that tumor based upon that profile. So, we've known for about a decade that about a third of follicular lymphomas have a very specific mutation in this gene called EZH2. And so, what those mutations do is actually positively affect the function of EZH2 in the cancer cells. And, we can shut that down with medications like tazemetostat. this medication was studied in a pretty large trial, largely in Europe of follicular lymphoma patients that have had multiple therapies recently fail them. And as you see here in the patients with EZH2 mutations, there's actually pretty favorable response rates. Even some patients that had complete remissions of lymphoma treated with this agent.

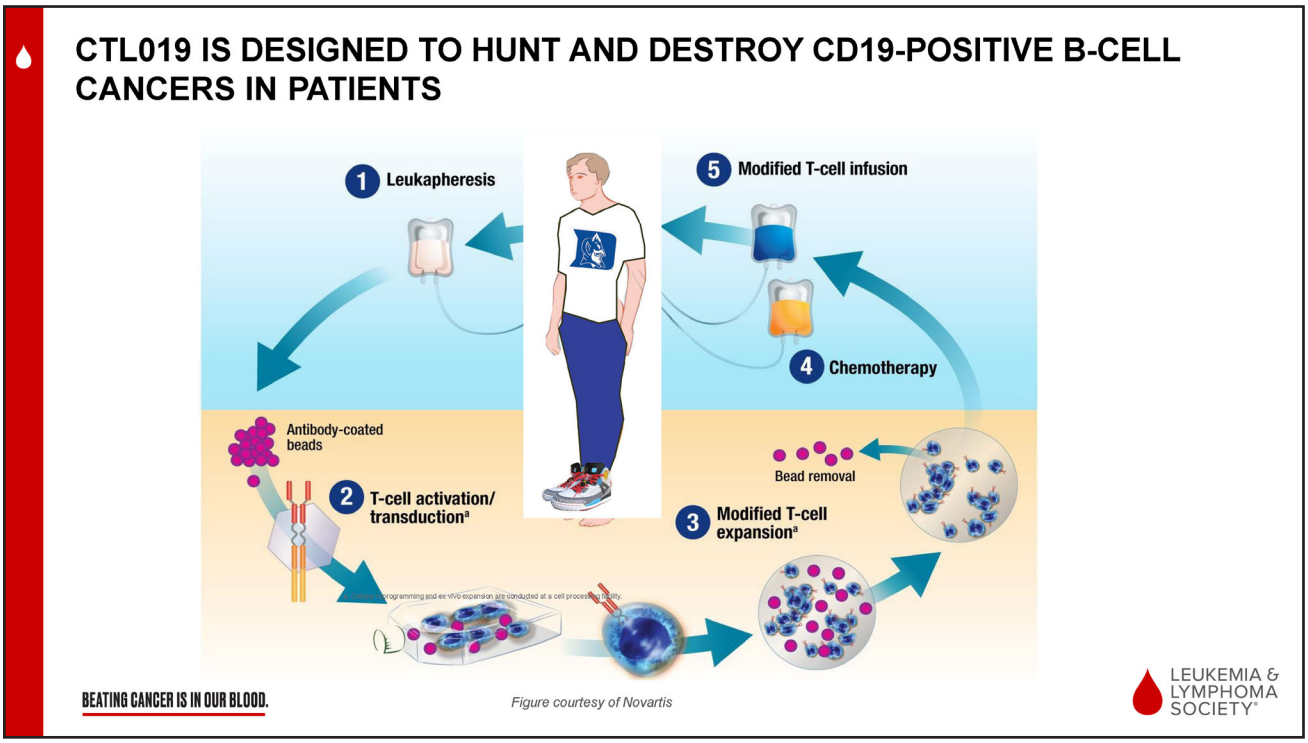
I think the exciting thing about this is, we now have the tools to identify EZH2 mutations, and then if we're able to get them onto tazemetostat, is that the side effects they have seem much, much less than other kinds of similar treatments with lenalidomide, chemotherapy, or with the PI3 kinase inhibitors. So, I think this is a wave of the future in terms of optimizing the response of our patients based upon what we call the molecular profiles of their tumor with minimizing side effects, and that's the Holy Grail of cancer medicine coming up in the future.



Slide 33: PRECISION MEDICINE HAS ARRIVED FOR FOLLICULAR LYMPHOMA–TAZEMETOSTAT

There are a number of other therapies which I think are very exciting. Unfortunately, we don't have the time to talk a lot about each individual one. They generally fall into 3 different types. One is, new combinations of existing things that are out there, so combining things like lenalidomide and other newer things like obinutuzumab or tazemetostat. There's also newer molecularly-targeted agents that are coming out. There recently was this medicine called lunkasarine, which was approved in a different type of lymphoma, but very applicable for treatment of follicular lymphoma patients.

There's also very exciting immunotherapies, and I would say a lot of the excitement and hope I have for treating slow-growing lymphoma patients in the future really revolves around some of these things like CAR-T cells and this other class of medicines called bispecific antibody treatments. And, we're involved in a lot of investigation to figure out how best to use these and can we get these treatments established for our follicular lymphoma and other slow-growing lymphoma patients.

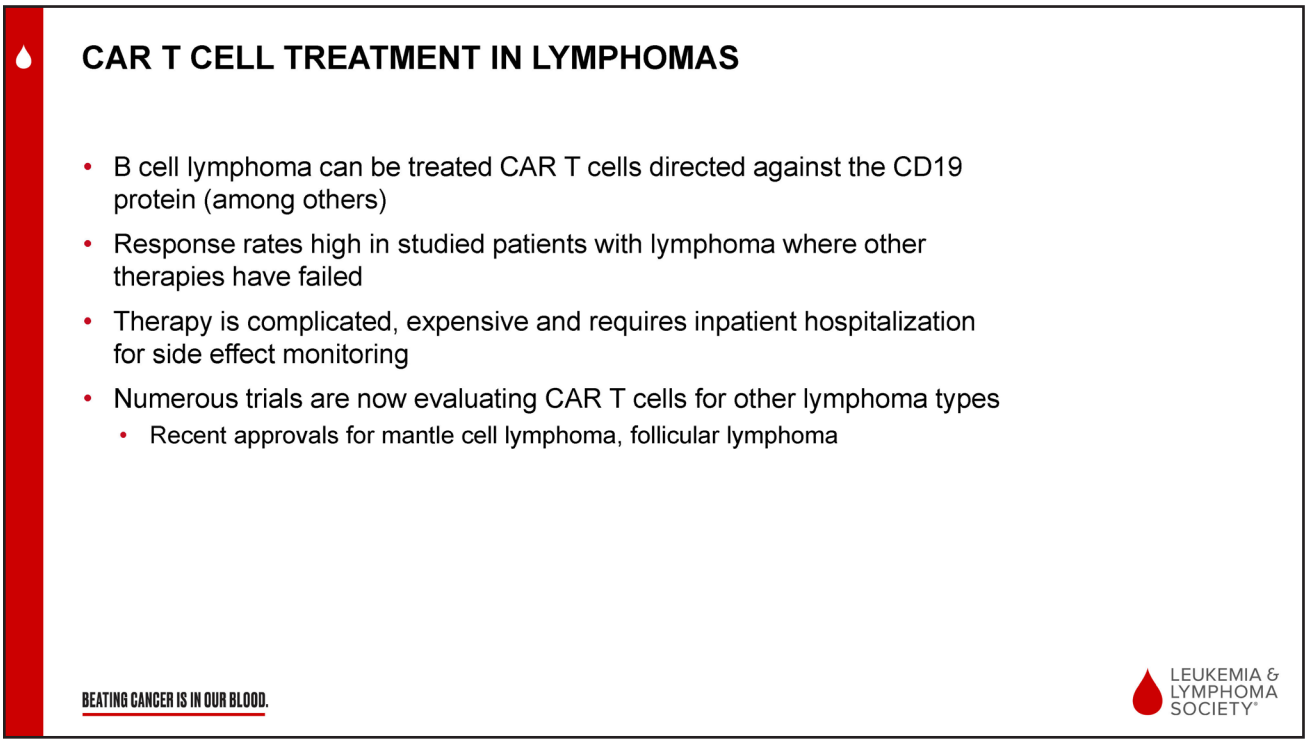


Slide 34: CTL019 IS DESIGNED TO HUNT AND DESTROY CD19-POSITIVE B-CELL CANCERS IN PATIENTS

I will talk a little bit about CAR-T cells. Many of you have heard about this technology. CAR-T is an acronym that stands for chimeric antigen receptor modified T-cell therapy. This slide depicts the process of CAR-T at the level of a patient. Once we've decided to do this, we basically filter off some of the immune cells, called the T-cells, from the patient's blood. These then go to a laboratory where they're actually genetically engineered to have a protein which allows it to recognize some of the cell surface molecules like CD19 or CD20 that we talked about earlier, on the surface of the cells. And, that same process also activates and expands those cells, that they're ready to go back in, proliferate, grow, and then actually attack the lymphoma in a very specific manner.

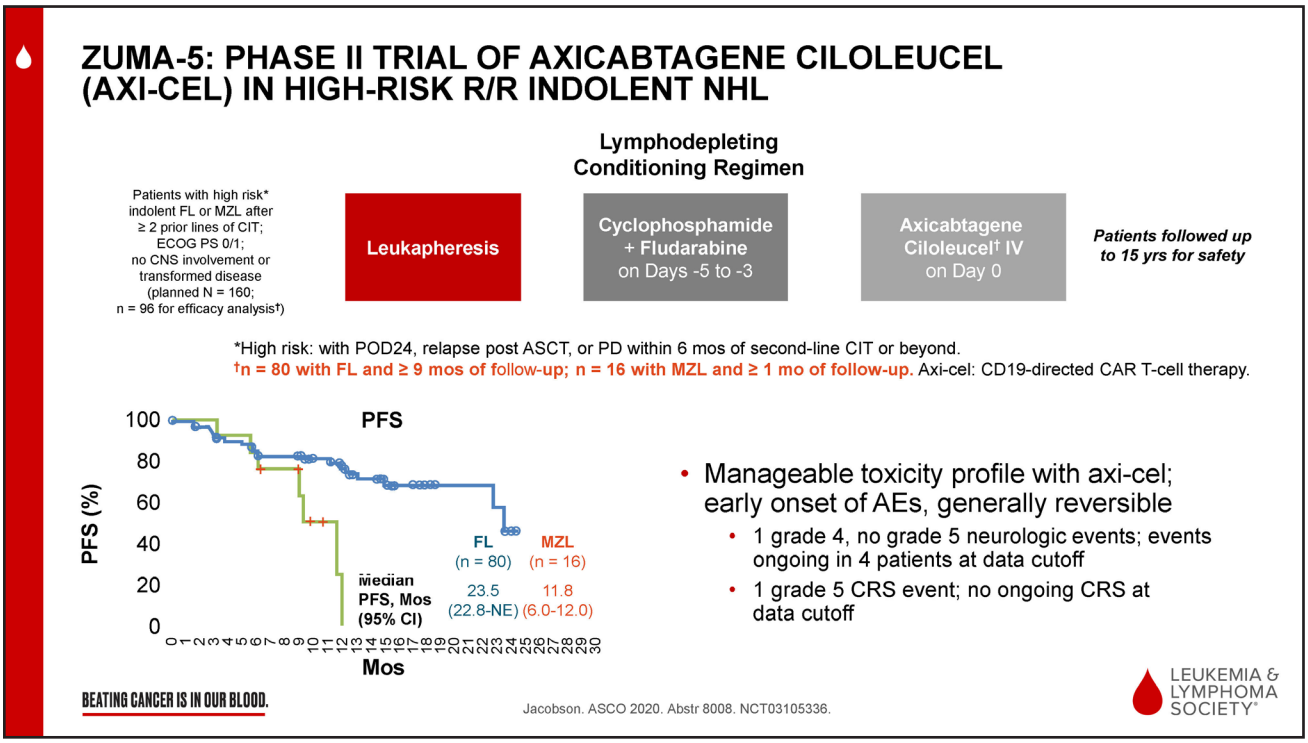
And so, once those cells are purified and then genetically engineered, they're then basically given back to the patient after a very specific type of chemotherapy to clear some of the lymph system, so they can accept the cells. And then, the patient is monitored, and the lymphoma is reassessed. So, I'll talk a little bit about the follicular lymphoma data around this.

I show this specific slide because it taught me a very important lesson in terms of doing patient education a very similar presentation to this, and the patient came up to me and asked me, can the patient wear clothes as they're going through this? And I said, you know, yes, of course, so don't take this literally. So, if I were doing this, I would put the patient in very appropriate clothing here, even stylish down to the Air Jordans, and the like.



Slide 35: CAR T CELL TREATMENT IN LYMPHOMAS

So, a few points about CAR-Ts again. There's a lot of different products actually out there. Fortunately, we're seeing now new approvals in indolent lymphoma. You know, this is a very new therapy. Fortunately, patients can still have very high rates of even complete response when other therapies have failed to shrink or eradicate their lymphoma. The only thing I will say is, as I was trying to point out in that slide is that therapy is very complicated, it is a little bit time-consuming, it's very expensive. It does generally require in most patients a couple weeks hospital stay for monitoring, it requires a caregiver, a lot of those things. Fortunately, we are now seeing uptake of this therapy and sort of promising responses, especially in follicular lymphoma.



Slide 36: ZUMA-5: PHASE II TRIAL OF AXICABTAGENE CILOLEUCEL (AXI-CEL) IN HIGH-RISK R/R INDOLENT NHL

This slide coming up next shows results, some of the results from the ZUMA-5 trial. So, ZUMA-5 investigated axicabtagen ciloleucel. That's the long, complicated name for the engineered CAR-T product. It can also go by Axi-Cel, the trade name for that is Yescarta®, or the brand name. And so, ZUMA-5 looked at CAR-T therapy in a pretty large cohort of slow-growing indolent, follicular, and marginal zone lymphoma patients. Again, the process is what I showed on the previous slide, the patients had their cells harvested and the cell product was made. They then underwent very specific chemotherapy to condition them to receive their cells. And then, those cells were infused.

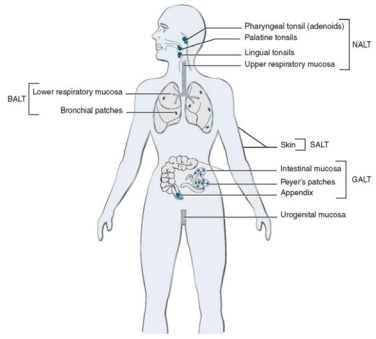
The bottom panels show a little bit of overview about their response in these lymphoma subtypes, as well as the side effects. But, I will say that the ZUMA-5, or the Axi-Cel was a big success in follicular lymphoma patients. The clinical CR rate, the rate that lymphoma completely disappeared by CT scans was about 80%, which I think would make it probably the most effective single therapy for any stage of follicular lymphoma.

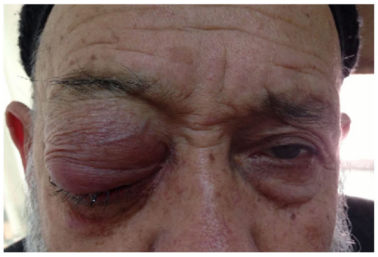
Unfortunately, those data didn't look the same in mantle cell, and it probably owes to the fact that mantle cell is just a different disease. And, whatever is going on in those cells, it just doesn't make CAR-T therapy work as well.

I will say, some of the side effects are important to consider with CAR-T cells. Again, this is a pretty cumbersome therapy to undergo, but fortunately we're getting better and better with the side effects in terms of management and getting patients treated. And, even at Duke we're moving now to outpatient CAR-T therapy, because it's important to understand that this is not a therapy that you can just go to your local oncologist, show up and get. But, we're certainly working on that, and I think CAR-T is very exciting. Because, my hope would be that, some of these immune therapies, at least in theory, may be curative for some of our patients.

MARGINAL ZONE LYMPHOMA

- 3 types:
  - Extranodal (MALT) lymphomas
    - Mucosa associated lymphatic tissue
  - Nodal MZL
  - Splenic MZL
- Association with chronic antigenic stimulation by infection or autoantigens in lymph tissues
- 70% are mucosal associated lymphoid tissue (MALT) lymphomas
- Gastric MALT lymphoma in 30% of cases





Ocular adnexal marginal zone lymphoma

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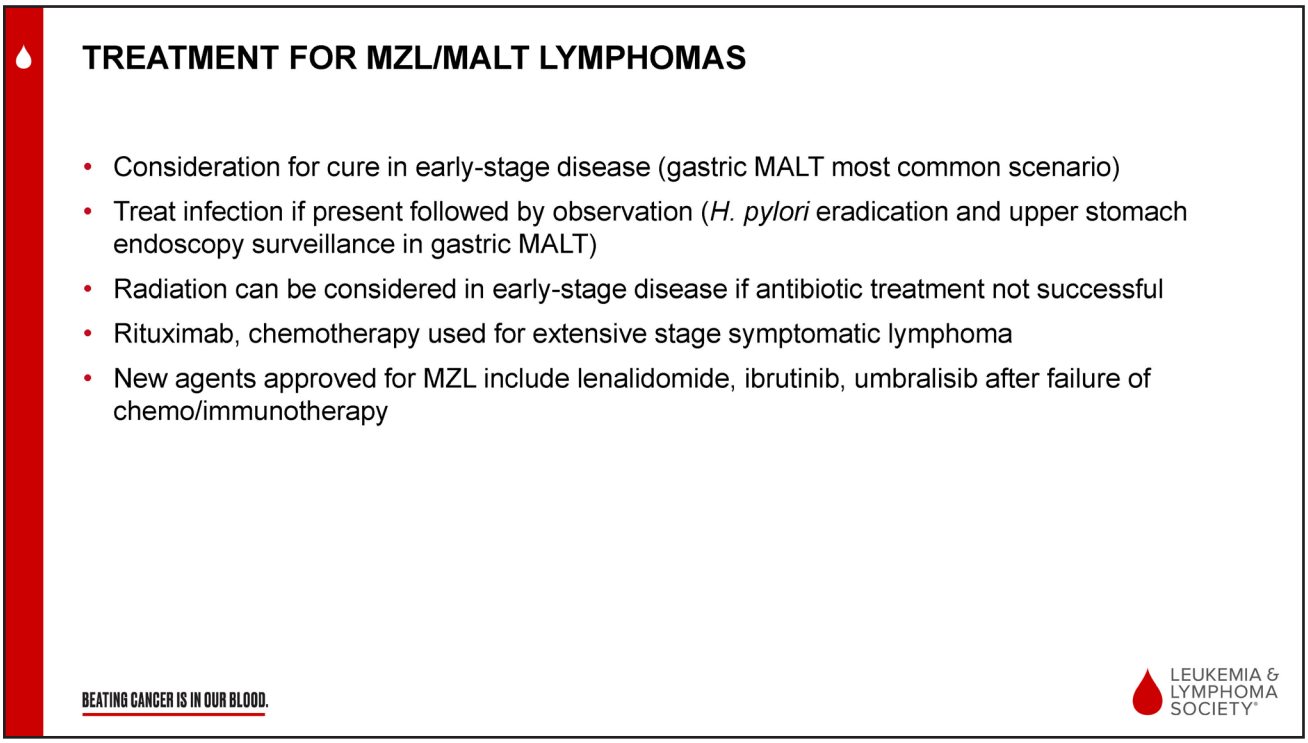
Slide 37: MARGINAL ZONE LYMPHOMA

I'm going to talk a little bit about other indolent lymphomas, such as marginal zone lymphoma or MALT lymphoma, as well as Waldenström's. There are 3 main types of marginal zone lymphoma. I think it's important to understand a little bit about how we diagnose this. So, what this panel on the right upper area is supposed to show is that in the human body, there are areas of lymph tissue that do not sit in either things like spleen or lymph nodes, which is the usual areas where you think of lymph cells being. And so, if you get a lymphoma that arises from that tissue, often we'll call it the mucosal-associated lymphatic tissue or MALT and that's where that name comes from.

You can also have marginal zone lymphomas that come up in lymph nodes, so they present very similarly to what a follicular lymphoma or other lymphoma would be in lymph nodes. You can also get what is called a splenic marginal zone lymphoma, so that's where the cells generally live, in the spleen and often bone marrow and blood. All of those different diseases have different presentations and clinical behavior.

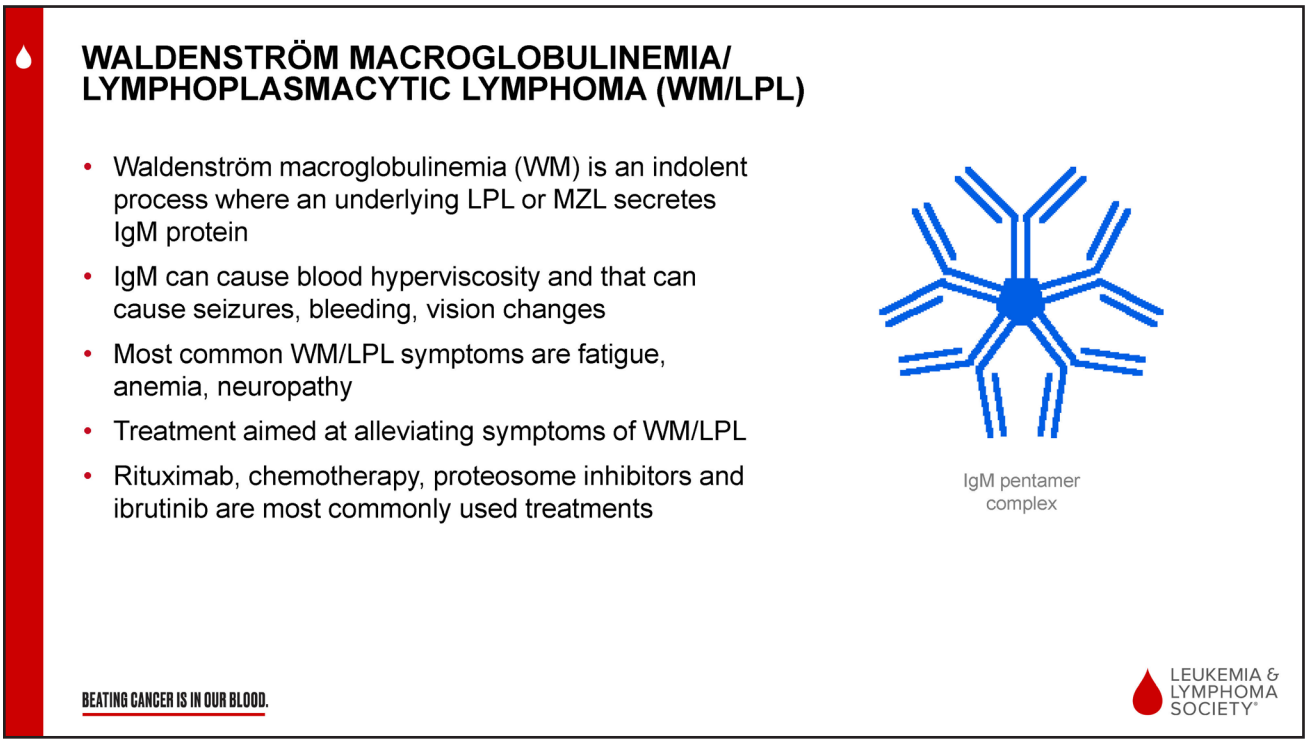
Many of these are associated with chronic infections, so the most common MALT lymphoma is gastric MALT lymphoma. And so, at least half of gastric lymphoma cases are associated with *H. pylori* infection, which is a bacteria that can chronically infect the mucosa of the stomach and can cause ulcers, irritation and pain in the stomach, but also cause the MALT lymphoma.

This is an example of an what's called an ocular adnexal marginal zone lymphoma, this is basically a MALT that forms in the lymphoid tissue of some of the glands of the eyes. And, you can see this pretty massive swelling there in the eye.



Slide 38: TREATMENT FOR MZL/MALT LYMPHOMAS

Some considerations around treatment for MALT or marginal zone lymphomas. Again, speaking of the general philosophy of, is this a curable disease as we look at that, so, many gastric MALT lymphomas, even the ones that are *H. pylori* negative, are very curable. The first consideration if there's an infection that's identifiable, such as *H. pylori*, as we put patients on treatment for that, and then often we can just look every now and then with an upper endoscopy to look via camera into the stomach and make sure the lymphoma is resolved and often avoid the patients any therapy like radiation or rituximab or chemotherapy. Outside of that, infection eradication, all of the other treatments can be applicable for marginal zone lymphomas or MALT. If infection eradication doesn't work or is not applicable, then we can move to radiation, again, things like bendamustine, rituximab, and even newer therapies like lenalidomide, ibrutinib, umbralisib are now approved and out there.



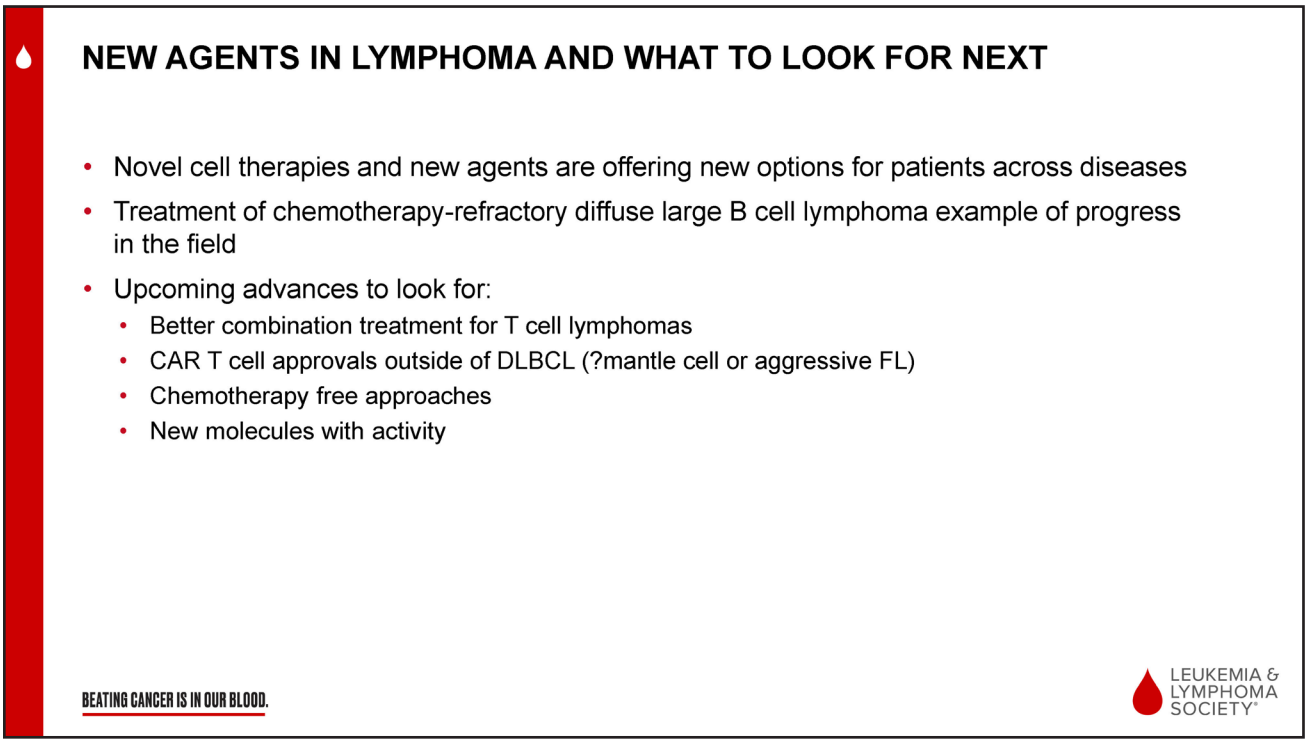
Slide 39: WALDENSTRÖM MACROGLOBULINEMIA/LYMPHOPLASMACYTIC LYMPHOMA (WM/LPL)

The other type of slow-growing lymphoma that comes up is lymphoplasmacytic lymphoma or what is basically a clinical syndrome, Waldenström macroglobulinemia. So, these are 2 very complicated terms and hopefully I can enlighten you a little bit about what each means.

So, Waldenström is a syndrome where, in your blood you can find a very specific protein called immunoglobulin-M or IgM. In the right panel on this slide is basically a picture of what IgM looks like. So, IgM is also similar to rituximab or obinutuzumab, it's an antibody, but the way that it exists in the blood is that 5 of these things come together in what we call a pentamer. And, that has very important implications because the way that this protein forms and the way that it exists in the blood is that if it gets to be at a high enough level, it can actually cause the blood to thicken and get really viscous, kind of like motor oil. And so, if that happens, then the patient can have very specific symptoms, they can have things like bleeding because the blood gets clogged in the blood vessels. Patients can even have things like seizures, changes in their vision, vision loss, if that IgM level gets too high. And so, that's a much different situation than other lymphomas that don't have that.

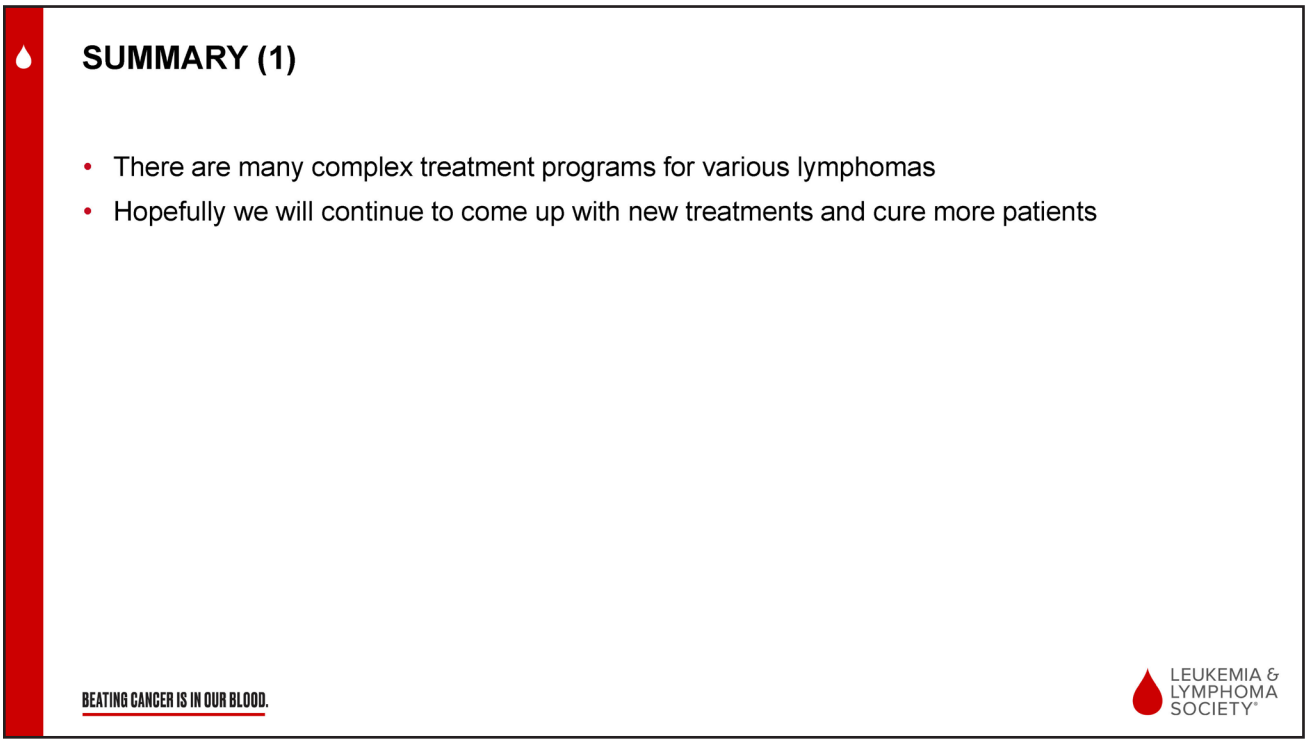
And so again, if you have IgM in the blood, we call Waldenström's macroglobulinemia. Most Waldenströms are caused by an underlying lymphoplasmacytic lymphoma. That's what we see in the microscope. In some cases, that condition can be seen with things like marginal zone lymphoma, and then sometimes it's hard to make a determination between LPL and marginal zone lymphoma. But, that's what those things mean and I think that can be very confusing as well.

Again, similar to other low-grade lymphomas, we try to monitor Waldenström's patients if they're not symptomatic or that IgM is not at a high level, where we're concerned it's going to cause hyperviscosity. But there's a number of things now out there, including rituximab, chemotherapy, also sometimes we use what's called proteasome inhibitors, things like Velcade®. Also, ibrutinib is now approved in Waldenström's macroglobulinemia and very effective for many of our patients and also affords them a kind of chemotherapy-free treatment.



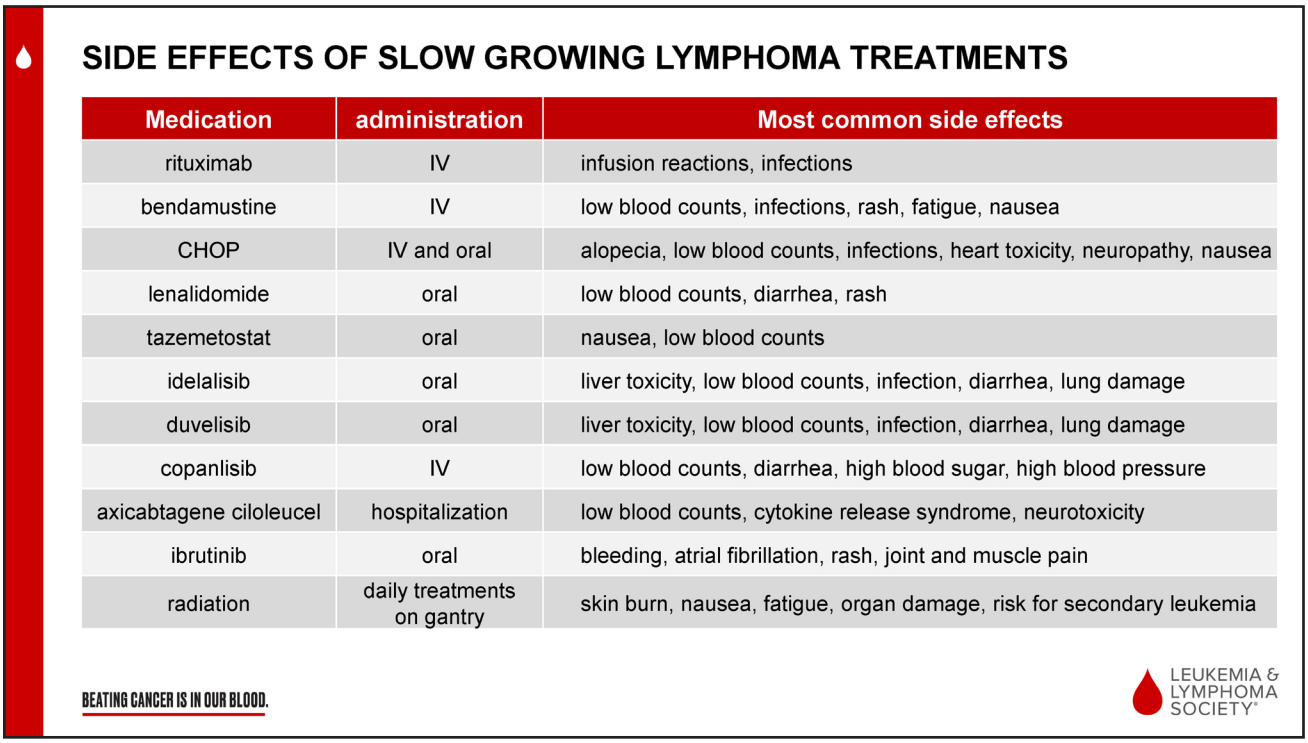
Slide 40: NEW AGENTS IN LYMPHOMA AND WHAT TO LOOK FOR NEXT

So, I'll talk a little bit about things to look for. I talked about most of this already.



Slide 41: SUMMARY (1)

But in summary, at least as far as treatment, do remember that there's many complicated kinds of treatment programs or algorithms for these lymphomas. All of that kind of treatment decisions should be individualized for the patient. And, I am very hopeful that we'll continue to come up with better and better treatments to have less side effects, and hopefully for low-grade lymphomas, change the paradigm that we can't cure more patients. And so, I think there's a lot of reasons to be hopeful in the coming years as we get better and better with our therapies.



SIDE EFFECTS OF SLOW GROWING LYMPHOMA TREATMENTS

Medication	administration	Most common side effects
rituximab	IV	infusion reactions, infections
bendamustine	IV	low blood counts, infections, rash, fatigue, nausea
CHOP	IV and oral	alopecia, low blood counts, infections, heart toxicity, neuropathy, nausea
lenalidomide	oral	low blood counts, diarrhea, rash
tazemetostat	oral	nausea, low blood counts
idelalisib	oral	liver toxicity, low blood counts, infection, diarrhea, lung damage
duvelisib	oral	liver toxicity, low blood counts, infection, diarrhea, lung damage
copanlisib	IV	low blood counts, diarrhea, high blood sugar, high blood pressure
axicabtagene ciloleucel	hospitalization	low blood counts, cytokine release syndrome, neurotoxicity
ibrutinib	oral	bleeding, atrial fibrillation, rash, joint and muscle pain
radiation	daily treatments on gantry	skin burn, nausea, fatigue, organ damage, risk for secondary leukemia

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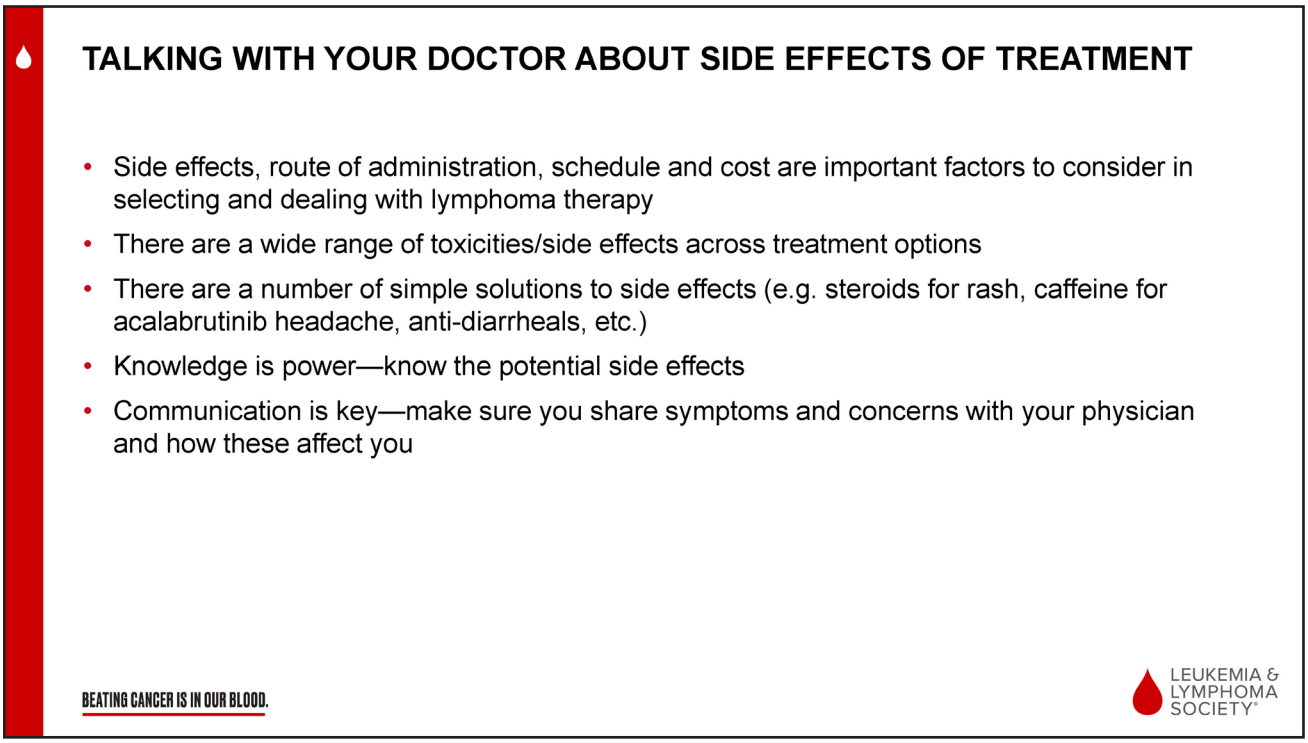
Slide 42: SIDE EFFECTS OF SLOW GROWING LYMPHOMA TREATMENTS

I will talk a little bit now about side effects. I think this is perhaps the more important thing to think about at the level of the patients. In this table I tried to list all of the different variations and some of the side effects, as well as how these drugs are administered. Again, you can see there's a lot of different regimens in terms of what the side effects are. And so, I think the more that you and your treating doctor understand what the expected side effects are and what resources are out there for dealing with those, I think, those discussions and that treatment is going to be better. And, I think that will allow you as a patient or you as a caregiver, for there to be less kinds of side effects that you have to deal with, and also avoid the chance that you're going to have to stop an effective therapy because of a side effect that's out there.

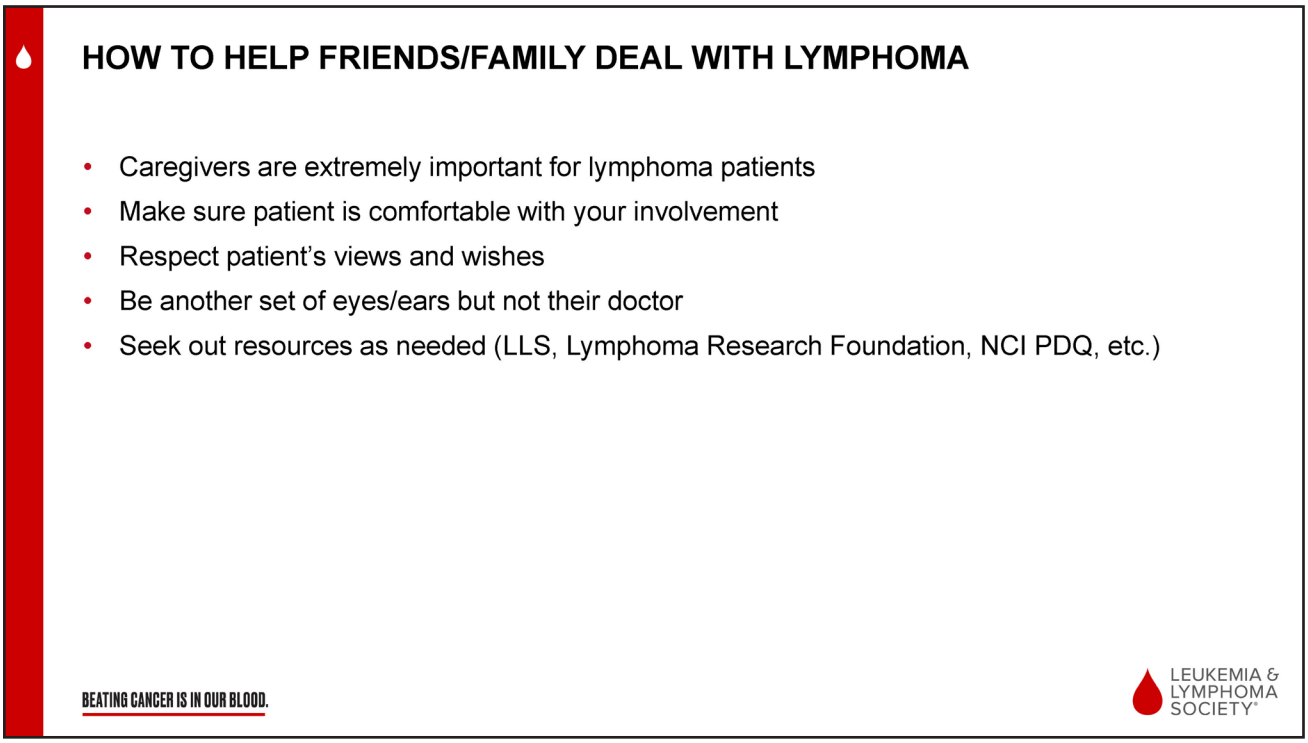


Slide 43: TALKING WITH YOUR DOCTOR ABOUT SIDE EFFECTS OF TREATMENT

And so, Some tips on talking to your doctor or healthcare team about side effects. Again, remember, the kind of side effects and the way that these medicines are administered vary pretty significantly based upon the individual treatment that's chosen. And I think it's important to understand all of those aspects.

That the level of the individual patient and individual side effects for different medications, again, there are a lot of resources out there that list what those side effects are likely to be. And, very often in many cases, fairly simple interventions, but it just takes knowing with those side effects, what the antidote and treatment is.

So, I think knowledge is power and also communication is key in terms of letting your healthcare team know what's going on and that you know what to expect.



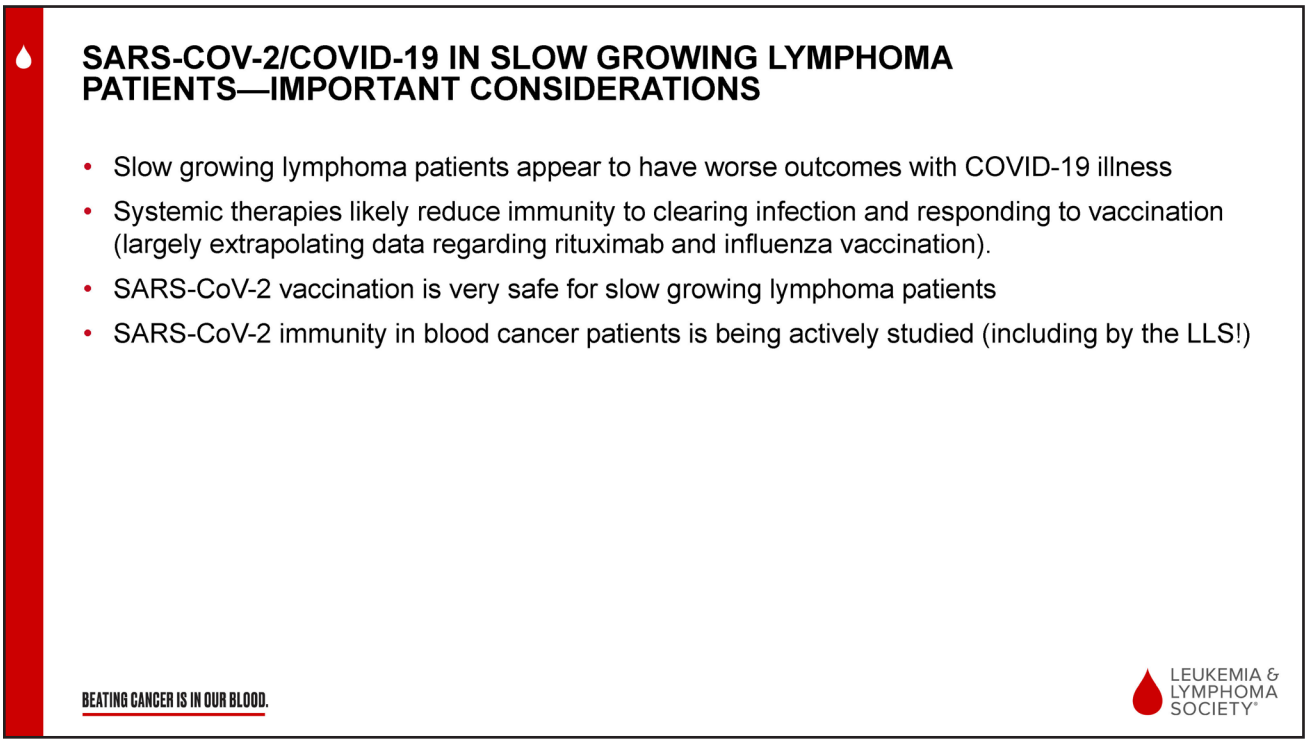
Slide 44: HOW TO HELP FRIENDS/FAMILY DEAL WITH LYMPHOMA

A couple of things that also come up with patients is the idea around caregivers. I think having family support or caregiver support is probably one of the most important things in terms of lymphoma patients' care. Again, things like CAR-T therapy or bone marrow transplant, we won't even advise for patients unless they have good caregiver support because they require caregiving.

I think there are some things that are important to understand for the caregivers that are on this call. One is just make sure that there's open lines of communication, make sure that the patient is comfortable with whatever level of involvement, and that there's certainly boundaries set between what the patient wants and what the caregiver's involvement is. And I think, just be respectful of their views and wishes, kind of across the trajectory of their dealing with slow-growing lymphoma.

I think it is important that you know your resources, that you're another set of eyes or ears or a scribe for some of the information that's out there. You can also be someone that communicates either through e-mails with your doctor or help call into the clinic to discuss things. I think it's important to remember you're not their treating physician, so, let the doctor take care of those things, don't do things on your own and get that person in trouble.

And then, obviously the last bullet point, as most of you have already figured out, appropriate resources like The LLS. Other things I tell patients about are things like the LRF (Lymphoma Research Foundation), which is also a good organization with a lot of experts that have put together very detailed sets of information. The National Cancer Institute actually has pretty good treatment information, both for physicians and patients as well.



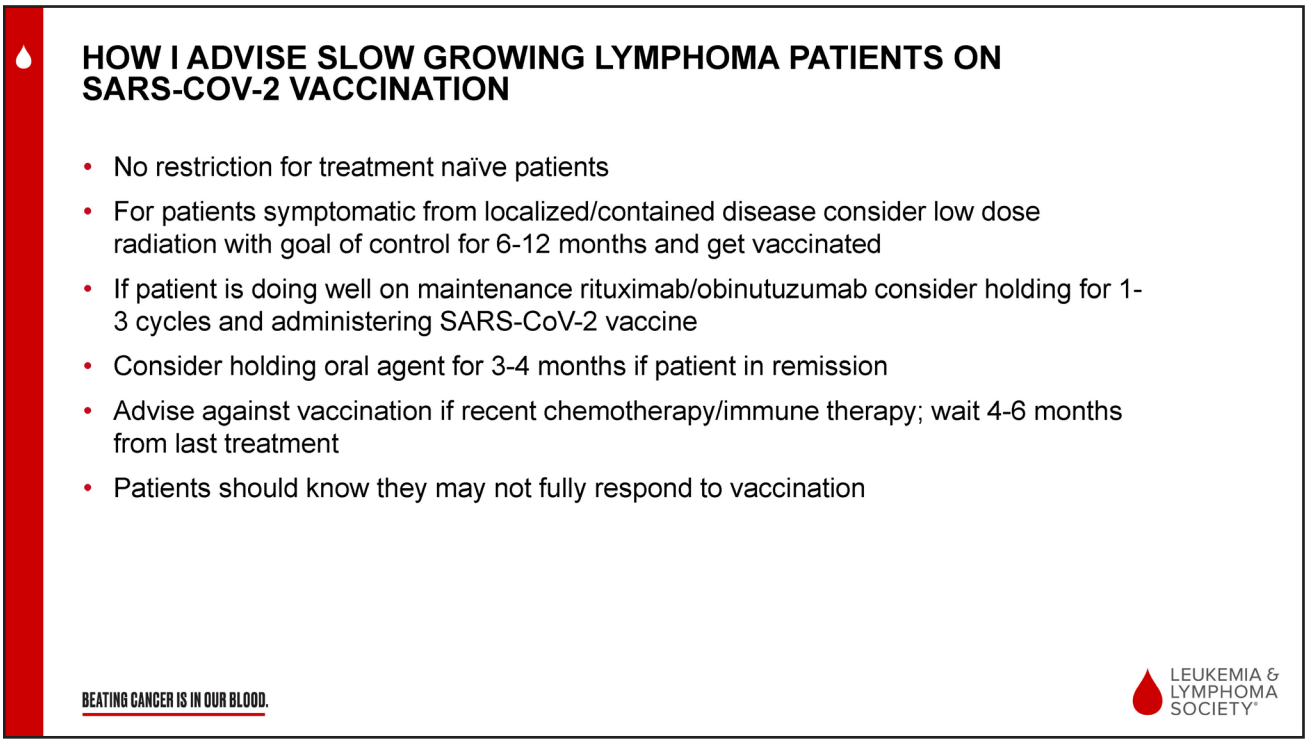
Slide 45: SARS-COV-2/COVID-19 IN SLOW GROWING LYMPHOMA PATIENTS—IMPORTANT CONSIDERATIONS

In the last few slides, I'm going to talk a little bit too about the SARS-COV-2 coronavirus and COVID-19 pandemic, particularly how it may affect slow-growing lymphoma patients, what I think the key things are, and what information we have. Again, this is a rapidly changing environment. If I gave this talk 3 months ago, I wouldn't be talking to as many people that have perhaps been vaccinated against COVID-19. But now, changing pretty rapidly and there's a number of studies also looking at that in blood cancer patients.

So, I think the first thing to be aware of is, if we think that patients with some of these low-grade, slow-growing lymphomas and things like CLL/SLL seem to have some worse outcomes with COVID-19 illness. And, some of that can certainly be linked to the underlying disease and some of that can be linked to the past treatments, such as rituximab and chemotherapy. Many of those treatments certainly can reduce the immunity to coronavirus and also potentially decrease the response to vaccination. And, I'll say we're still sorting out how much those things affect those responses. But, there's a lot of information from studies that have looked at things like response to flu vaccination after medicines like rituxan and ibrutinib and other small molecules, and it definitely seems like there are patients that don't respond after those therapies to vaccination, so we have to be very cognizant of that.

The one thing I absolutely tell patients is we think that SARS-COV-2 vaccination is very safe. There's no reason to think that there's any adverse reactions in lymphoma patients compared to the normal population. But, we are careful with patients that have had recent therapy, that they may not respond as well and so vaccination, in terms of efficacy, it may be futile.

This is a rapidly changing, investigated thing in the field by a lot of groups. One of my patients recently e-mailed me that he was on a study that was sponsored by The LLS, where he got vaccinated and then got a COVID-19 antibody-based test, which you can do, but I would say we don't quite know how to navigate what the results of those tests mean in terms of infection risks and those kind of things. So, he was asking me to interpret the test that he got on that study.



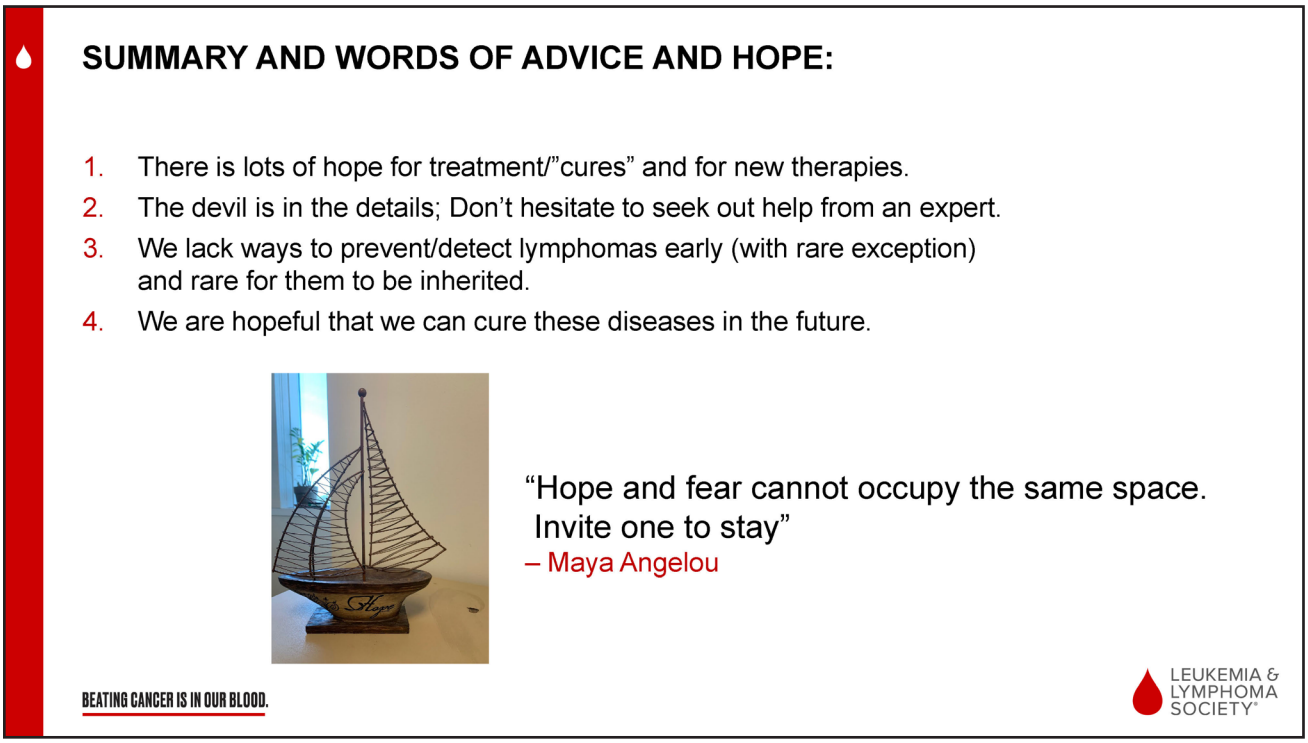
Slide 46: HOW I ADVISE SLOW GROWING LYMPHOMA PATIENTS ON SARS-COV-2 VACCINATION

How I advise patients on coronavirus vaccine is in this slide. So, especially for things like follicular lymphoma, generally all treatment-naive patients, I generally advise and recommend coronavirus vaccination. We have had a series of patients, especially in follicular and marginal zone lymphoma, that have had symptoms from localized disease, and in that situation really low-dose radiation, so a couple of doses of radiation actually have a lot of good control locally. So, I've had a series of patients where we've tried to get patients, 12 months or so, tided over before they're going to have to start something like rituximab, so they can go ahead and get vaccinated without thinking that it's not going to work well, and then, be protected hopefully until we can ride this pandemic out. And, I think that's been very useful in probably half a dozen of my patients so far.

Other considerations, if a patient is on a maintenance therapy and they're in remission, we sometimes will come up with a strategy where we hold therapy for several months to try to get their immune system working better to where they can respond to vaccination. And so, the way that this can be done is if you're on something like rituximab or obinutuzumab, is hold anywhere from 1 to 3 or 4 cycles and give the patient 4 to 6 months for that medication to wash out and then do the vaccine. And, I think that's very consistent with guidance from other big guidelines organizations. Also, we have a couple of clinical trials that involve maintenance therapy that are active, and that's been the approach, is to allow up to 4 doses to be skipped to get through to vaccination after a period of watching.

There are a number of folks that have also advocated for things like ibrutinib or immune-suppressive oral therapies. There's potential also to hold for a few months and then do vaccination. I've done that in a couple of folks that had basically things like marginal zone lymphoma and mantle cell lymphoma that was really in a complete remission. Again, that's an individualized decision. It gets harder to do with things like CLL or Waldenström's, where the disease can rapidly flare, so you take that on a patient-by-patient basis.

And then again, after recent chemo and immune therapy, if therapy is on hold, if the patient is more than about 4 months out, we'll then advise to go ahead and get whatever vaccine that you can get. And, I'll generally tell patients, we don't know how well people respond and in what time points out from therapy, so just still be very cognizant with being out in public where you could be exposed to the virus. I'm hopeful that patients benefit from these vaccines and avoid very morbid, potentially fatal illnesses. But, I think until we better understand who can be out and about safely, it is best to still isolate and social distance and mask.



Slide 47: SUMMARY AND WORDS OF ADVICE AND HOPE

The last slide I'll show is some general words of advice and hope that I have for my lymphoma patients. Hopefully, I've shown you some aspects of the newer therapies that are out there for slow-growing lymphomas. I think there's a lot of hope even in the near future for better and better therapies and even cures of our patients.

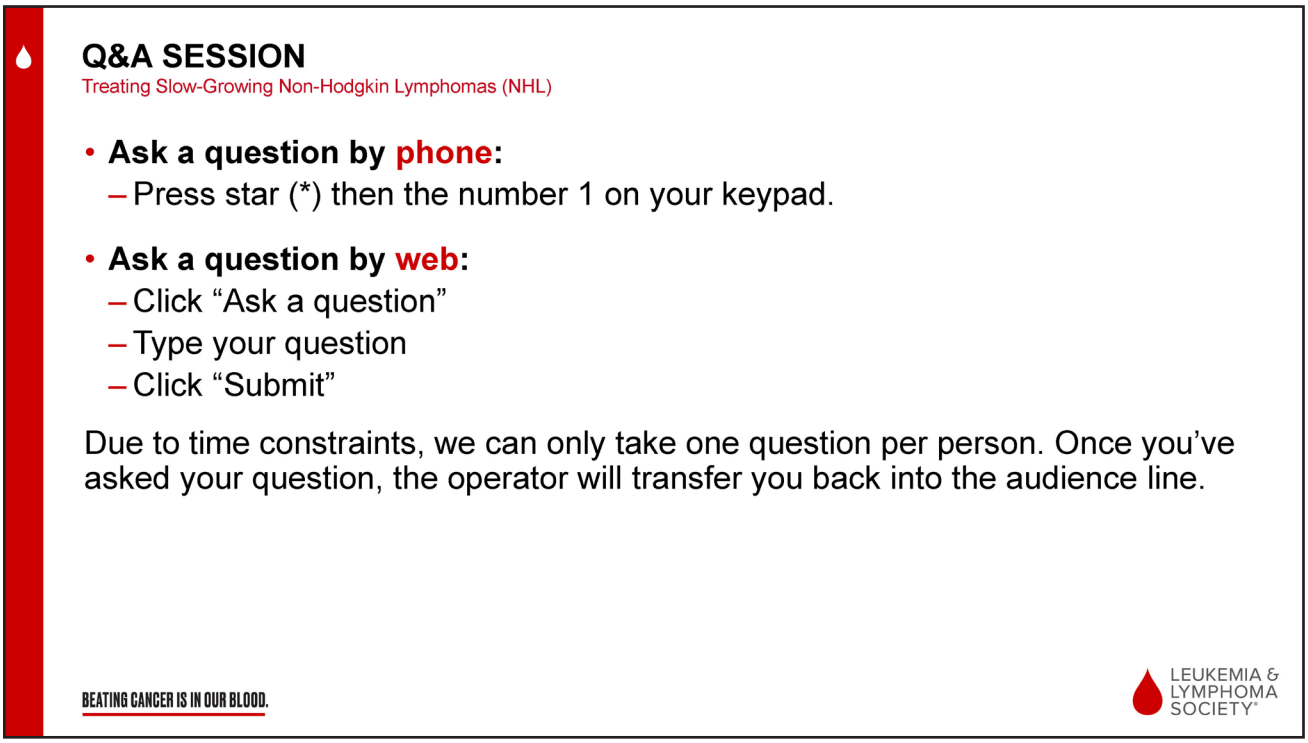
Point I'll take from one of my ex-mentors, he would always say the devil is in the details. Which I think is true in cancer and medicine in general. So, if things are not making sense, often these decisions are very individualized, so don't hesitate to speak out for expert care.

We're still trying to get better and better ways to detect lymphoma earlier, hopefully cure it. I'm very hopeful that some of these novel immunotherapies we may be looking at cure these diseases.

And so, this reminded me of a gift that a follicular lymphoma patient gave me, which is this boat that sits in my office. And, you may not be able to see this, but the name of the boat is actually Hope and I think this is very fitting for a follicular lymphoma patient, that using hope to navigate the very tough waters of living every day with a slow-growing lymphoma.

And, the same day I made this slide, I actually saw this other quote from Maya Angelou that I've never seen and I think is also very applicable to the care of lymphoma patients. And, I'll leave you with that. It says that "Hope and fear cannot occupy the same space. Invite one to stay."

With that, I will conclude, and we'll take questions.



Slide 48: Q&A SESSION

Ms. Figueroa-Rivera:

Thank you so much, Dr. McKinney. It’s time for our question-and-answer portion of our program.

And our first question Doctor, are there any new treatments as opposed to watch and wait? And can indolent lymphomas be cured?

Dr. Matthew McKinney:

Yeah, so I think hopefully the information earlier in the presentation was helpful as to when we time therapy. Again, there’s not a curative therapy out there, which is the reason that we advise watch and wait, and I think the other fact I talk with patients about is that all of our therapies often have side effects that the patient has to live with. And so, I think that drives a lot of the decision around watching and observing versus more active therapy. Again, I think that’s a very individualized kind of patient-centered decision. And, there’s lots of things like rituximab which are relatively non-toxic therapies that potentially you could use earlier, if the patient is real worried about progression or living day-to-day with their diagnosis.

I think until we get some of the immune therapies and we’re really good at giving them and we start to understand some of those are curative, we may use those earlier, but that still remains to be seen.

Ms. Figueroa-Rivera:

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

Operator:

We have Jennifer from California. Please go ahead, Jennifer.

Jennifer:

Hello. I would like to know for patients who are on wait and watch and have not had treatment, what is the percentage for whom treatment never becomes needed?

Dr. Matthew McKinney:

That's a great question. So, I think each patient is different. I think the other thing is that studies like that are a little bit hard to do, but I think if you look out 5 or 10 years of following those, patients like yourself can see up to a third of 1 in 5, 1 in 3 patients go out 5 to 10 years and not need treatment. So, it can be a really, really long time, which is the other argument for trying to watch because there's patients that may live out their entire rest of their lives with really no complication from a slow-growing lymphoma just because some of these are very slow-growing. But, there are some of these lymphomas that do behave more aggressively, but it is very individualized around what the individual lymphoma is doing.

Ms. Figueroa-Rivera:

Thank you. And the next question from comes from Naseem. Naseem asks, does precision medicine exist for MALT lymphoma?

Dr. Matthew McKinney:

So, in a way it does, we're still looking at some of the individual kinds of mutations and things that we can really directly target. Some of the precision medicine is indirect, so there's actually some specific genes we can look at in some of the gastric MALT lymphomas to predict whether or not things like the infection treatment will work. And so, if you find those, you can say that giving antibiotics for *H. pylori* is probably not going work and that you should plan for radiation. There's also some of that in terms of predicting ibrutinib response. So, that's the state of the art right now, is we do send some of those things for MALT lymphomas. But we're still investigating are other things we can hit directly like, EZH2 or other molecules. So that's a great question.

Ms. Figueroa-Rivera:

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

Operator:

We have Albert from Pennsylvania. Albert, please state your question.

Albert:

Yes, I was told that there's a good chance that I would not expire from my lymphoma and I'm on wait and watch or watch and wait, and I'm just wondering, is that actually something that can happen, that you can live a very long time with it. I have follicular.

Dr. Matthew McKinney:

Yes. It's important to understand that these diseases can cause very serious things to happen in people. There are also people that live their full life with things like follicular lymphoma or marginal zone lymphoma or CLL/SLL, Waldenström's, that you live sort of your full life expectancy without having any kind of complications from lymphoma. So, there's a pretty big spectrum of those things. And so, I think because of that, I try to monitor people. The other term that people have used and actually one of my colleagues came up with this is not watch and wait, I think people get a lot of anxiety around the waiting, is dynamic observation. And so, if something changes, that you can react dynamically in that kind of strategy, and then, again rediscuss treatments or scans or whatever else you're going to do.

But, the answer to your question Albert is, yes, it is possible to live out a normal life and never need treatment for follicular lymphoma.

Ms. Figueroa-Rivera:

Thank you for the question. And the next question comes from Summer. Summer is asking, how often do indolent non-Hodgkin lymphomas convert to a more aggressive form?

Dr. Matthew McKinney:

That's a great question, too. I didn't talk a lot about this just in the interest of time. One consideration is that a small percentage of these can go to a more aggressive lymphoma, and those tend to be harder to treat. That number is about 5 to 10% of cases, really across follicular and marginal zone lymphoma, as well as there's also this phenomenon called Richter's transformation in CLL or SLL, which is really specific for CLL going to some other more aggressive lymphoma.

Sometimes those things can be predicted by stage or aggressiveness and other markers like LDH, that we can use. There's actually some now published data around this. But, I think if you quoted 5 to 15% across these slow-growing lymphomas, that would be the appropriate number.

Ms. Figueroa-Rivera:

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

Operator:

We have Earl from South Dakota. Earl, please state your question.

Earl:

I have non-Hodgkin's follicular lymphoma, it's been from 2008 on clinical trials for 6 months and it came back in April of 2021. And, they're using low-level radiation treatments. I've had 2 about 2 weeks ago. Any comments?

Dr. Matthew McKinney:

It sounds like you did well for more than a decade with initial therapy, so I think like you, I see patients back that were on the original rituximab clinical trials and, in a remission 15, 20 years later. And so, I think there's a lot of different treatments that relapse. Again, we're using a lot of different radiation strategies and really trying, hopefully the one that you're on is also kind of protective of your immune system with the COVID-19 pandemic. So, it sounds like you're on the right track.

Ms. Figueroa-Rivera:

Thank you. I have another radiation question. Michelle is asking, does radiation still work if there is bone marrow involvement?

Dr. Matthew McKinney:

So, yes, that's a great question. I think it depends on the goal of radiation. So, if the goal of radiation is to alleviate symptoms for some period of time, if not indefinitely, then, I think doing radiation to a specific area can be very helpful. If your goal is that this is a very early-stage lymphoma and that you're going to completely cure it, then I think that's going to be less of a scenario for the bone marrow involvement because you're not going to be able to treat that in that scenario. But, if it's radiation for a very specific kind of site, treating pain or some other complication, I think that we certainly have done that in certain patients as well.

Ms. Figueroa-Rivera:

Thank you. And, I'll go to a question from the web. Hugo is asking, does the immune system of an NHL patient ever get back to normal after treatment?

Dr. Matthew McKinney:

That's a great question, Hugo. Definitely patients can have very prolonged problems with the immune system even for years after therapy. And, sometimes that's manifested by more infections, we can check either T-cell numbers or B-cell numbers or immunoglobulins. My impression is for most people, if you're years out from therapy, it's probably your immune system, mostly recovering pretty close to normal, if not indistinguishable from normal in many instances. It kind of depends on individual factors of the patient. But, I think there's certainly a lot of hope that after some period of recovery, depending upon the therapy that was done and what the situation is, that the immune system can recover.

Ms. Figueroa-Rivera:

Thank you. And Steven's asking, what is PFS on the rituxan slide?

Dr. Matthew McKinney:

So, PFS stands for progression-free survival. Sorry if I wasn't clearer. And so, that's the length of time basically from when you start measuring in a clinical trial, or say you hit complete remission or some sort of response with therapy, it's the response of time until that lymphoma starts – you can detect that it's growing again.

Ms. Figueroa-Rivera:

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

Operator:

We go to Gerald from Florida. Gerald, please ask your question.

Gerald:

I was diagnosed with non-Hodgkin's lymphoma B-cell stage II in December of 2015. I took the aggressive chemotherapy for 6 months, a week in the hospital around the clock, and then 3 weeks staying at home. And, I developed this peripheral neuropathy in my feet like someone with diabetes, but my blood work is always pristine. What could I do to take the aches and pains out of my feet and knees and hands with this peripheral neuropathy chemo-induced?

Dr. Matthew McKinney:

That's an important question. So, some of the treatments for lymphomas, particularly there's a chemotherapy called vincristine and there're some programs that have more vincristine in them than others. Vincristine can cause damage to the nerves, and that damage is often dependent to the length of the nerves in the body. And so, the most common way that can come up is what you described. You can have numbness, you can have pain, you can have tingling, which often is worse in the toes or the feet or the legs or the hands. There's a number of things that you could ask your doctor about if pain is one of the big issues, there's not ways to make the nerves grow back and improve like numbness, but there are medicines, including things like gabapentin and other medicines that are approved for what we call neuropathic pain, the pain and discomfort around that nerve damage. But, I think that's certainly something to talk to your doctor about because there may be treatments that can make that better.

And, I think the other thing, too, is they can look over things and just make sure there's not something else, like diabetes or some other condition, that's also making the neuropathy worse, that's important to look at as well.

Ms. Figueroa-Rivera:

Thank you. And the next question comes from Jane. Jane asks, is the FLIPI scale still used or is it obsolete in light of the new treatments, such as CAR-T?

Dr. Matthew McKinney:

So, the FLIPI score is, I didn't explain it in the talk just again for simplicity and time. So, she's asking an excellent question around what's called the Follicular Lymphoma International Prognostic Index. This came from some research studies that looked at different features that you can measure in a patient, things like age, the stage, whether there's stage IV disease, whether there's elevation in certain markers like the beta-2 macroglobulin, which can actually be detect in the blood, it can come from lymphoma cells, also the LDH or lactate dehydrogenase number can also come from that.

The FLIPI's already been kind of updated. There's a couple reiterations and updates of the FLIPI score in the era first of rituximab. I think it's an excellent question, is that, you know, is it relevant with things like lenalidomide's widespread use, CAR-T cells? You know, my take is that it probably would need to be updated. I mean it's a prognostic score, it gives you a percentage of, you know, in 10 years what, you know, how many percent of patients are going to be alive with lymphoma, and those treatments are very much changed. So, I think you can use it, you have to use it very carefully because again the therapies I think are very different and much better than they were when those numbers were calculated.

Ms. Figueroa-Rivera:

Thank you. And just for our slow-growing lymphoma patients, for CAR-T cell therapy, are there any CAR-T cell therapies that have been approved for slow-growing lymphomas?

Dr. Matthew McKinney:

Yeah, so the Axi-Cel is the one product which was recently approved, I think 1 or 2 months ago, so very recently this year, based upon that data from the ZUMA-5 trials, that's the Kite/Gilead CAR-T product.

Ms. Figueroa-Rivera:

Thank you. And Amy's asking, is there a level of white blood count at which treatment should be started?

Dr. Matthew McKinney:

So, yeah, so if you're referring to different slow-growing lymphomas can kind of grow and accumulate in the blood. We don't necessarily always treat for a number. Again, some people have used guidelines like 50, you know, 50,000 cells per microliter, that's the measurement as being kind of the cutoff. I think the, more important thing would be is the lymphoma also causing some other problems in lowering the other blood counts, like the patient has anemia, has low platelets. So, that would be probably more important reason to treat if those were low than just the white blood cell count.

Often, I find that patients, with follicular lymphoma that start to get elevated lymphocyte counts, so they start to get lymphoma counts kind of circulating in the blood, often those escalate pretty rapidly, so most of those patients, if they're over, 40,000, 50,000 per microliter, most of those people do go on treatment, soon thereafter. So, it's a both yes and no kind of answer.

Ms. Figueroa-Rivera:

Sure, thank you. And we'll take the next question from the telephone audience, please.

Operator:

We have Wendy from Washington. Wendy, please state your question.

Wendy:

Hi, I realize it's a very rare condition, but for somebody with Li-Fraumeni syndrome, the genetic GP53 mutation, do you have any comments about prognosis, how often you've seen this in follicular lymphoma patients, or any other comments?

Dr. Matthew McKinney:

Yeah, so I think, the important things would be, to just explain, Li-Fraumeni is a condition you inherit, basically a mutation in one of the genes that's important for regulating cancer development in your body, and people with Li-Fraumeni are at a higher risk of certain types of cancers. Usually that's not related to follicular lymphoma, but I guess it could be in some situations.

I think the key things if someone had that condition and also a lymphoma, the main thing I would make sure that we're doing all the other appropriate cancer screening and interventions that we would do for other things associated with Li-Fraumeni.

I don't know off the top of my head of any information around specific prognosis questions for the follicular lymphoma. I would suspect all of the usual therapies would be available to you. Probably the bigger question is just making sure that we're looking after the other types of cancer that a person could get.

Ms. Figueroa-Rivera:

Thank you for your question. The next question comes from Edwin. Edwin's asking, how much working activity and personal activity should I be allowed to do to prevent the NHL from growing or spreading faster?

Dr. Matthew McKinney:

I think that is a more generalized question people ask, what ways can I do to suppress lymphoma recurring and, are there specific things in either exercise, diet or activity? So, I think there's a lot of interesting research being done into this. I think about 2 or 3 main things. One is, there seems to be some interaction between aerobic exercise and suppressing cancer growth. You know, if you can get aerobic exercise where you're getting your heart rate up 3 to 4 times a week, I think that seems beneficial. We're still looking at that in slow-growing lymphomas. There's also a lot of information around Vitamin D levels and with the fact that low Vitamin D may be a bad prognostic sign. And so, in my clinic we pretty heavily check that and supplement Vitamin D if it's low. The other thing would be things like diet. I think the main consideration of diet is just try to control your weight and in tip-top shape as much as you can.

I think, you know, diets are very complicated and so, I don't have specific advice I necessarily give patients, but, I definitely do look at trying to optimize how much level of aerobic activity and things like Vitamin D and keeping the rest of yourself healthy so you can hopefully live for, as long as you're otherwise going to live, aside from the follicular lymphoma.

So that's a great question.

Ms. Figueroa-Rivera:

Thank you. Yes, we had many folks asking about lifestyle with a slow-growing lymphoma. And our last question today, Mary is asking about radiation dangers from regularly scheduled CT scans for those in remission. Are they necessary if there are no symptoms?

Dr. Matthew McKinney:

Yeah, that's a great question. We didn't really touch on this much in the main slides. So really, the question of how often to do things like CT or PET scans or PET/CT scans to look at lymphoma growth. I guess my answer would be to do them as little as necessary because there is a risk of other what we call secondary cancers and leukemias associated with the radiation connected, to CT and PET scans. And so, I'll say my general practice there is often patient's that have high burden disease and we do treatment, often they get some scans related to their response, and then if, the patient's feeling completely well and there's really nothing remarkable on exam, then in most of those patients there's not going to be anything that we would ever assign a different treatment based upon a scan. So, I'm really cautious about the numbers of scans in those patients. Most of the follow-up is just, labs or physical exam, you take a good history, see how the patient is doing, and then, only ordering those scans, as necessary, to check for lymphoma growth.

I think outside of that the other guidelines we go through if, we were scheduling scans and do them no more frequently than yearly for patients doing well with low-grade lymphomas, but certainly I think, absolutely agree with trying to minimize the radiation associated with those scans.

Ms. Figueroa-Rivera:

Well, thank you, because we did have a lot of questions in regard to the frequency for scans. And thank you, Mary, for your question, which was our final question today. And thank you, Dr. McKinney, for your continued dedication to patients. And for those who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

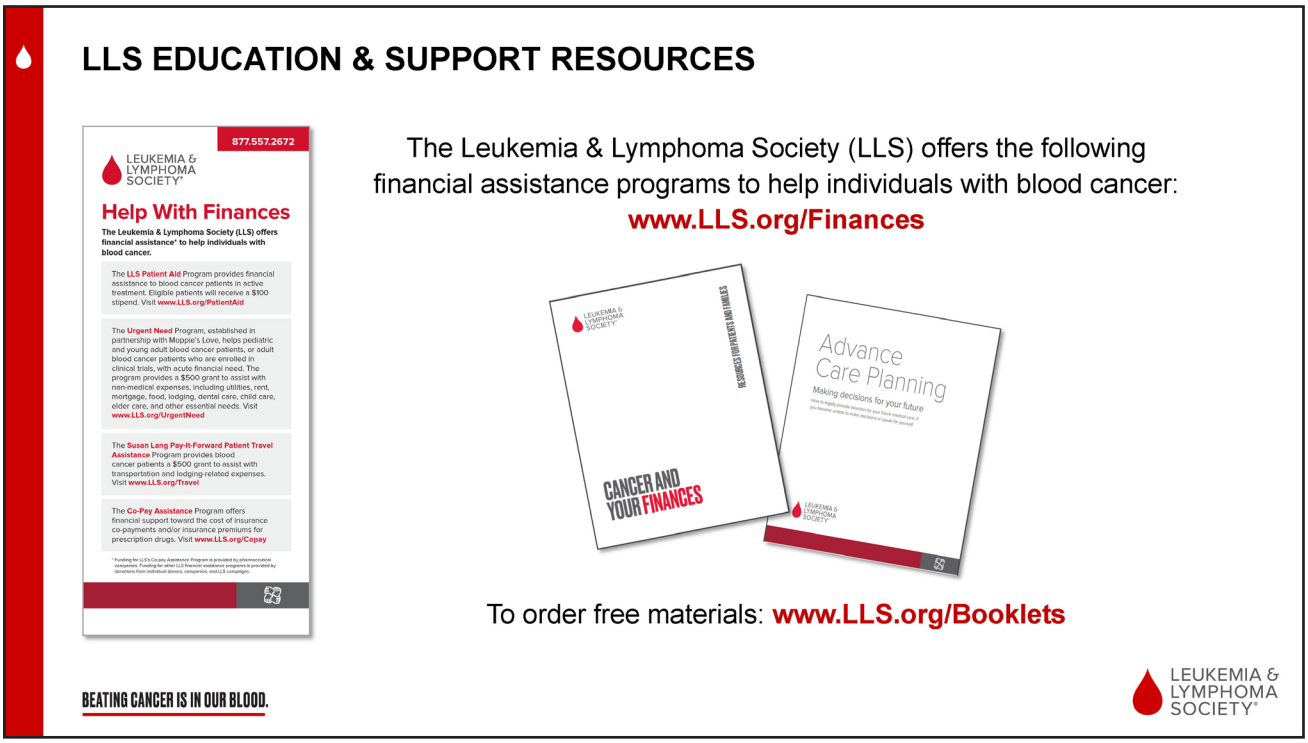
Slide 49: LLS EDUCATION & SUPPORT RESOURCES

If we weren't able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us by e-mail at **infocenter@LLS.org**. Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.

We also have Clinical Trial Support Center where Clinical Trial Nurse Navigators, who are registered nurses with expertise in blood cancers, can assist you in finding out if a clinical trial is right for you. And they can be found at LLS.org/Navigation.

Slide 50: LLS EDUCATION & SUPPORT RESOURCES

Also Dr. McKinney was mentioning our new research from our patient registry. And for more information you can visit LLS.org/Registry.



Slide 51: LLS EDUCATION & SUPPORT RESOURCES

As a reminder, you can download and print the slides as well as listen to the audio for today's program from our website at www.LLS.org/Programs.

Again. we would like to acknowledge and thank Bristol-Myers Squibb, Epizyme, Genentech and Biogen, and Pharmacyclics, an AbbVie Company, and Janssen Biotech for support of this program.

Slide 52: THANK YOU

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

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