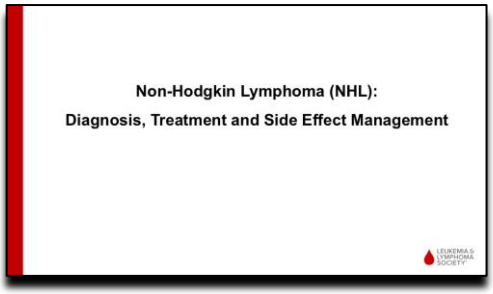
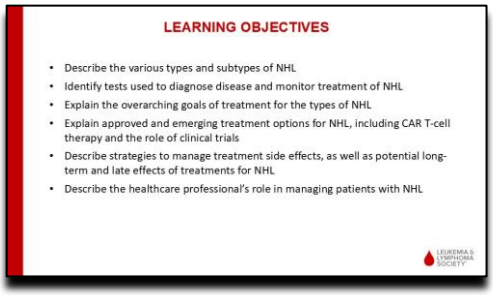



## Slide 1: Non-Hodgkin Lymphoma (NHL): Diagnosis, Treatment, and Side Effect Management

**Lauren Berger:** Hello everyone. On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us for this continuing education program on Non-Hodgkin Lymphoma: Diagnosis, Treatment, and Side Effect Management.



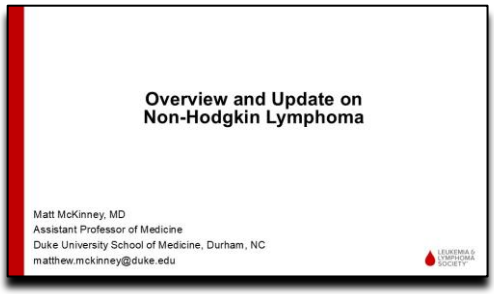

## Slide 2: Learning Objectives

The learning objectives for this program are listed on this slide.


## Slide 3: Faculty

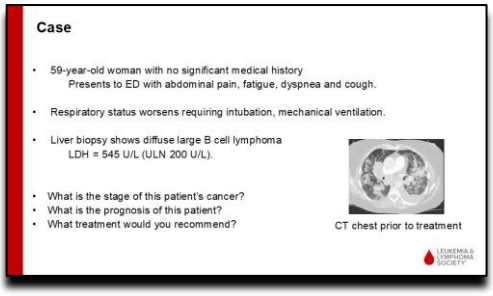
We're fortunate to have as our presenters Dr. Matthew McKinney, a leading expert in lymphoma and his colleague, Dr. Meredith Moorman, a clinical pharmacist. We appreciate their dedication and their commitment to caring for patients living with blood cancer. Dr. McKinney is Assistant Professor of Medicine, Duke University School of Medicine in Durham, North Carolina. Dr. Moorman is a Clinical Pharmacist, Adult Outpatient Leukemia and Lymphoma Clinic, Duke Blood Cancer Center in Durham, North Carolina.

Dr. McKinney and Dr. Moorman, I am now privileged to turn the program over to you.




## Slide 4: Overview and Update on Non-Hodgkin Lymphoma

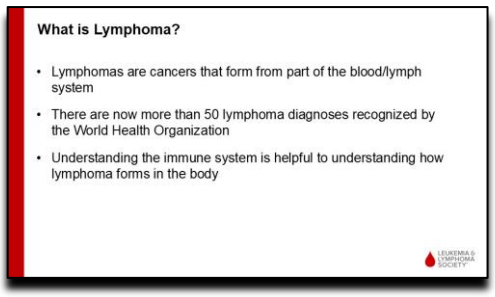
**Matt McKinney, MD:** Hello, I'm Matt McKinney. I'm Assistant Professor of Medicine at the Duke Cancer Institute, and it's my privilege to be here today and discuss an overview and update on non-Hodgkin lymphomas via this LLS event.




## Slide 5: Case

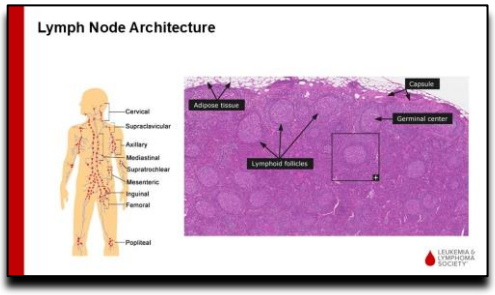
So, I'll start with a case of a woman that I took care of with Meredith Moorman, who's from our pharmacy here at the Duke Cancer Institute, recently. So, it was a 59-year-old woman, transferred from another hospital, originally came with abdominal pain, several month history of fatigue, some shortness of breath, and cough, had some lung infiltrates, some liver masses, actually got so sick that she basically needed our ICU and as I was meeting her, actually, was intubated and put on a mechanical ventilator because of respiratory failure.

Around that time, we had found out that an outside biopsy was showing a large B-cell lymphoma that was from one of the liver masses. At that time, her labs were relatively unremarkable. She was fairly healthy at baseline, CBC and chemistries were unremarkable; but her LDH was significantly elevated at 545, which is a couple times our upper normal value. So, I'll use this case to illustrate some of the advances in lymphoma treatment, and we'll also talk about how we would go about the diagnosis and staging and prognostication and treatment of this kind of patient.




## Slide 6: What is Lymphoma?

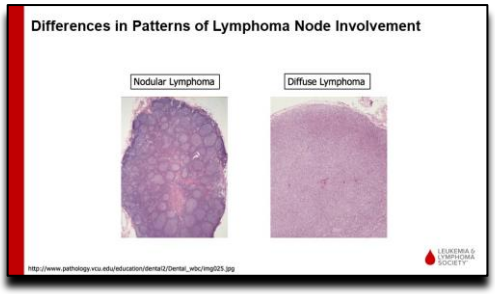
So, to start an overview, what is lymphoma? So, lymphomas are blood cancers. There are many types of recognized individual lymphoma diagnosis entities by a couple of organizations, including the World Health Organization. And for me as a lymphoma researcher and clinician, I think it's helpful to understand how the immune system works in terms of understanding all the different lymphoma subtypes and how some of our treatments work and how some of these treatments affect the patients.




## Slide 7: Lymph Nodes Architecture

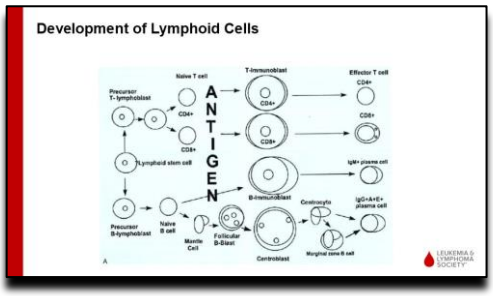
So, just in terms of an overview, there's lymph nodes all over the human body. They kind of get lumped into groups, shown in the figure there at left. And they sort of looks usually little pea size or smaller organs. The biopsy of a somewhat enlarged lymph node is shown there at the right.

And lymph nodes are part of our amazing normal immune system, and they contain many different immune cells. They're not simply just sacks of white blood cells. They actually have a three-dimensional structure, which is illustrated in this two-dimensional picture. But within lymph nodes, there's complicated networks of immune cells. These immune cells form things like follicles and germinal center. There's other things like mantle or marginal zone, and those are important for how lymphomas form in the body and also, to some degree, mirroring the lymphoma diagnosis kind of goes along some of these lines as well.




## Slide 8: Differences in Patterns of Lymphoma Node Involvement

And so many lymphomas mimic the pattern that you see in normal lymph nodes. So, sometimes we see nodular lymphomas, such as the figure there on the left. This would be a biopsy from a patient who had nodular sclerosis Hodgkin lymphoma which is not a non-Hodgkin lymphoma but very similar to some of the other non-Hodgkin lymphoma diagnosis to have a nodular pattern such as follicular lymphoma. And then we see lymphomas that have a much more kind of anaplastic or diffuse appearance such as the right, which would be a photomicrograph of a diffuse large B-cell lymphoma such as in the patient case that we presented.

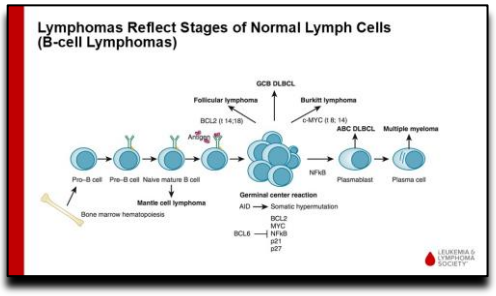



## Slide 9: Development of Lymphoid Cells

And I do think it's helpful to understand the many different lymphoma subtypes that are out there. We sort of usually think of these as mirroring basically various subtypes of normal lymphoid or immune cells. And you could think about lymphoid maturation sort of shown in this old slide is basically in the bone marrow you have lymph progenitor or stem cells. They then give off to both B- and T-cells. T-cells go to the thymus, and they mature. They then become more mature T-cells.

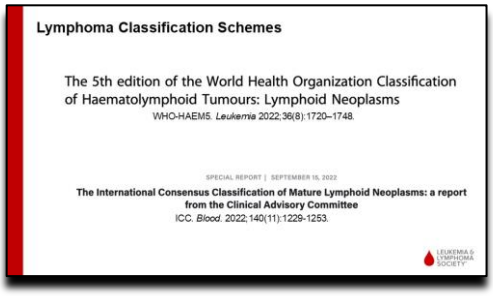
B-cells then mature a little bit differently. They usually go to lymph nodes or other lymphoid organs first, and then they seek out things like germinal centers, and they divide very rapidly. And then their goal basically is to divide into cells that can make antibodies that protect us from infectious diseases; and they're doing this basically constantly.

And so, if we look across the different kind of phenotypes of various lymphoid cells, many of the lymphoma diagnosis, diagnoses that we make kind of mirror the histology and some of the phenotypic markers such as protein expression or cell surface markers using tools like flow cytometry or immunohistochemistry. And that helps us kind of make divisions of individual lymphoma diagnosis.




## Slide 10: Lymphomas Reflect Stages of Normal Lymph Cells (B-Cell Lymphomas)

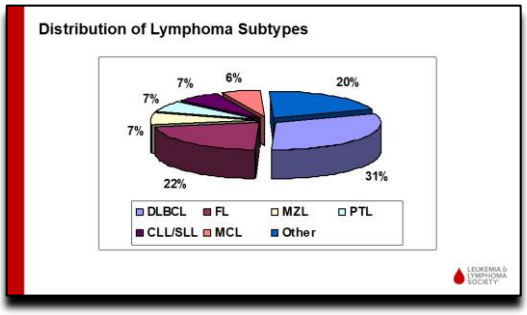
And this is an example of thinking about this across B-cell lymphomas where sort of the mirror image of many of the normal components of B-cell maturation kind of give rise to what we think of in terms of individual diagnostic lymphoma entities such as, usually mantle cell lymphoma has kind of a naïve B-cell phenotype; and sort of that helps us understand kind of the behavior and some of the molecular features of some of these cells whereas more mature lymphoma such as activated B-cell type diffuse large B-cell lymphoma have a more mature, almost like plasma cell-like sort of terminal differentiated type phenotype. And that helps us with some of those diagnoses in the clinic.




## Slide 11: Lymphoma Classification Schemes

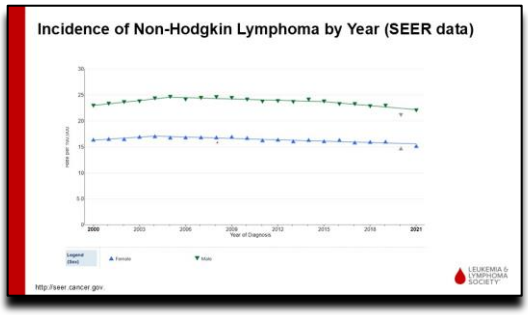
The classification schemes for lymphoma are now incredibly complex, and we actually have, internal debates at our institution about which of the current classification schemes to sort of rely on. There's really two main schemes overall. There's the WHO scheme, the hematopoietic neoplasm version 5, or HEM5, as well as the International Consensus Classification, which is a separate clinical committee which basically divides the individual diagnoses and how pathologists and how clinicians make these individual diagnoses.

When I used to give this talk, there would be a slide of all the different lymphomas, and now these, some of these schemes are so complicated, it's actually too much to give. It's kind of a separate presentation unto its own. So, it gets, it gets very complicated.




## Slide 12: Distribution of Lymphoma Subtypes

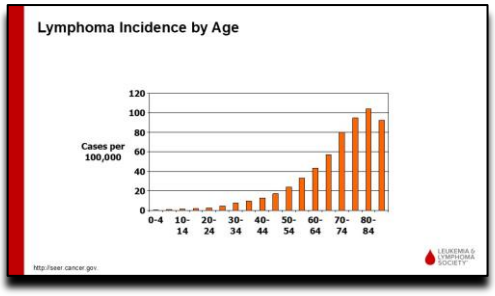
In terms of the common diagnoses of non-Hodgkin lymphoma with what we see, this is kind of a breakdown of the different diagnoses in this pie chart. The most common diagnosis of lymphoma of adults in the US is diffuse large B-cell lymphoma. It's about a third of cases. The second most common diagnosis is follicular lymphoma, which tends to be a slow growing or indolent lymphoma. And then there's other more rare subtypes such as some of the other more rare indolent lymphomas and some of the highly aggressive lymphomas like Burkitt lymphomas, as well as T-cell lymphomas that are in this distribution of various subtypes. But it is helpful to know if you're suspecting lymphoma, sort of the expected diagnoses; and we'll kind of focus in this talk in terms of treatment on some of the more common lymphoma subtypes.




## Slide 13: Incidence of Non-Hodgkin Lymphoma by Year (SEER data)

In terms of some of the epidemiologic or features of demographics of persons that get lymphoma, lymphoma is more common in males in the US. This is SEER cancer data which is the most up-to-date sort of data cut that we have available.

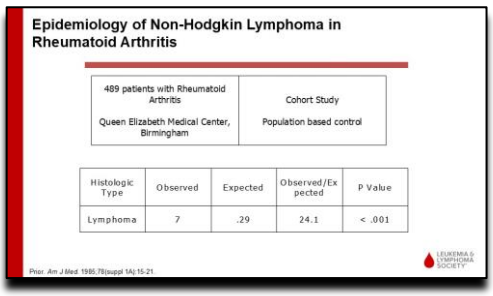
Lymphoma incidence has gone down somewhat since the early 2000s. Prior to that, it had several decades of rising incidence. The reasons for that are not completely clear. Some of the inflection on the curve here may represent some of the better control of some of the risk factors for lymphoma such as HIV and the AIDS pandemic; and some of our advances in treating some of those patients may have changed some of the incidence later on in terms of lymphomas that we see.




## Slide 14: Lymphoma Incidence by Age

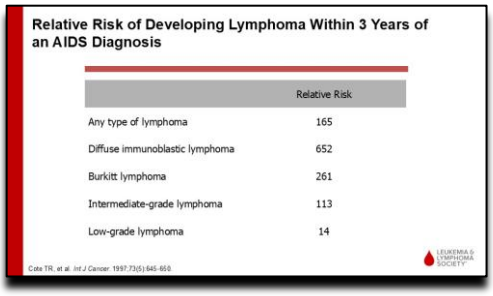
In terms of age and incidence of non-Hodgkin lymphoma, non-Hodgkin lymphomas tend to be a disease of older persons. The median age of most non-Hodgkin lymphoma cases runs about 68 to 70 years of age, as sort of shown in this graph here, which is again taken from the SEER data set.

And some of the age and comorbidities of patients that we see can also make us need to tailor or modify some of the treatment programs; and we sometimes work very closely with our pharmacy colleagues in terms of figuring out appropriate dosages for patients based on their functional status and organ function. And I think in that way that pharmacists are critical to our properly treating patients to have the most efficacious as well as safest lymphoma treatment regimens possible.




## Slide 15: Epidemiology Non-Hodgkin Lymphoma Rheumatoid Arthritis

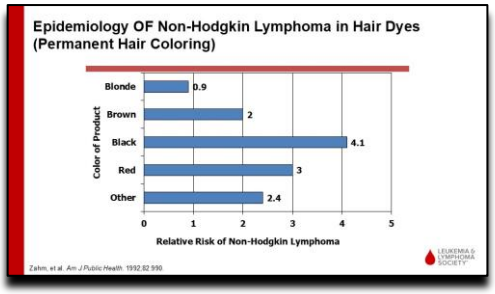
In terms of other risk factors of lymphoma, inflammatory conditions are one of the key risk factors that we see, although most patients that have a non-Hodgkin lymphoma diagnosis don't have any specific risk factor. And we think that the real driving force for lymphoma formation in most people is just simply intrinsic natural errors in DNA synthesis and things like gene rearrangements and mutations. But there are some patients that may be at elevated risk of lymphoma. Some of those can be patients with autoimmune disease. So, this is some tables from a series of patients with rheumatoid arthritis; and basically, in some of these inflammatory or autoimmune conditions, you can see higher rates of non-Hodgkin lymphoma. And we certainly see this in the clinic. It's very frequent that patients that have a lymphoma diagnosis in my clinic have an autoimmune disease like RA or Sjogren's syndrome or other immune condition.




## Slide 16: Relative Risk of Developing Lymphoma Within 3 Years of an AIDS Diagnosis

Other things, as I mentioned before, things that kind of change the immune system, inflammatory or immune suppressive conditions, things like HIV or AIDS can cause an increased risk in persons for non-Hodgkin lymphoma diagnosis. The other thing that we see in a place like Duke where there's a lot of patients getting organ transplants like heart, lung, kidney, liver transplants, is immune suppression-related lymphomas as well.

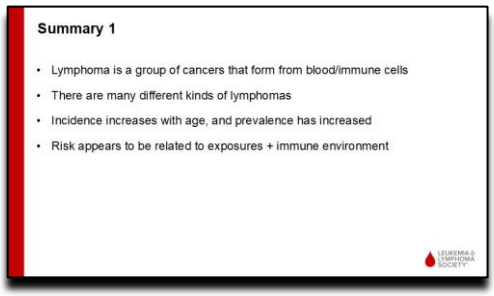
This is older data, but basically kind of the relative risk of persons really in the early days of the AIDS pandemic, so it's the relative risk of chance for lymphoma development in persons with HIV and AIDS versus sort of an immune competent normal population. And as you can see, many of these lymphomas, especially some of the aggressive lymphomas, the risk is many-fold higher than it would be in kind of a controlled population.




## Slide 17: Epidemiology, Non-Hodgkin Lymphoma Hair Dyes (Permanent Hair Coloring)

There are a few exposures that have been studied in terms of lymphoma epidemiology. I think one of the more interesting studies is some of the older data around things like chemical exposure. This is an older study basically looking at exposure to certain hair dyes, and basically epidemiologic researchers were able to actually ascribe the increased risk or relative risk to even the color or concentration of hair dyes.

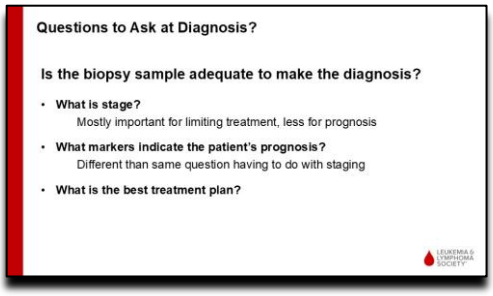
The odds ratios for many of these exposures tends to be low, and there's a lot of issues in some of the epidemiologic literature about control for biases and recall bias in some of these things. But there probably are minor contributions to certain exposures that had been looked at in the literature.




## Slide 18: Summary 1

So, in terms of a summary of an overview of lymphoma and some of the risk factors and epidemiologic features, again, lymphoma is a group of cancers that forms from blood or immune cells. There's a tremendous number of individual lymphoma diagnoses. Really, for thinking about individual diagnoses and treatment, it's very important to consider the individual lymphoma diagnosis or even subtypes that we've recognized within a lymphoma diagnosis.

The incidence of lymphoma does increase as persons age. The prevalence has sort of leveled off a little bit, and probably any individual's risk of lymphoma is probably related to a complicated sort of mix of features including their baseline medical history, exposures, their underlying immune environment, and the like.




## Slide 19: Questions to Ask at Diagnosis?

So, we'll kind of move on a little bit to talk about how to make a diagnosis and kind of how to stage and prognosticate lymphomas. I think questions that I make sure that we're fully asking and answering at a lymphoma diagnosis are sort of listed here. I think the first thing is your biopsy sample adequate to make the diagnosis? Sometimes patients have very limited biopsies, and so sometimes we're recommending more extensive biopsies to make sure we have the exact diagnosis because that's very important for designing a treatment plan.

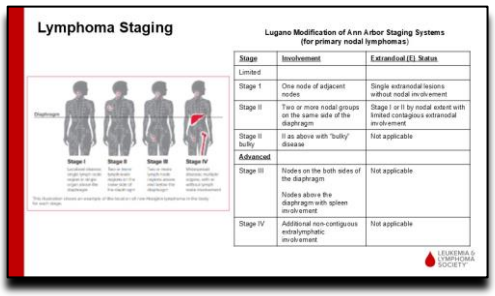
The second question is, what is the stage? Often, this is mostly important for limiting treatment. Sometimes it's less important for thinking about are lymphomas treatable with things like immune therapy or chemotherapy or targeted therapy as opposed to other cancers. Saying that someone has an extensive stage lymphoma is seemingly less important for prognosis because many

lymphomas are still very curable and treatable, even if diagnosed at extensive stage or sort of Stage IV kind of stage.

We also look at different markers around prognosis, which is a separate question than simply just staging the patient. And we sometimes get into patient features or things about looking at things like age and performance status and laboratory studies to best prognosticate the patient.

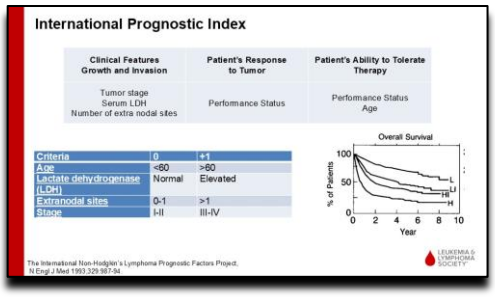
We're really now just getting into where some of the prognostic models really affect our treatment, and I'll get into some of the updates around that sort of when giving an overview of some of the common treatment for lymphomas.

And then finally, I think that we have to consider what is the best treatment plan; and, I think being at a big academic center like Duke, we really try to use our, the best evidence-based, literature kind of backed, evidence-based medicine to make those decisions and use evidence and clinical trials and discussion with colleagues to make the best treatment plans.




## Slide 20: Lymphoma Staging

I'll talk a little bit about lymphoma staging. This is a little bit different than many other cancers you may be familiar with. This is a modified scheme, so the kind of traditional staging system for non-Hodgkin lymphoma especially is the Ann Arbor Staging System. And basically, this looks at where in the body that you may have enlarged lymph nodes or spread to other organs. So, if you have one lymph node group in an area, let's say the right side of the neck or, a certain level of cervical nodes, that would be Stage I lymphoma. If it's in multiple areas but on the same side of the diaphragm of the body, that would be Stage II. Stage III would be more extensive multiple different groups run throughout the body of lymph nodes. And then if you get into more extensive stage like lymphoma that appears to be on your staging, things like CT or PET scans in organs, like, well, the liver, the bone marrow, or the lung, that would be, Stage IV, basically a Stage IV lymphoma, by these, Ann Arbor/Lugano schemes. And there's other criteria around things like bulky disease or other extra nodal sort of spread that we also ascribe as well.



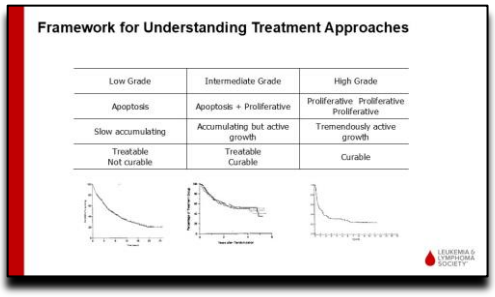

## Slide 21: International Prognostic Index

Staging, at least for prognosis, is a little bit different question than other cancers. So, in lymphomas, we use the stage to help us with prognosis, but it's less certain for making some of those prognostic kind of conclusions.

And so, one of the models that we use very frequently is what's called the International Prognostic Index. And so, the International Prognostic Index or IPI uses the staging of the lymphoma plus other features. So, it uses things like patient age, the LDH levels, which are, and if they're elevated, that's an adverse prognostic sign in non-Hodgkin lymphoma. That also uses other patient features such as the performance status. So, patients that have worsening performance status like say they're bed-bound or wheelchair-bound, they'll tend to do worse when

you treat a lymphoma than patients that are less symptomatic or kind of have better performance status and endurance and these kind of things.

And so, the IPI is basically a score based on these five features – the age, lactate dehydrogenase, extranodal sites, and stage to basically have a scoring system. And you can basically separate prognosis by each of these points sort of along the curve. And at the right is the Kaplan-Meier curve from the original series; and this has been updated many times and kind of revalidated and really is still the kind of best, easiest prognostic scheme for non-Hodgkin lymphomas that we have.

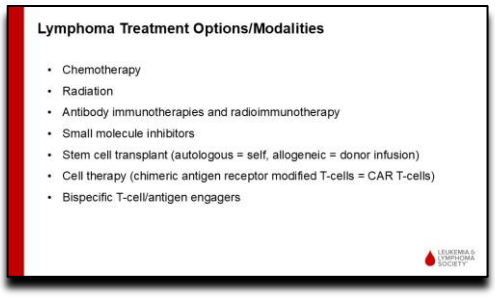



**Slide 22: Framework for Understanding Treatment Approaches**

So, I talked about the fact that there's many different lymphoma diagnoses. We can kind of start to split these into some groups. We generally think about these as sort of this table and these kind of outcome curves versus, think about many lymphomas are very slow growing or low grade. And basically, many of these we treat, basically for symptoms. And many patients can have these lymphomas only slowly progress over many years and sometimes decades of time. And so, some of our treatments, need not to be very aggressive or necessarily curative. They just need to sort of, get the patient out of trouble or treat symptoms in terms of medical things that may happen to some of these patients.

And then we get into kind of more higher grade or more aggressive lymphomas, and you can kind of think about many of these are highly treatable; and not only are they treatable, but with many of these they will be cured with the initial immunotherapy or chemoimmunotherapy strategies that we pick.

Sometimes in the setting where they don't respond initially, they can be more aggressive and certainly, very rapidly cause the patient to get sick or the lymphoma can even be fatal. But many of these we sort of always have to have a plan if the patient has active lymphoma in the body with the goal, usually, that it's sort of very definitive, very curable or curative treatment.

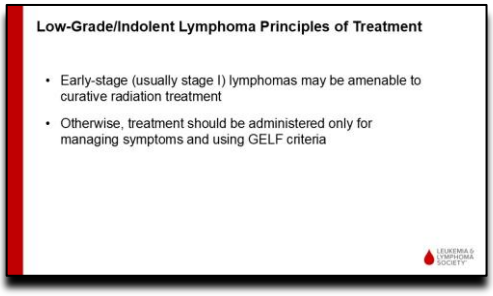



**Slide 23: Lymphoma Treatment Options/Modalities**

I'll talk a little bit about various lymphoma treatment modalities. I kind of think of these as being split into a lot of different sort of groups. The kind of old standard is just chemotherapy where you're kind of killing things in the body that are fast growing. Chemotherapy approaches sometimes can be very hard on patients because there's a lot of side effects of sort of the collateral damage kind of damaging tissues that are fast growing. So, you get things like hair loss, low blood counts, infections, nausea/vomiting, fatigue; and so, we look to other modalities often to improve those therapies and to lessen our reliance on chemotherapy.

Other things that we use, sometimes radiation is important in specific situations. We have now very powerful antibody and cell-based immunotherapies. There are many different small molecule

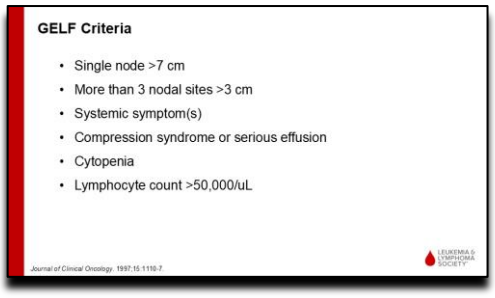
inhibitors. Many of these inhibit kinase or signaling pathways in the lymphoma, and many of these have been very effective with very little side effects for some of our patients. For many years we've used stem cell transplants, either autologous where you're using the patients own stem cells or allogeneic where you're using someone else's donor stem cells to further lymphoma responses and hopefully provide more curative treatments. I think what's exciting is we're able to move away from some of those approaches which, again, have a lot of morbidity and sometimes mortality in our patients and move to things like cell therapies like CAR T therapy or other new powerful immunotherapies. I'll talk a little bit about some of the bispecific T-cell engagers which have improved the care of not only lymphoma patients but also other diseases like multiple myeloma and other solid tumors.




**Slide 24: Low Grade/Indolent Lymphoma Principles of Treatment**

I'll talk a little bit about the aspects of various principles of lymphomas in terms of the subtypes and treatments. I'll just make some statements about low-grade lymphomas. Usually those are extensive staged, so more than three-quarters are going to be extensive stage. And usually with those, we kind of monitor for high disease burden; and there's some arbitrary criteria that we use to assess that. And also monitor for symptoms.

Occasionally, in the early stages of indolent or slow-growing lymphomas, some of those may be able to be treated with a curable approach which is often radiation treatment or some combination of radiation and chemotherapy or immune therapy.

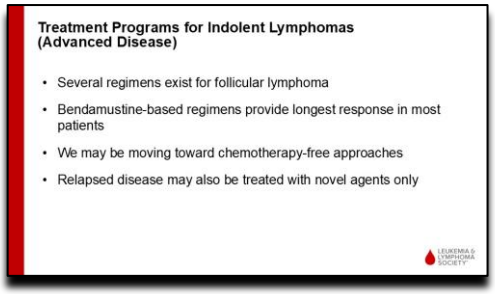



**Slide 25: GELF Criteria**

In terms of making decisions around treating low-grade lymphomas, often we'll use criteria for disease burden. This is the GELF criteria, which is probably the most common criteria that we use. GELF is just the acronym for one of the French lymphoma study groups, so they helped derive this criteria for some of their research and treatment protocols.

But basically, it looks at, how burdensome is, are the lymph nodes or tumors in the body; and so, it looks at things like lymph node size, are patients having a lot of symptoms, are they having a lot of lymphoma cells show up in the blood, are they having anemia, thrombocytopenia due to lymphoma as a symptom? And those can be things that we make treatment decisions to say, "Hey, this patient needs a definitive kind of chemotherapy treatment plan versus, seeing patients that may not need any treatment and can be simply observed for years at a time.

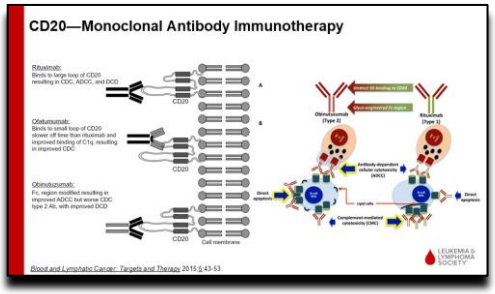
I'll just say that I was in my clinic yesterday, and I actually saw two men that had really been watched for lymphoma for years and years at a time just because their diagnosis was a low-grade follicular lymphoma; and they didn't have significant burden of disease, had no symptoms, and were otherwise doing very well.




## Slide 26: Treatment Programs for Indolent Lymphomas (Advanced Disease)

So, in terms of thinking about treatment programs if they're needed for indolent lymphomas, there's a bunch of these. Many of these patients are treated with combinations of chemotherapy such as bendamustine (Treanda®). Bendamustine's a chemotherapy that has been around a long time but really has just in the past couple decades been used for a lot of these diseases. It seems to sort of afford us the best response with the best side effect profile. Patients that get bendamustine (Treanda®) have less neutropenia. They generally don't have alopecia. They keep their hair. Generally, don't have a lot of fatigue and can tolerate the treatment program pretty well.

For many of these lymphomas, we're kind of moving also toward chemo-free, therapy-free approaches with kinase inhibitors and other immune therapies and those sorts of things. And then I think in the future we're kind of moving toward relapsed disease being treated potentially with only novel agents; and I think with some of the powerful immune therapies, we may get to a point where many of these lymphomas are cured with a chemotherapy-free approach, which would just, which is very exciting.



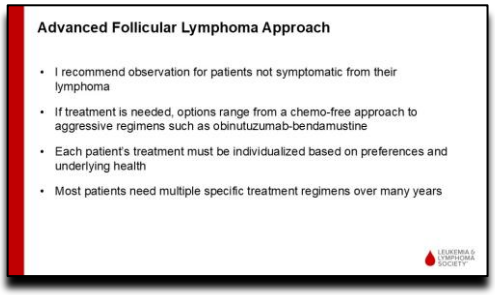

## Slide 27: CD20—Monoclonal Antibody Immunotherapy

One of the first things I'll talk about in terms of therapies, CD20 monoclonal antibodies. These have been a really significant advance over the past 30 years. Basically, the idea is that most B-cell non-Hodgkin lymphomas express a protein on their cell surface called CD20. And you can actually engineer antibodies that basically recognize the loops of CD20 that stick out from the cell surface. And then you can kind of leverage those antibodies to use the body's immune system for tumor killing, and what happens is these medicines go in and then they stick to the cells, and then things like macrophages and other immune cells can recognize those antibodies on the surface of tumor cells and go in and basically, kill through an immune attack through various mechanisms and you get, tumor shrinkage, get patients good lymphoma responses and help out their symptoms and tumor size and the like.

The scheme at the left shows several different antibodies. Rituximab (Rituxan®) is sort of the oldest one that's been approved for many lymphomas. It sticks out to kind of the longer finger of CD20. There's some updated newer antibodies. One of these is obinutuzumab (Gazyva®). The way it's different is that it tends to elicit a more powerful immune response against the tumor. It's kind of engineered to do some different things. And so, in some lymphomas, obinutuzumab (Gazyva®) is a much more powerful and kind of updated immunotherapy, as a treatment that we can use.

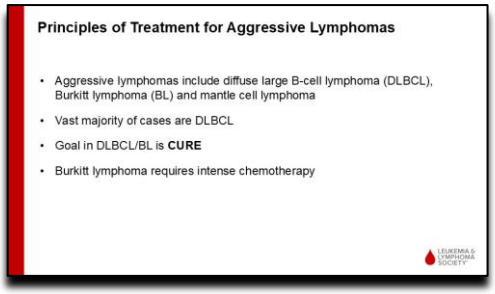
**Meredith T. Moorman, PharmD, BCOP, CPP:** And so, Dr. McKinney, you mentioned these are for B-cells, non-Hodgkin lymphoma. Can you tell us sort of the percentage of patients that have B-cell versus T-cell lymphoma?

**Dr. McKinney:** Yes, so that generally reflects the immune turnover in the body. So anywhere from 75% to 85% of non-Hodgkin lymphoma will be B-cell phenotype. Most of those will express CD20; and then the rest will be, basically T-cell lymphomas which generally don't express, B-cell antigens. Although in rare cases, some of those do. And so, we look to other antibody treatments that are specific to those neoplasms.




**Slide 28: Advanced Follicular Lymphoma Approach**

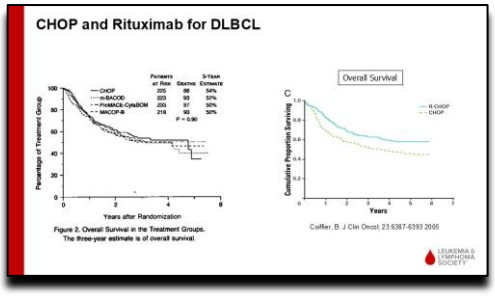
So, kind of getting back to an approach for advanced kind of low-grade lymphomas, including follicular lymphoma, just as an example. Usually when we see these patients, we recommend observation if patients are staged and they don't meet GELF criteria and if they're not symptomatic. If treatment is needed, really, we take a personalized approach. A lot of that is sort of how young and how fit, and how healthy the patient is. And really, the options can range from things like only rituximab (Rituxan®) immunotherapy to, more aggressive like bendamustine (Treanda®) with obinutuzumab (Gazyva®), which has high rates of response, but usually more side effects and more things that the patient has to be fit and healthy enough to be able to tolerate. And we use all of these sort of features and prognostic tools and the like to kind of help guide our therapies for these patients.




**Slide 29: Principles of Treatment of Aggressive Lymphomas**

I'll kind of change gears and think about some principles of treatment for more aggressive lymphomas. Examples of these would be things like diffuse large B-cell lymphoma such as in the patient case that I described. Burkitt lymphoma and mantle cell lymphoma. Most of these cases, again, are going to be diffuse large B-cell lymphoma. And then in most of these cases, including, I think, the patient case that I presented, the goal of the treatment is cure. So, we kind of embarked on treatment for this patient with curative intent.

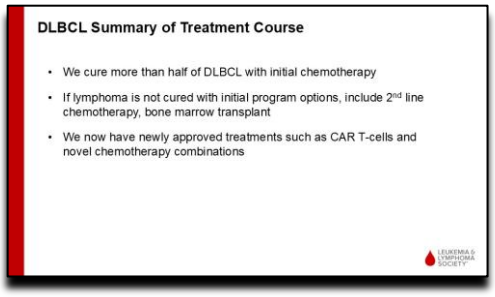
The other thing that comes up is an entity called Burkitt lymphoma. Many clinicians in the internal medicine space are familiar with Burkitt lymphoma. It tends to be a very aggressive form of B-cell lymphoma and usually requires basically emergency management and treatment; and usually the therapy needs to be more intense than it does for other large B-cell lymphomas, and so those are important considerations.




## Slide 30: CHOP and Rituximab for DLBCL

I'll talk a little bit about some of the history and some of the therapies that we've developed for large B-cell lymphomas. Many of the frontline strategies are sort of around what's called CHOP chemotherapy. CHOP chemotherapy is basically an acronym for the chemotherapies in the program. So, Cytoxan® (cyclophosphamide), hydroxydaunorubicin (Adriamycin®), Oncovin® or vincristine**,** and prednisone (Deltasone®). And basically, the data supporting CHOP therapy goes back 30 years, so this is a figure from an older study from the early 90s by Rick Fisher and colleagues, basically showing R-CHOP was at least equivalent to some of the older chemotherapies that were very toxic back in that timeframe.

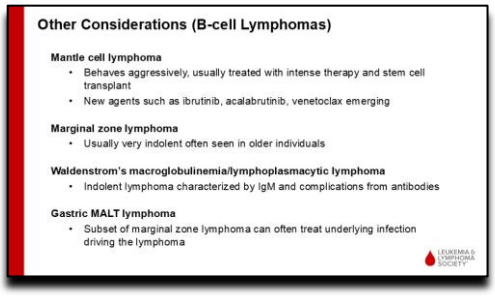
Around 20 years ago, we gained access and approval for rituximab (Rituxan®); and basically the trial that led to that approval was basically a trial that looked at adding rituximab (Rituxan®) to CHOP, and that actually improved the overall survival such that now with R-CHOP historically, most patients with large B-cell lymphoma diagnoses that receive that as their frontline therapy would be cured of their disease, such as in the Kaplan-Meier curves from the publication by Coiffier and colleagues there.




## Slide 31: DLBCL Summary of Treatment Course

So, the things I'll say about, , large B-cell lymphoma is that we now cure more than half of patients with initial chemotherapy, which for the past 20 years or so has been mostly R-CHOP-based therapy. I'll show you some updates to that based on some newer data here that's come out very recently.

And then if the lymphoma is not cured in that scenario with initial treatment options, we go to second- or third-line treatment. We try to get the patient a complete response or remission; and then we think about other things like bone marrow transplant and I think more recently have been moving towards things like CAR T-cell therapy, other novel chemotherapy combinations.

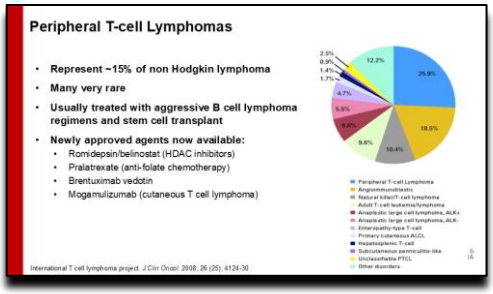



## Slide 32: Other Considerations (B-cell Lymphomas)

I'll just touch briefly on some other common non-Hodgkin lymphomas. Just a few points to make. Things, entities such as mantle cell lymphoma. Mantle cell lymphoma is another more rare non-Hodgkin lymphoma. It tends to behave aggressively, although there are some patients where it can kind of behave more slowly. We have some interesting new treatments, including CAR T therapy and things like BTK inhibitors, which, I think, are helping the outcomes for those patients.

Marginal zone lymphoma's another indolent lymphoma. Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma is also important to know about because of some of the syndromes

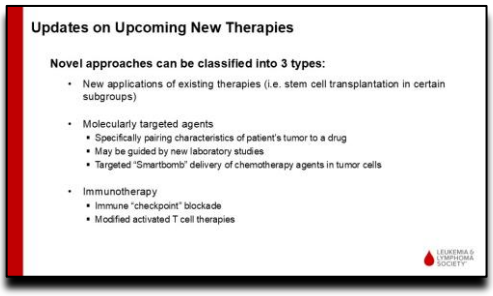
with hyperviscosity from the IgM. Both of those lymphomas have new treatments, including BTK inhibitors which are very exciting for treatments that we've developed in the past several years.




## Slide 33: Peripheral T-cell Lymphomas

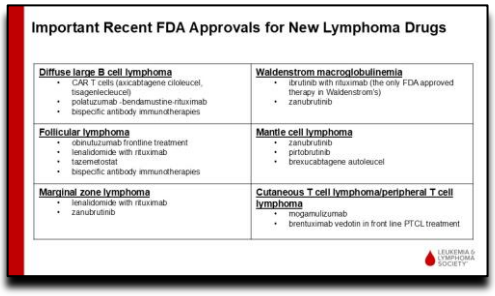
Meredith was asking about B- versus T-cell lymphoma. The other thing that comes up is T-cell lymphomas. These are more rare lymphomas. Many of these are highly aggressive, very difficult to treat, kind of rare tumors. And so, that kind of illustrates some of the challenges with T-cell lymphomas.

The pie chart at the right there shows some of the breakdown of the different diagnoses. Most of these are just what we call peripheral T-cell lymphoma, not otherwise specified. And then, I kind of listed some of the new kind of most recently approved treatments. Getting back to Meredith's question about antibody-based kind of therapy in B- versus T-cell lymphoma, things like brentuximab vedotin (Adcetris®), which is an antibody drug conjugate and mogamulizumab (Poteligeo®) have been more specific antibody treatments which are applicable to T-cell lymphomas.



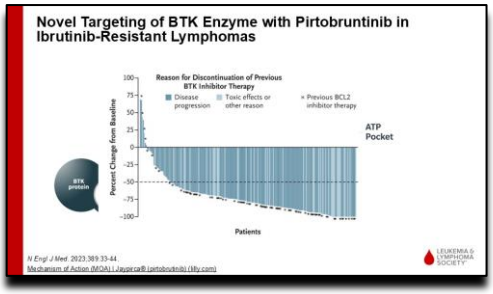

## Slide 34: Updates on Upcoming New Therapies

I'll then kind of change gears as I close this out and talk about some of the aspects of some of the new and upcoming therapies. I just want to think about these and kind of a breakdown of three different types of therapies. One is sort of new applications or new twists on sort of existing therapies or approaches. The next kind of thing to talk about is kind of novel, kind either molecularly targeted or protein or sort of antigen-targeted approaches. And I think the final thing that is exciting is novel immune therapies, and we'll kind of talk a little bit about some of those.




## Slide 35: Important Recent FDA Approvals for New Lymphoma Drugs

I think the exciting and reassuring thing, for both doctors and patients in terms of lymphomas has been there's been a number of exciting new agents over the past five to ten years. Many of the medicines on this slide weren't approved or didn't exist, five to six years ago. And many of these have really revolutionized our ability to treat patients successfully from symptoms or early mortality from their lymphoma and also do that safely.

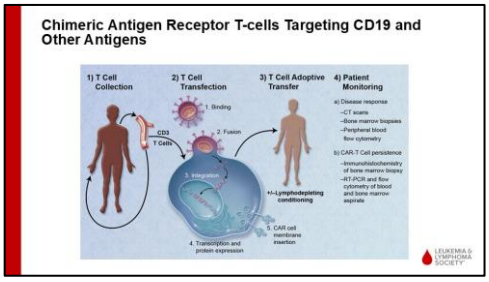



## Slide 36: Novel Targeting of BTK Enzyme with Pirtobrutinib in Ibrutinib-Resistant Lymphomas

I'll give a recent example. For a long time, we've used Bruton's tyrosine kinase inhibitors in many diseases such as chronic lymphocytic leukemia or marginal zone lymphoma or mantle cell lymphoma. And so often, patients will respond initially to some of these treatments, including things like ibrutinib (Imbruvica®) or acalabrutinib (Calquence®) or zanubrutinib (Brukinsa®). And one idea is basically these medicines go in and they stick to the BTK enzyme and result in blockade of the BTK signaling.

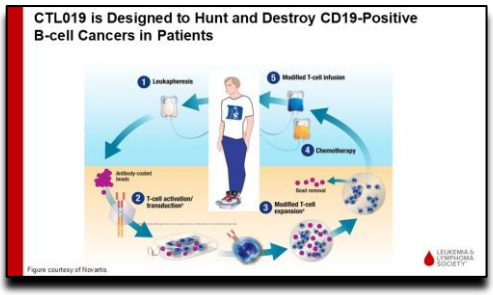
And, unfortunately, what can happen is patients can acquire point mutations in the part of the enzyme where those drugs bind. And so, there's new classes of inhibitors, pirtobrutinib (Jaypirca®) being the first one that we've kind of had full access to lately, is basically the molecule is kind of designed to kind of avoid that resistance and can kind of make the patient sensitive again to an approach with BTK inhibition.

And so, you can see very nice responses. This is what we call a waterfall curve, so this is the percent change of tumors of patients in the CLL trial treated with pirtobrutinib (Jaypirca®). And so, anything that goes, below the zero line is good; and you can see almost all of these patients responded very nicely in a setting where they had been resistant to older BTK enzyme inhibitors.




## Slide 37: Chimeric Antigen Receptor T-cells Targeting CD19 and Other Antigens

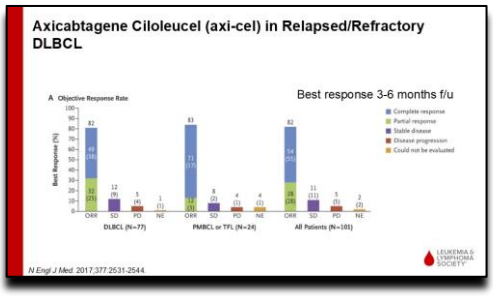
The other thing that's been exciting recently has been chimeric antigen receptor-modified T-cells or CAR T immunotherapy. And basically the idea around CAR T immunotherapy is that it's usually a therapy where we collect the patient's own immune cells and then basically genetically engineer them to be able to be given back to the patient and to be programmed to basically go after specific protein targets in the, in the patient's tumor and basically, through a cytotoxic T-cell type attack is very effectively treat that patient's cancer. Most of these were done in non-Hodgkin lymphoma against CD19 because, similar to CD20, CD19's a very common antigen that could be targeted and is on the cell surface of most of these non-Hodgkin lymphoma subtypes.




## Slide 38: CTL019 is Designed to Hunt and Destroy CD19-Positive B-cell Cancers in Patients

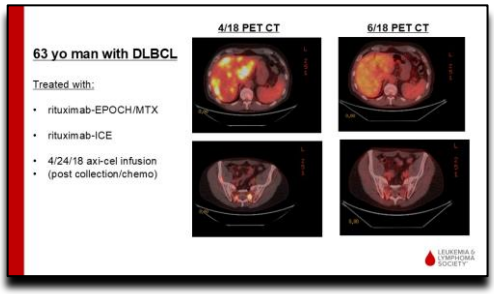
And kind of the idea for the patient is that they get hooked up to a leukapheresis machine. Their cells get collected. They then go off to a laboratory. They then become genetically engineered to be able to be given back to the patient. The patient then undergoes preparative chemotherapy basically to allow their immune system to take these cells back in, and then we monitor and treat the patient for some of the side effects of the cell.

And I always modify this slide slightly when I give this presentation because I gave this to some patients one time and got a question of whether the patient could wear clothing during the whole procedure; and, indeed, at Duke this is what they look like when they get CAR T therapy. There's no need to not wear clothing through the therapy.



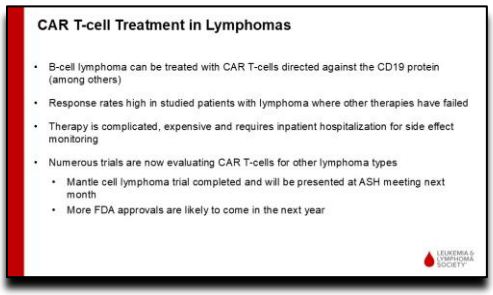

## Slide 39: Axicabtagene Ciloleucel (axi-cel) in Relapsed/Refractory DLBCL

This is the result from the original paper that became the basis for the first approval of CAR T therapy in non-Hodgkin lymphomas, a product called axi-cel (Yescarta®). Roughly half of these patients got complete responses, which is unheard of for kind of a relapsed/refractory patient population with older therapies; and this has been a very exciting treatment. And I have dozens of patients that come into my clinic doing very well that I don't think would have been around with older therapies for their lymphoma.



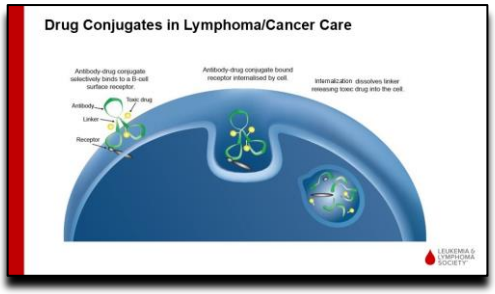

## Slide 40: Pet CT Image

This is an example of those responses. This is, I think, the first patient at Duke that we ever treated with CAR T therapy. You can see the difference basically before and after his CAR T therapy in terms of the liver lesions. Just to orient you, these are PET/CT scans, so basically the big yellow lesions there in the triangular-shaped organ being his liver basically went away and resolved very nicely with his axi-cel (Yescarta®) infusion. And again, this was a novel therapy that, sort of, afforded him a lymphoma treatment that otherwise we wouldn't have had access to.




## Slide 41: CAR T-cell Treatment in Lymphomas

So, the use of CAR T is expanding. We'll probably see other antigens in lymphoma being targeted beyond CD19. There's now two or three different medicines approved with CAR T therapy in multiple myeloma, sort of other blood cancers, and multiple other indications for these treatments.

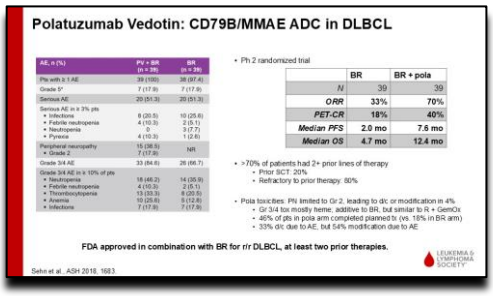



## Slide 42: Drug Conjugates in Lymphoma/Cancer Care

**Dr. Moorman:** Dr. McKinney, I think the other thing I would mention about CAR T, obviously, those were first introduced in generally like third-line settings; and they're trying to move those up earlier in the spectrum of patient's care so that, perhaps, patients are in better group, have better performance status as they go into CAR T. There's also some clinical trials looking at sort of off-the-shelf CAR T products, so that way patients don't necessarily have to go through the leukapheresis and genetic engineering of cells and seeing if that's a feasible option going forward.

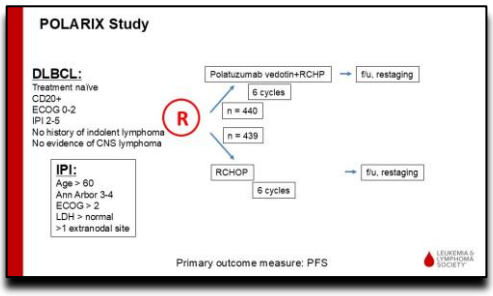
**Dr. McKinney:** Yes, those are all good points, and we'll probably improve the outcomes for lymphoma patients.

The next thing I'll talk about is antibody drug conjugate. Basically, the idea is kind of in this slide. And really these are almost like a smart bomb, so basically, you're delivering a powerful chemotherapy, basically via an antibody, antigen, your cell surface reaction or interaction. And then it, it lets you get chemotherapy into the cells more specifically and sometimes allows you to deliver drugs that you otherwise couldn't deliver systemically.



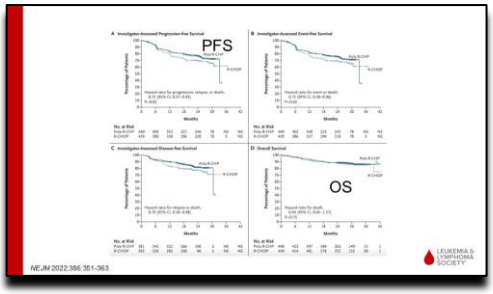

## Slide 43: Polatuzumab Vedotin: CD79B/MMAE ADC in DLBCL

One of the most recent approvals has been polatuzumab vedotin (Polivy®). I won't go into this slide in great detail, but this was some of the data in a relapsed/refractory population that led to its approval.



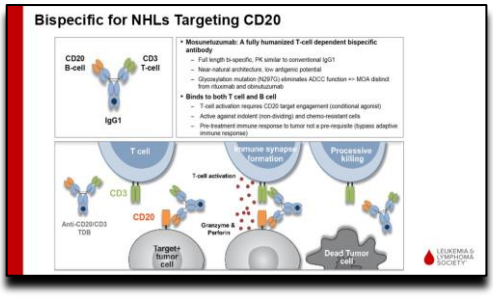

## Slide 44: POLARIX Study

What's been more exciting and relevant to the patient that we presented is that there's a randomized study basically in these high-risk patients, such as our patient. So, our patient would have had an IPI, I think of 3 based on the data that we had with performance status and extensive stage of disease in LDH. And so, this study, the POLARIX study added polatuzumab (Polivy®) basically to a backbone similar to R-CHOP; and the question is can you improve upon the old R-CHOP kind of standard?



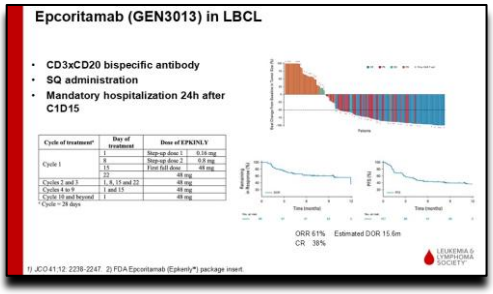

## Slide 45: Image of Graphs

And indeed, that's what the study showed. There was an increase in progression-free survival, which was its primary endpoint and improve the outcome for these patients. So, I'll say that as follow-up to the case, as we treated this patient with a standard six cycles of the polatuzumab (Polivy®) R-CHOP, she currently is in a remission. Immediately, actually came off the ventilator with chemotherapy very quickly, improved. She's actually ambulatory, off oxygen, doing really well.



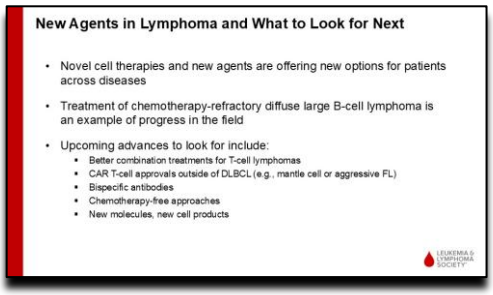

## Slide 46- Bispecific for NHLs targeting CD20

The last thing I'll talk about is CD3, CD20 bispecifics. Similar to CAR T, this is kind of an off-the-shelf immunotherapy. Basically, the idea that bringing the body's own CD3+ T-cells into tumor cells by an antigen interaction, so CD3 on the T-cells and then things like CD20 on the tumor cells.



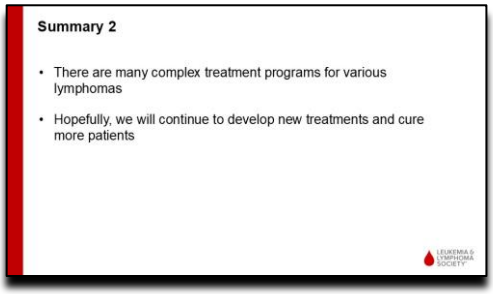

## Slide 47: Epcoritamab (GEN3013) in LBCL

This is some data from one of the approved bispecific antibody therapies in a relapsed/refractory large B-cell population. Again, the waterfall plots there show that most of these patients respond with pretty dramatic tumor shrinkage pretty rapidly with relatively good side effect profile.




## Slide 48: New Agents in Lymphoma and What to Look for Next

So, I'll kind of wrap up and think about where we are now and toward the future. I think the future is very bright for new lymphoma therapies, sort of newer kind of takes on existing therapies or use of some of these medicines in kind of new context.




## Slide 49: Summary 2

And I think it is very exciting because I think, and I hope, that we'll certainly, and I actually think we will, continue to come up with new treatments and cure more patients.


**Slide 50: Thank You**

Thank you very much, and we'll look forward to Meredith Moorman's discussion of some of the aspects of pharmacy care of non-Hodgkin lymphoma patients.

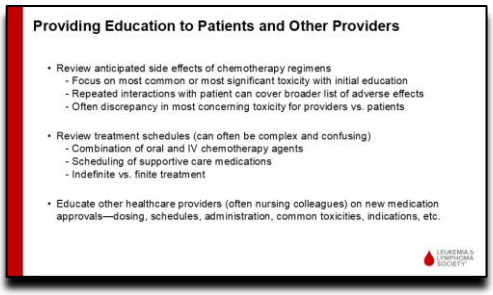

**Slide 51: The Role of the Pharmacist in Treatment of Non-Hodgkin Lymphoma Patients**

**Dr. Moorman:** All right, well thank you very much for that introduction. So, I'm very fortunate to work at Duke with a variety of different physicians and APP providers in the treatment of both non-Hodgkin lymphoma and with leukemia patients. And so, I'm going to talk a little bit more directly about some of the pharmacists' role in considerations that I take into account when I'm treating these patients.


**Slide 52: Primary Roles for Clinical Pharmacists**

And so, I think for me, the primary roles and the things that certainly I enjoy most, the first one is providing education. Also, reviewing drug interactions; looking at chemotherapy dosage adjustments; supportive care, certainly a major part of my role; as well as preventive, preventing different issues like tumor lysis syndrome or possible viral reactivation.

There is some therapeutic drug monitoring included in my clinic, and then I think the other two big pieces of my role include medication access and regulatory compliance, particularly with some of the new CAR T and BiTE products, and then prior authorization and patient assistance. And so, I'll talk in more detail about each of these different aspects.




**Slide 53: Providing Education to Patients & Other Providers**

For me, the more, the most enjoyable part of my role is providing education to patients and families, as well as to other staff members. And so, the primary thing here is reviewing anticipated side effects of whatever particular regimen, whether it's IV drugs or oral drugs that the patient's going to be treated with.

I find one of the challenging things to be often when I meet patients, they're sort of on information overload at that point. They just have found out about this diagnosis generally within the past couple weeks; and they've had sort of a laundry list of tasks that they needed to complete to confirm and finalize their diagnosis.

And so, I do find that often I have to limit my patient education to some degree to really focus on the most significant toxicities from our perspective. And then either myself or nurse coordinators, nurse practitioners, or physicians with repeated interactions can talk about some of the additional toxicity that we might see with a particular treatment.

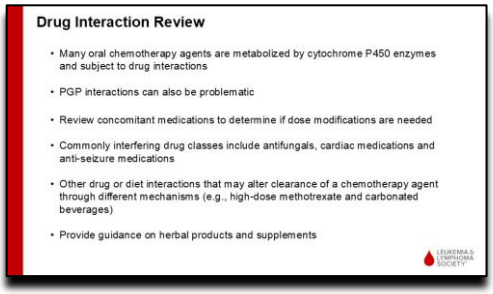
The other thing that I've noticed over the course of my career is that often there's a discrepancy in what is most concerning from a toxicity perspective for us, from the provider side versus the patient side, and so, for me generally, if I'm discussing a regimen that causes neutropenic fever in a large percentage of patients, that really, for us, is the biggest and most important thing.
And if the patient hears nothing else, that's the biggest thing that we want them to pick up on versus, I think oftentimes for patients, they think of family or friends that have gotten chemo and have lost their hair and have had all these nail changes and perhaps more physical changes with chemotherapy. And that often is more important from the patient side. So, sort of finding a happy medium between those two pieces, I think, becomes really important as the pharmacist.

The next thing with patient education is reviewing treatment schedules. As often these can be very complex and very confusing for patients that have limited medical knowledge, sometimes we're giving regimens that are all IV. Sometimes we're doing all oral. Sometimes we combine those two modalities. And so, I think you just have to be very specific, very thorough with patients to make sure that they understand the schedule. I generally will give our patients a calendar that has the day of the week, day of the cycle, and then outlines exactly what drugs they're going to be getting on each day.

The other thing that's important is scheduling of supportive care medications. And so certainly for medications that the patient receives in clinic or in our infusion area, we, obviously, have a bit more control over scheduling and administration of those supportive care medications. But with the invention of new therapies and particular oral agents, there is a lot of treatment that patients are self-administering at home; and so making sure that patients understand how best to take those medications, with or without food, if there's other supportive care things like antiemetics that they should be taking at the same time, and just making sure that patients really understand what their day is going to look like on these particular treatment regimens.

The other thing that I think is very important and often will get lost in the shuffle of sort of the time period around initial diagnosis is duration of treatment and whether it's an indefinite treatment which does tend to be more common more recently with some of our oral agents versus a finite treatment. So, a certain number of chemotherapy cycles or like something with CAR T, generally, a one-time event, though there may be multiple pieces. CAR T in current state is really a one-time situation; and so, making sure that patients are aware and understanding of exactly that timeline.

The other piece is educating other healthcare providers, and this is most often nursing colleagues on new medications that have been approved. It sort of seems like in the space of hematologic malignancies, there are new drug approvals every couple weeks or every month. And so, making sure that everyone is kept up-to-date on those new drugs and those new approvals is really important.



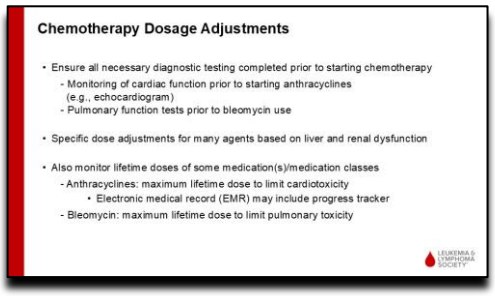

**Slide 54: Drug Interaction Review**

The other piece of my job that I think is especially important, particularly with the advent and introduction of all the new oral therapies for non-Hodgkin lymphoma, includes reviewing drug interactions. So, the vast majority of these small molecule inhibitors are metabolized by cytochrome P450 enzymes and thus are often subject to lots of drug interactions.

The other drug interaction that's becoming more significant is P-gp interactions, and so just making sure that you're doing a thorough review of patient medication profiles and seeing if there's any dose adjustments or modifications that should be made based on other concomitant medications.

Some of the most common interfering drug classes include antifungals, certain cardiac medications, and then antiseizure medications. There also are some interesting drug and diet interactions. So, particularly with oral drugs, metabolized by 3A4, things like grapefruit, grapefruit juice should be avoided by patients. And then particularly some of our regimens for treatment of non-Hodgkin lymphoma include high-dose methotrexate (Trexall®) and actually something like a patient drinking carbonated beverages can affect the clearance of that medication for the patient. So, just making sure that patients are aware of that and that they're not ingesting any of those problematic foods or beverages during the course of their therapy.

The other thing that you see a lot in treatment of cancer patients is patients requesting to use certain herbal products or supplements. And so there are certain products that generally tend to be problematic. Things that I frequently find are turmeric-containing supplements or mushroom-containing supplements. And so, we generally ask all of our patients if you would like to take something over the counter, some herbal or some supplement product, just check with us first. We'll review all the ingredients and then give confirmation as to whether it's appropriate to take.




**Slide 55: Chemotherapy Dosage Adjustments**

**Dr. McKinney:** Meredith, do you find that most of the stuff that patients come in on you're sort of aware of or how often do you have to search for those? I feel like I see all kinds of different things, and it is very challenging to know what's what.

**Dr. Moorman:** Yeah, I think it's generally most problematic with the supplement products. Patients will say, "I'm on turmeric," for example. But, I generally go one step further and say, "Can you tell me the exact brand" because, there's 100 different brands of the vast majority of supplements. And so, oftentimes, there's other additive ingredients that can also be problematic. So, I generally, in the vast majority of circumstances, want to know exactly what product. I'll ask patients, if you can't, if you don't have it with you, can you send us a picture of the label just so we can review all of the ingredients, active and inactive, just to make sure there's nothing problematic.

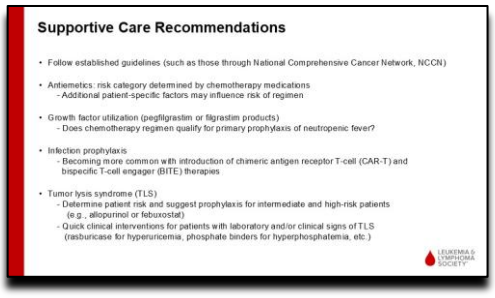
**Dr. McKinney:** Sure.

**Dr. Moorman:** The other thing that is very important as a pharmacist is looking at chemotherapy dosage adjustments. And so, as Dr. McKinney mentioned in his presentation, there, obviously, are patient-specific factors when we're determining what the best regimen is for a particular patient.

And so, the two big things that you tend to think of are dose adjustments, and this is probably more with traditional IV chemo agents, but dose adjustments based on liver renal dysfunction. And so given the population of patients that are generally impacted by non-Hodgkin lymphoma, because they're elderly, that can often become a significant part of our treatment discussion. The other thing that is important as a pharmacist, doing something like R-CHOP that contains an anthracycline, there are certain diagnostic tests that should be completed prior to the start of a chemotherapy regimen, just to make sure that the patient has adequate cardiac function or adequate pulmonary function in the case of bleomycin (Blenoxane®) for us to actually treat the patient with that particular medication.

In addition to making sure that their organ function is adequate prior to the initiation of chemotherapy, the other thing that can be important, particularly, in an older population of patients who may have had another prior cancer diagnosis, is we often do lifetime monitoring of certain medications, particularly anthracyclines; and so we actually have embedded within our EMR sort of a progress tracker that includes all the anthracyclines and looks at their maximum lifetime dose because we know that once patients cross a certain threshold, they're more at risk for different types of cardiac toxicity.

So, we will look at previous treatments. If they've gotten something for breast cancer, that often will include an anthracycline; and we'll take that into account as we're determining the regimen that we're going to treat patients with going forward.




**Slide 56: Supportive Care Recommendations**

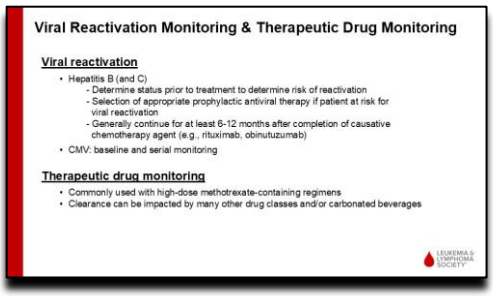
Supportive care is probably one of the big mainstays of my position. So, fortunately, there are lots of guidelines; and I would say, our institution tends to rely heavily on the National Comprehensive Cancer Network, or NCCN. And so, I as the clinical pharmacist am responsible for getting the builds, the chemotherapy regimen builds into our electronic medical record. And so, as part of that, including the appropriate antiemetic therapy, should the regimen include growth factor-like pegfilgrastim (Neulasta®) or filgrastim (Neupogen®), are their infection prophylaxis things that we need to be providing or considering with our patients? And so that is generally all included as part of the chemotherapy regimen build in the computer. Some of that, particularly with antiemetics, is determined by the chemotherapy drugs themselves. But there also are patient-specific factors that may sort of change the antiemetic risk of the regimen. And so that's generally a conversation that I would sit down and have with the physician and the APP to determine if there's something different or additional that we should do for patients.

Infection prophylaxis, I think, is something that's becoming more common and more significant with the introduction of CAR T and BiTE therapies. As often we can see, prolonged myelosuppression or prolonged neutropenia after administration of CAR T, in particular. After that, something that

with more widespread use, we're continuing to learn more about, but it is something that's becoming more prominent with some of the new therapies.

Tumor lysis syndrome is also something that can be ideally prevented but can be a very significant problem if it does develop in a patient with non-Hodgkin lymphoma. This generally is something that we would see in someone who has a more advanced or more rapidly growing disease like diffuse large B-cell or Burkitt lymphoma. And so definitely we should be recommending prophylaxis in these patients, and then we should be intervening quickly for patients that have either laboratory or clinical indicators of tumor lysis syndrome.

The other particular medication that tumor lysis is very well known is venetoclax (Venclexta®), which is a new oral agent for the treatment of both acute myeloid leukemia and chronic lymphocytic leukemia. And so there are some inherent dose changes or dose escalations that are part of the recommended dosing from the FDA to minimize the risk of tumor lysis in addition to other, some of these other preventive factors that we would recommend.



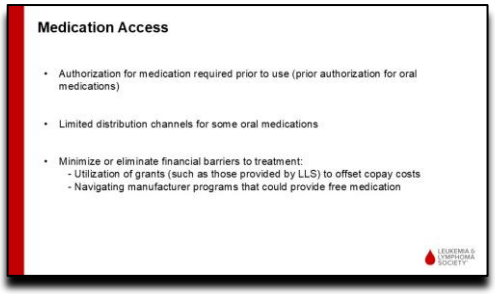

**Slide 57: Viral Reactivation Monitoring & Therapeutic Drug Monitoring**

Particularly with the anti-CD20 monoclonal antibodies that Dr. McKinney discussed, so rituximab (Rituxan®), ofatumumab (Arzerra®), and obinutuzumab (Gazyva®), there is, there's very substantial data to suggest that those agents in patients who have a prior history of hepatitis B can potentially lead to reactivation of hepatitis B. And so that is generally something that as a pharmacist I'm checking. Have we looked at their hepatitis B status? And then are we providing appropriate prophylactic antiviral therapy in patients who might be at risk?

Hepatitis C, obviously, with the advent of newer therapies for hepatitis C, that has sort of changed. But for patients who do have active hepatitis C, that is part of the discussion when we're deciding on the appropriate regimen, sort of which one is the more pressing issue to treat? Should we institute therapy for their hepatitis C versus instituting therapy for their non-Hodgkin lymphoma?

The other viral reactivation that we worry about in a small percentage of patients, and this is really drug-specific, is reactivation of CMV or cytomegalovirus. And so, the vast majority of us have been exposed to that at some prior point in life, and that can, in the setting of chemotherapy, if it reactivates, can actually be a very significant clinical problem. So, we generally will do baseline and then serial monitoring for some specific drugs that we use in the setting of non-Hodgkin lymphoma.

Therapeutic drug monitoring is also commonly used in particular with high-dose methotrexate (Maxtrex®) regimens, and so there are a variety of other drug classes and/or foods that can impact the clearance of methotrexate (Maxtrex®). So, part of our review for these particular patients is making sure that they're not on any of those offending drugs from those other drug classes and then also keeping track of the dietary recommendations and making sure that they're following those.




**Slide 58: Medication Access**

The other part of my position that has become more significant, I would say over the past five to ten years is medication access. And so, while the advent and introduction of oral therapies, I think, has been wonderful for patients, I certainly would say it has increased the administrative burden for particularly me, but I would say all providers within our clinic.

And so, for oral agents, generally authorization with a patient's insurance company is required prior to using a particular therapy. The other thing that we find with some of the newer therapies is, there often are limited distribution channels for some oral medications. So, while we have two different specialty pharmacies here on our campus, sometimes either because of a patient's insurance or because of the drug itself, we're not able to fill the prescription onsite for the patient; and the prescription has to be sent to a different pharmacy.

The other big challenge, and I'm very fortunate to have pharmacy technician support for this particular aspect of my position, but there's a lot of financial barriers to treatment with the introduction of these new therapies. And so, one of the things that we generally will look for is we really try to ideally eliminate but certainly minimize those financial barriers or financial toxicity for our patients.

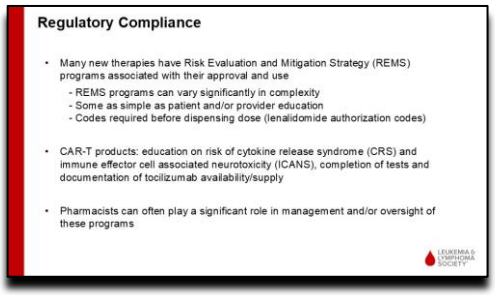
So, grants through organizations like The Leukemia & Lymphoma Society are extremely important for this patient population to help offset copay costs. There are also a variety of different grant programs through The Leukemia & Lymphoma Society and other organizations, but, that help not just with drug cost but can help with transportation, copays of other deductible things associated with insurance, and so really having someone to help advocate and navigate this process for patients, I think, is really important. If we're unsuccessful in tracking down a grant for our patients, then we do generally have access to potentially free drug through manufacturer programs. But again, that's a process that can be time intensive; and so, you have to sort of figure out the right channels to help navigate that process. But that is something that we do on a regular basis.

**Dr. McKinney:** Meredith, I think the distribution of like, novel oral agents is very interesting. So, if, just because an agent gets approved, like we talked about pirtobrutinib (Jaypirca®), doesn't mean you can immediately get it. What's your take on like the usual sort of turnaround time between like an FDA approval was announced and like a new drug like that, that you can actually get it into patient's hand?

**Dr. Moorman:** Yes, so I would say, in my experience particularly for oral drugs, I would say we generally have access to those drugs within one to two months, depending on the manufacturer. And so, I think, everyone, generally once a drug gets approved, I often have providers asking me within a week. Say, "Hey, I want to use this drug." And so, I think part of my position is also tempering expectations. Unfortunately, that just because a drug's approved doesn't often mean that it's immediately available for clinical use and clinical consumption.

The other piece with IV drugs. The same sort of situation. We often run into delays with access and being able to order the medication. But there often are different clinical pathways and clinical

processes and financial processes, to be honest, that we as an institution have to consider and how we're best going to handle those. So, those are all pieces of the puzzle that have to come together before we can really move forward with some of these new treatments.




**Slide 59: Regulatory Compliance**

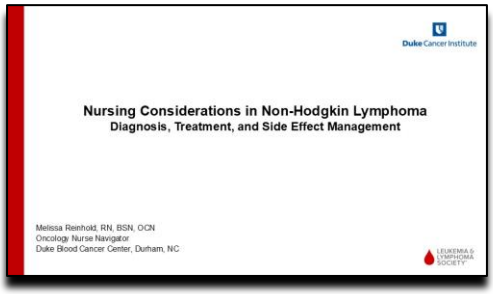
The other thing that I would say is more prominent with newer therapies that have come to market are REMS programs or Risk Evaluation and Mitigation Strategy programs. And so particularly with the CAR T products and BiTE therapies, these drugs definitely have REMS programs in place.

The challenge with REMS programs, sometimes they're very simple, and it can just be patient or provider education. Sometimes it's much more complex. So, with CAR T products, providers that are involved in the care of patients have to be educated on different toxicity profiles, like cytokine release and ICANS. We then, as providers, have to take tests. We have to document supply of certain supportive care medications. And so really, we as an institution have to have an audit trail generally if we were audited by the specific manufacturers documenting that we are in compliance with these different programs.

Lenalidomide (Revlimid®) is another drug that is used with some frequency in non-Hodgkin lymphoma, and it was brought to market before the REMS terminology was used. But that's another example of a fairly complicated process, getting from the physician making the decision that we're going to treat with this particular medication to the patient actually receiving drug. So, the provider has to get a code. The pharmacy has to get a code. We can only do one month at a time. So, there's different nuances like that for the vast majority of each drug that is approved. And so, with that, I appreciate your attention.


**Slide 60: Thank You**

**Lauren Berger:** Thank you, Dr. McKinney and Dr. Moorman, for your very clear and informative presentations.



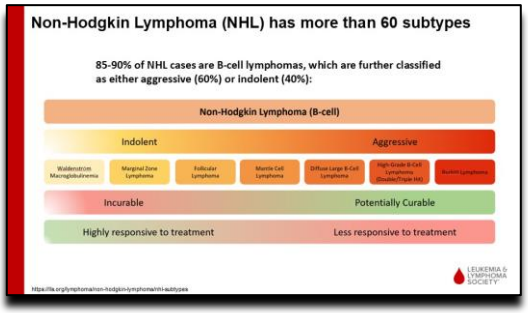

**Slide 61: Nursing Considerations in Non-Hodgkin Lymphoma: Diagnosis, Treatment, and Side Effect Management**

I am now privileged to introduce Nurse Melissa Reinhold. Ms. Reinhold is Oncology Nurse Navigator, at Duke Blood Cancer Center, in Durham, North Carolina. Ms. Reinhold?

Melissa Reinhold , RN, Hello, my name is Melissa Reinhold. I am an Oncology Nurse Navigator at the Duke Blood Cancer Center in Durham, North Carolina. Today I'll be speaking on non-Hodgkin

lymphoma, specifically the Nursing Considerations at Diagnosis, during treatment, and with regard to overall side effect management.

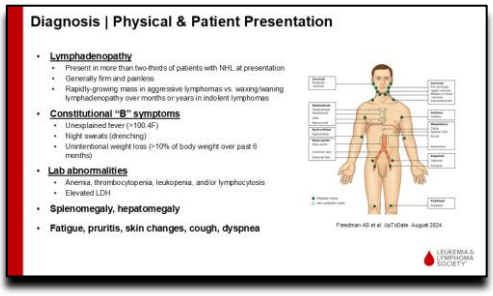
Given the broadness of this topic and the diverse spectrum of lymphoma subtypes that fall within the category of non-Hodgkin lymphoma, I'm going to be painting with fairly broad strokes; and we'll try to keep this generally applicable to nurses who may encounter these patients in their practice.




**Slide 62: Non-Hodgkin Lymphoma (NHL) has more than 60 subtypes**

If you're not overly familiar with this disease, I'll give a quick rundown. Non-Hodgkin lymphoma isn't just one disease but rather a heterogeneous group of blood cancers that all arise from lymphocytes. It generally develops in the lymph nodes and lymphatic system, and it can involve virtually any organ or tissue. There are more than 60 different subtypes of non-Hodgkin lymphoma that are categorized by how quickly they spread and by the type of cell they originate from, whether that be B-cells, T-cells, or the natural killer cells. Since about 90% of cases arise from B-cells, we'll spend most of our time in this presentation on these particular subtypes.

Aggressive B-cell lymphomas account for about 60% of all non-Hodgkin cases. Diffuse large B-cell lymphoma or DLBCL is the most common aggressive subtype. While life-threatening and often requiring immediate treatment, more than half of all aggressive cases are considered cured with treatment that we currently have available. Indolent or low-grade lymphomas, on the other hand, tend to grow much more slowly, have fewer signs and symptoms when first diagnosed, and may not require any immediate treatment. These represent about 40% of cases with follicular lymphoma being the most common subtype. They typically respond really well to treatment, when treatment is needed. However, we don't typically think of these diseases as curable. Indolent lymphomas can occasionally transform into more aggressive lymphomas.



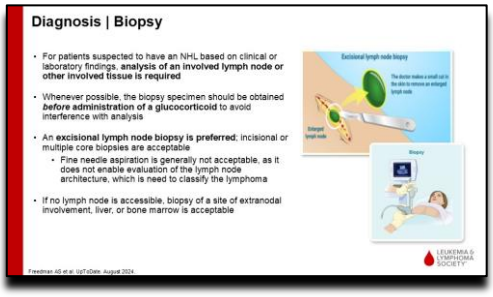

**Slide 63: Diagnosis | Physical & Patient Presentation**

Patient presentation is going to vary greatly, depending on whether the lymphoma is indolent or aggressive. However, the most common early sign of non-Hodgkin lymphoma is painless swelling of one or more lymph node. This lymph node enlargement is called lymphadenopathy, and it's most classically found in the neck, the armpit, or the groin, though it's important to evaluate all potential sites of lymphoid involvement.

For the aggressive lymphomas, this lymphadenopathy may be experienced as a rapidly growing mass, whereas for indolent lymphomas, lymphadenopathy tends to wax and wane over several months or years. The presence of constitutional symptoms also varies with the subtype. B symptoms or fevers, night sweats, weight loss – that's what we consider B symptoms – are much more common in patients with aggressive and highly aggressive subtypes. By contrast, only a small percentage of patients with indolent lymphomas actually have these symptoms. And it's

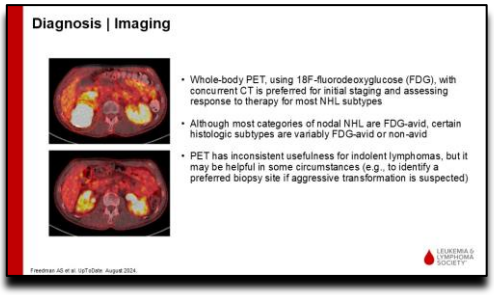
important to note that the presence or absence of these symptoms is significant for staging and prognosis.

We also see lab abnormalities in these patients. Anemia, thrombocytopenia, leukopenia, and/or lymphocytosis are quite common, as is an elevated serum LDH. And LDH levels are of prognostic importance and can be used to monitor treatment response and even recurrence. And for some folks, patients don't present with symptoms at all. Their disease was caught incidentally, and they come to us seemingly quite healthy.



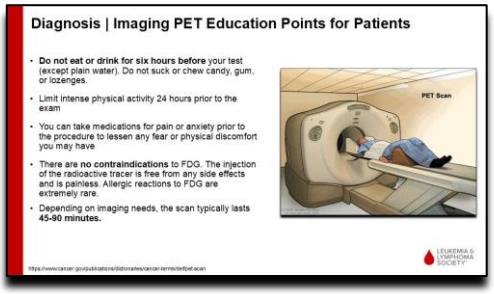

**Slide 64: Diagnosis | Biopsy**

If we do suspect that a patient has non-Hodgkin lymphoma, based on their clinical and/or laboratory findings, a biopsy of the involved lymph node or other involved tissue is required for diagnosis and classification. Preferably, this is obtained with an excisional lymph node biopsy; although if that's not possible, incisional or core biopsies are acceptable. This should be obtained urgently if an aggressive subtype is suspected. And ideally, this should be done before a treatment with steroids, which may obscure the diagnosis because they're lympholytic. Fine needle aspiration is generally considered not acceptable as it does not enable evaluation of the lymph node architecture, which is needed to classify the lymphoma.




**Slide 65: Diagnosis | Imaging**

Also important in the diagnosis and staging of non-Hodgkin lymphoma is obtaining imaging. For FDG-avid subtypes, which include Burkitt lymphoma, mantle cell lymphoma, nodal marginal zone lymphoma, lymphoblastic lymphoma, DLBCL, and follicular lymphoma, FDG-PET with concurrent CTs play a really important role in staging, restaging, prognosticating, planning appropriate treatment strategies, evaluating treatment response, and detecting recurrence. PET's not useful, however, for all types of non-Hodgkin lymphoma. Some subtypes are variably FDG-avid or non-avid. We see the new low rates of FDG-avidity and T-cell lymphomas, CLL, SLL, extranodal, and marginal zone lymphoma. And for this reason, PET has kind of inconsistent usefulness with these indolent lymphomas.




**Slide 66: Diagnosis | Imaging PET Education Points for Patients**

Since your newly diagnosed lymphoma patient likely has never seen the inside of a PET machine before, it can help to provide some nursing education points before the procedure. Most importantly, patients are instructed to remain NPO for six hours prior to the procedure. This actually includes gum, mints, lozenges, basically anything except clean water; and they're pretty strict on this. So, education's really important upfront.

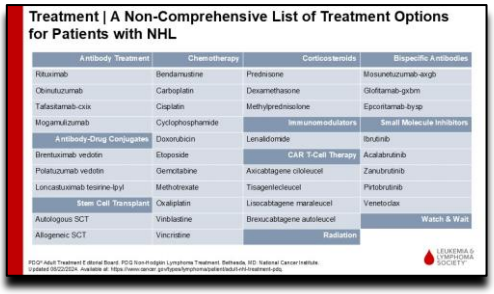
Preprocedure medications are completely fine. Some patients do require pain medication or anxiolytics, that they can tolerate lying in that machine for the duration, which is like 45 to 90 minutes, depending on what our imaging needs are. Patients are comforted to know that the injection of the radioactive tracer is free from any side effects and is painless. It can be given through the port or peripheral IV. Allergic reactions to the FDG are extremely rare, and that's all very comforting for the patient. Most PET scans are performed with concurrent CTs, but these CTs are typically noncontrasted and low dose. If the PET is done with contrasted CTs, appropriate precautions should be taken in those patients with iodine allergies or renal impairment.


**Slide 67: Diagnosis | Nursing Considerations & Interventions at Diagnosis**

Once your patient has a confirmed diagnosis and the oncologist outlines an initial plan, this is a really great opportunity for a few key nursing interventions and assessments. I personally think now is a really ideal time to assess for potential barriers to care. From a nurse navigator perspective, I'm thinking about transportation needs, communication or literacy barriers. Do they have enough caregiver support for the treatment we're proposing? Do they have any baseline needs that would be improved with early referrals to palliative care, counseling, social work? Are we recommending a regimen where they might lose all their hair and would benefit from some education around wigs or boutique services? Do they qualify for financial resources or grants that we could actually start, like, applying them for now? And I like to find out if they're interested in joining a support group or engaging with peer-to-peer counseling.

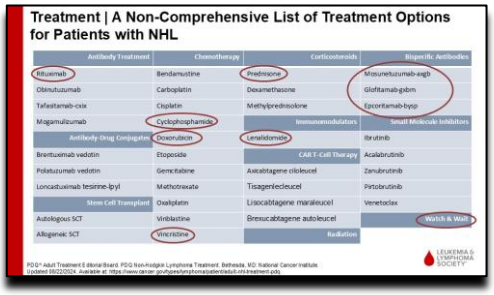

**Slide 68: Diagnosis | Nursing Considerations & Interventions at Diagnosis**

Their oncologist has likely, at this stage, just given them a lot of verbal information to digest; and they may need some of that information distilled into written, patient friendly language that they can take home and spend some time with as they process all of this. I find the LLS disease booklets and fact sheets to be really great resources for these newly diagnosed folks, and I also like to provide written chemotherapy teaching sheets provided by Duke for their proposed treatment regimen. I also like to include treatment calendars so they can start to make plans and arrangements. And then I like to provide really clear written instructions for when and how we want them to call with new concerns.



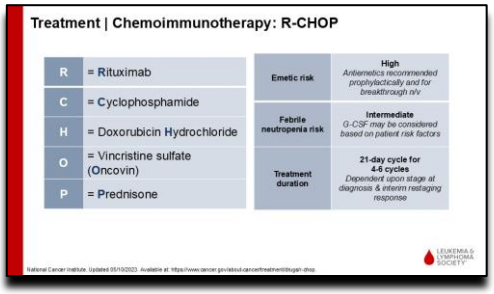

## Slide 69: Treatment | A Non-Comprehensive List of Treatment Options for Patients with NHL

So, moving on from diagnosis to treatment. Options for treatment are as diverse as the subtypes they're treating. There is everything from no treatment to traditional cytotoxic chemotherapy, to radiation, immunotherapy, targeted therapy, stem cell transplant, CAR T, bispecifics, and with much, much more than I could even get into in this presentation.



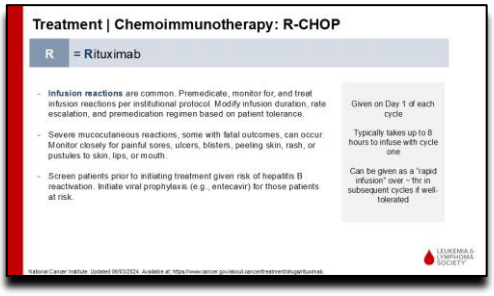

## Slide 70: Treatment | A Non-Comprehensive List of Treatment Options for Patients with NHL

So, I'll focus on just a few that you may or may not encounter in your practice.




## Slide 71: Treatment | Chemoimmunotherapy: R-CHOP

To start, I'll talk about the tried-and-true chemoimmunotherapy regimen R-CHOP, which has been FDA approved for first-line treatment in DLBCL since about 2006. Typically, this combination of drugs is given every 21 days for about four to six cycles, depending on their staging and how they're responding to treatment. It's considered highly emetogenic, so we do recommend prophylactic antiemetics immediately prior to infusion and then as needed at home for breakthrough nausea and vomiting. It's considered intermediate risk for febrile neutropenia, so growth factor may or may not be recommended based on patient risk factors.

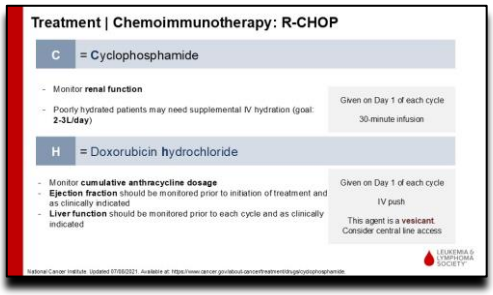



## Slide 72: Treatment | Chemoimmunotherapy: R-CHOP

I'm going to hit each drug in this regimen really quickly, just the highlights and like key teaching points for patients and some nursing interventions you might find relevant.

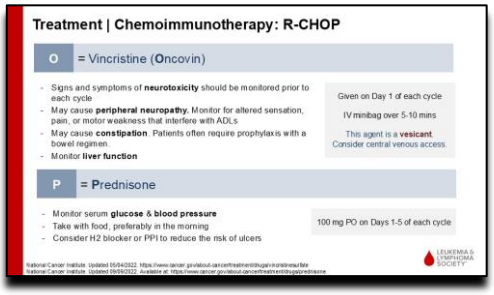
To start, the R in R-CHOP is for rituximab (Rituxan®). It's a humanized, monoclonal antibody that targets a protein on the surface of B-cells called CD20. It's given on day one of every cycle, and infusion reactions are extremely common with this drug, particularly with the first infusion; and for this reason, that first infusion is titrated very slowly over eight hours or so. If a reaction does occur, despite that slow titration and lots of premedication, it's going to typically develop within about 30 minutes to two hours after the drug is initiated.

If you're the treating nurse, it's really important that you can identify early signs of a reaction. This often looks like fever, chills, dyspnea, rigors, flushing, itching, low back or abdominal pain, nausea, vomiting, diarrhea, or even just like a rash. The reactions are very typically well-managed with pausing the infusion, administering hyper-sensitivity medication, and then restarting the infusions more slowly. Some patients don't react at all; and if that's the case, they tolerate it, we can give subsequent infusions as rapid infusions over about an hour, though the nurse will always be assessing for reactions because it is possible with any cycle of treatment.



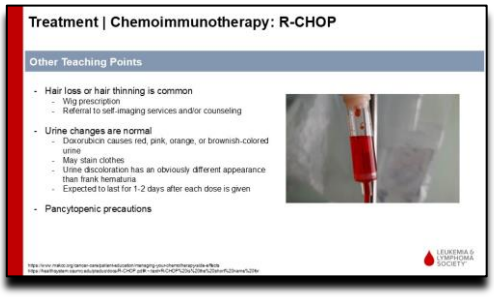

**Slide 73: Treatment | Chemoimmunotherapy: R-CHOP**

The C in R-CHOP is for cyclophosphamide (Cytoxan®), which is also given on day one. We really just want to make sure they're well-hydrated for this drug, whether it's orally or through the IV. The H is for doxorubicin hydrochloride (Adriamycin®) given on day one as well. This is considered cardiotoxic, so a baseline ejection fraction must be obtained prior to starting treatment. This is also a vesicant, so central line access should be considered, especially in patients with poor peripheral access.




**Slide 74: Treatment | Chemoimmunotherapy: R-CHOP**

The O in R-CHOP is for vincristine or Oncovin®. It's given on day one, also a vesicant and really important with this drug that we're monitoring for neurotoxicity, peripheral neuropathy, and constipation, which are really common side effects of vincristine (Oncovin®) and ought to be very aggressively managed. And finally, the P in R-CHOP is for prednisone (Deltasone®). This is an oral steroid given on days one through five of each 21-day cycle. Teaching points include taking this medication with food, ideally in the morning, and just letting your patient know that it can cause insomnia, restlessness, hyperglycemia, hypertension, mood changes, weight gain, or swelling.



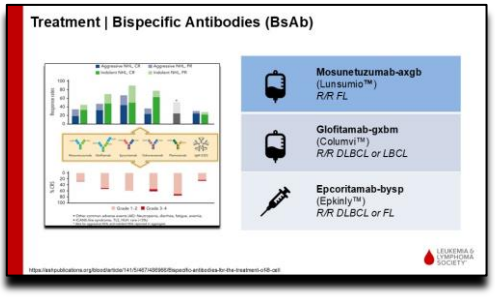

**Slide 75: Treatment | Chemoimmunotherapy: R-CHOP Other Teaching Points**

Other important teaching points, hair loss or hair thinning is likely going to happen at some point in their treatment on R-CHOP. We offer our patients prescriptions for wigs to help offset the costs. We also refer them to our self-imaging services for free wig consultations at our boutique. Some patients may also benefit from a referral to a counselor. Even though hair loss isn't a life-threatening consequence, it is highly distressing.

Other things I like to teach patients about, urine changes. I do think patients deserve a bit of a heads up on this one because the doxorubicin, or the Red Devil, as it's fondly known, does cause urine discoloration. This typically looks reddish or orangish in color. Fortunately, it's going to look really different than like frank hematuria, so there shouldn't be any confusion there. This does last

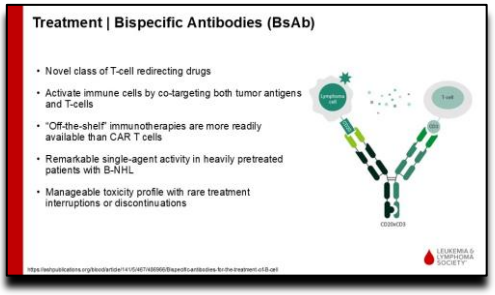
for like a day or two post-treatment, but you can reassure your patient that this is a completely normal expected finding. And finally, like most chemotherapy regimens, patients are going to experience a nadir in their blood counts about 7 to 10 days post-treatment. Not all patients will require transfusion support in their nadir, but some will. We give neutropenic, anemic, and thrombocytopenic precautions to our patients; and we do something called the midcycle check where we look at their counts and their nadir to try to get a good sense of like how low and how transfusion-dependent they'll be with subsequent cycles.

Overall, the 12 to 18 weeks that patients are on R-CHOP can be really tough. Infusion days can be very long, and the side effects can take some working out to really well manage. But for most people, the benefit of R-CHOP is well worth it. More than half of our DLBCL patients are cured with first-line R-CHOP, so just really great patient education and preparation and good nursing support through the duration of treatment is going to help these patients get to the finish line.



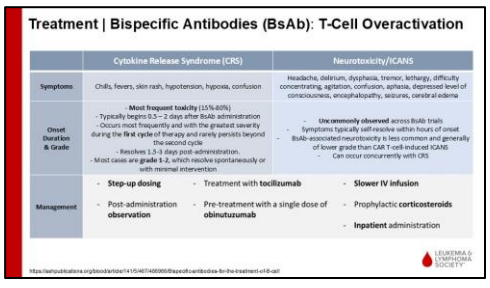

**Slide 76: Treatment | Bispecific Antibodies (BsAb)**

Moving on to a much, much newer treatment option for non-Hodgkin patients, bispecific antibodies. These have only been FDA approved within the last two years or so, but they are among some of the most promising immunotherapeutics for lymphoma today. The three products we're currently using in our B-cell folks are mosunetuzumab (Lunsumio™), glofitamab (Columvi™), and epcoritamab (Epkinly™).




**Slide 77: Treatment | Bispecific Antibodies (BsAb)**

So, what are bispecifics? These are a novel class of T-cell redirecting drugs that activate a patient's immune cells by co-targeting both the tumor antigens and the T-cells. So, unlike CAR T, these are off-the-shelf products, which means they are more readily available than CAR T-cells, which reduces treatment delays and the need for bridging therapy, which is really great. They've demonstrated absolutely remarkable single-agent activity in patients with heavily pretreated disease. And they have a very manageable toxicity profile with rare treatment interruptions or discontinuation.



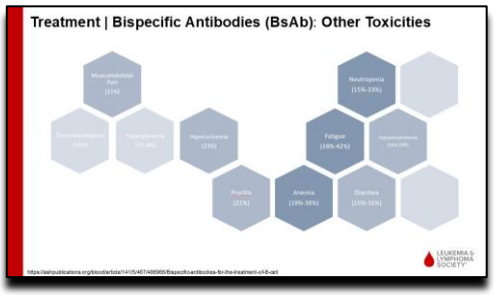

**Slide 78: Treatment | Bispecific Antibodies (BsAb): T-Cell Overactivation**

Toxicities, if any, are generally related to T-cell overactivation among the cytokine release syndrome or CRS was the most frequent occurring in 15% to 80% of patients. Clinically, this syndrome presents with any combination of chills, fevers, skin rash, hypotension, hypoxia, and confusion, typically beginning about half a day to two days after administration and generally resolving within like a day and a half to three days. It occurred most frequently with the greatest severity during the first cycle of treatment, and it rarely persisted beyond the second cycle. Most folks only

have like a Grade 1 or a Grade 2 that resolves spontaneously or with very minimal interventions like fluids, Tylenol®, maybe some corticosteroids.

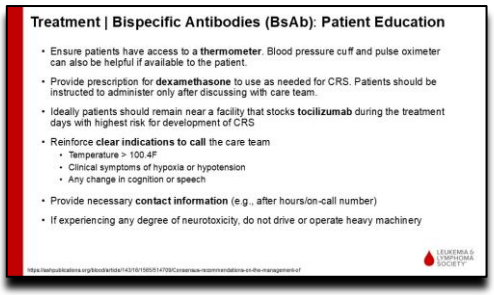
Neurotoxicity or immune effector cell-associated neurotoxicity syndrome called ICANS is another consequence of T-cell overactivation. But, fortunately, this is much less commonly observed in the bispecifics, so I'm not going to get too much into it. But we do take a few measures to mitigate the CRS and the potential neurotox, and one way we do that is with step-up dosing. So, patients are given like a very small priming dose up front, followed by an intermediate dose, before receiving their full dose. And this can really lessen the, the CRS and, and the neurotox. Another way is to give a pretreatment dose of obinutuzumab (Gazyva®) before we give the glofitamab (Columvi™), and this depletes the circulating B-cells and dampens that T-cell activation, so you may see that in your glofitamab (Columvi™) patients.

Something else we are doing and would recommend is post-administration observation. So, for mosunetuzumab (Lunsumio™), this looks like a relatively short, 4-hour, post-dose observation in the outpatient setting. For glofitamab (Columvi™), this is a bit longer. We monitor for 24 hours post dose, which we start that observation in the outpatient setting but finish it up in-patient since clinic does eventually close.




**Slide 79: Treatment | Bispecific Antibodies (BsAb): Other Toxicities**

Other toxicities we see with bispecifics, fatigue, diarrhea, pruritis, musculoskeletal pain, cytopenias, and a few other lab abnormalities.



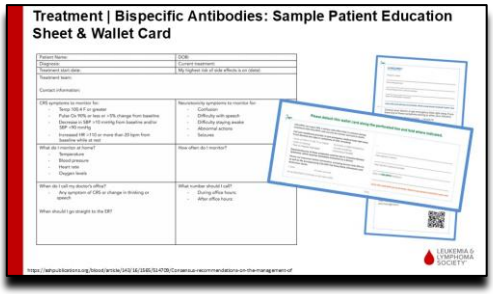

**Slide 80: Treatment | Bispecific Antibodies (BsAb): Patient Education**

And we'll sort of wrap up bispecifics with a few important teaching points for patients. It's really important that these folks have access to a thermometer at home, given that fever is a sign of CRS. It can also be really helpful if they have a blood pressure cuff and a pulse oximeter because hypotension and hypoxia are also signs.

If patients do spike a fever, if they experience hypoxia or hypotension, or if they have any changes in cognition or speech, they have to call. It's really important that these patients know who to call, especially who to call during normal business hours and who to call after business hours.

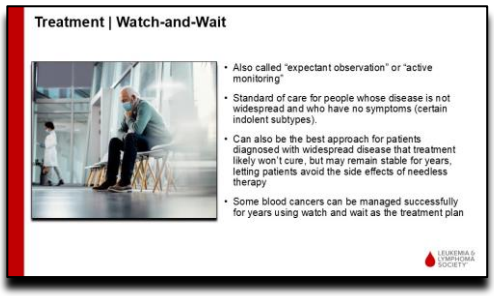
Based on the severity of symptoms they report on that phone call, they may be instructed to take the oral dexamethasone (Decadron®) they were given before discharge, or they may be instructed to head to the emergency room. Ideally, these patients are already staying near a facility that stocks a drug called tocilizumab (Actemra®), at least for those first days post-treatment when their risk for CRS is highest. And finally, really important to tell your patients if they're having any

degree of neurotoxicity, which could be like confusion, speech changes, mental status changes, they absolutely should not be driving.



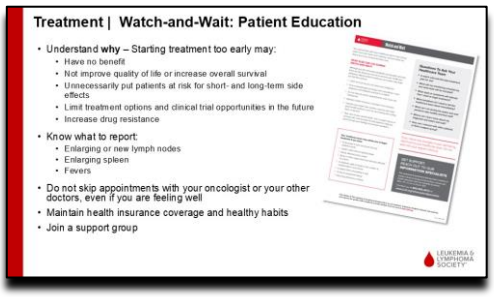

**Slide 81: Treatment | Bispecific Antibodies: Sample Patient Education Sheet & Wallet Card**

We can send these patients home with some written instructions just to really reinforce when and why they need to call, and a lot of the pharmaceutical companies will actually make these wallet cards that you can send home with your patient, which can be really helpful for any providers they encounter that aren't familiar with bispecifics.




**Slide 82: Treatment | Watch-and-Wait**

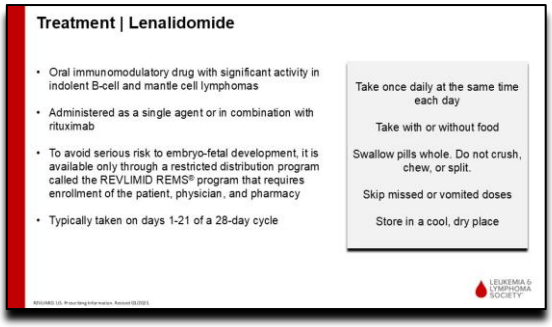
Moving on, I think I would be remiss not to mention watch and wait, which isn't treatment, but it is the standard of care for non-Hodgkin lymphoma patients whose disease is indolent and for patients who have no symptoms. This is also referred to as expectant observation or active monitoring; and it's commonly the approach for patients with follicular lymphoma, CLL, SLL, mantle cell, Waldenström, and marginal zone lymphoma.




**Slide 83: Treatment | Watch-and-Wait: Patient Education**

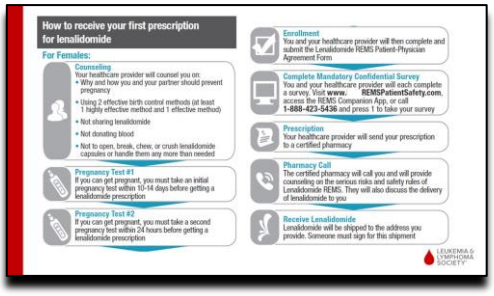
Because it can feel really counterintuitive and anxiety provoking, it's like do nothing about your cancer, really thorough patient education is essential when you're proposing watch and wait. If patients understand like the why of it all, it definitely makes it easier to get onboard with a strategy. So, why do we wait? Starting treatment immediately at diagnosis may have no benefit, may not improve quality of life, it unnecessarily puts patients at risk for short- and long-term side effects. It can limit their treatment options and clinical trial opportunities in the future, and it can increase drug resistance.

It's really important to empower these patients and make them active participants in their care. They need to know what to report, like enlarging or new lymph nodes, an enlarging spleen, fevers, or anything else they're, they're concerned about. They should absolutely not be skipping their oncology follow-up appointments, even if they're feeling really well. And they should continue like good preventative care visits with their other doctors. And because they may need to start treatment like at any time, it's really important that they maintain active health insurance coverage.



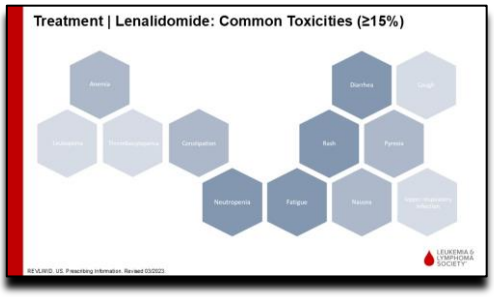

## Slide 84: Treatment | Lenalidomide

So, the final treatment option that I'm going to talk about in this presentation, though I know I've barely scratched the surface of available treatment options, is lenalidomide or Revlimid®. This is an oral immunomodulatory drug with significant activity in follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma. It can be administered as a single agent or in combination with rituximab (Rituxan®). Do know if it's used in pregnancy, it can cause very serious birth defects or even embryo fetal death; and for this reason, it's only available through a restricted distribution program called the Revlimid REMS program.



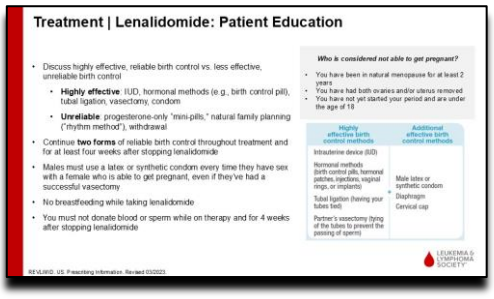

## Slide 85: How to Receive your First Prescription for Lenalidomide

There's a series of steps required to get your first prescription of lenalidomide (Revlimid®). I'm not going to go through each step, but just know that depending on your patient's sex and age, it requires counseling, multiple pregnancy tests, enrollment in a REMS program, monthly surveys completed by the patient, the provider. More counseling after that and then coordination of drug delivery to the patient's home. So, it's really worth considering like is your patient a good candidate? Are they going to be compliant? This is a tedious process. It is home dosing. Is this going to work for your patient?



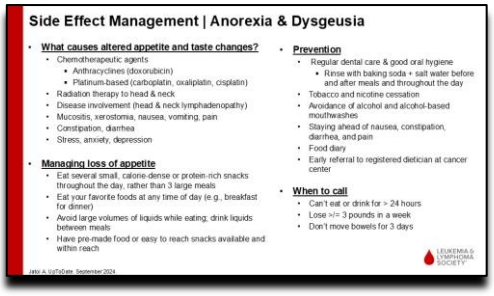

## Slide 86: Treatment | Lenalidomide: Common Toxicities (≥15%)

Other toxicities include neutropenia, thrombocytopenia, anemia, diarrhea, fatigue, and rash, just to name a few.




## Slide 87: Treatment | Lenalidomide: Patient Education

Really important patient education here includes distinguishing between what is highly effective, less effective, and unreliable birth control. For female patients who are considered able to get pregnant, two forms of reliable birth control are required throughout treatment and for at least four weeks after stopping Revlimid®. And for your male patients, they are instructed to use a condom like every time they have intercourse with a female who's able to get pregnant, even if they've had a successful vasectomy. So, we just want to make sure our patients really understand what this all means.

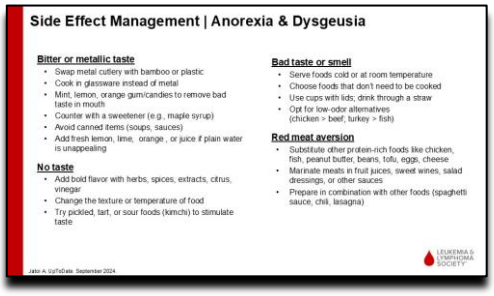



## Slide 88: Side Effect Management | Anorexia & Dysgeusia

Moving on from treatment onto side effect management, and again I can't cover everything your patients are going to experience; but I'm going to try to hit a few of the more common complaints within this population. Two of those really common complaints are anorexia or loss of appetite and dysgeusia or altered taste. They can be caused by chemotherapy, particularly your platinum-based drugs, your anthracyclines, both of which we give, or a variety of other factors.

We can't always completely prevent either of these side effects, but there are some great ways to reduce their severity. Excellent oral hygiene, that includes frequent rinsing with baking soda and salt water has been shown to have great benefit. Cessation of tobacco, nicotine, and alcohol are really important as well. It can be helpful to keep a food diary to track what's working, what's not working; and I'm a really huge proponent of referring chemotherapy patients to our registered dietitian early on in their treatment course before they've lost weight or developed food aversions or anticipatory nausea.

When your patient is experiencing loss of appetite, sitting down for three square meals a day is generally a nonstarter. Instead, recommend that your patient try several small calorie-dense or protein-rich snacks throughout the day. It can really help to have premade food and like really easy-to-reach snacks out and available for whenever the mood strikes. Give your patients full permission to eat whatever tastes good to them, whenever. I know, we're always pushing oral hydration on our patients, but consuming really large volumes of liquids while they're eating can fill them up prematurely. So, ideally they're drinking their fluids between meals instead of during meals. And even though altered taste and appetite are an expected part of treatment, we still want patients to know when they should call us about it. If, for example, they're not eating or drinking for 24 hours, if they're losing three or more pounds a week, or if they're not moving their bowels for three or more days, we do want to intervene.



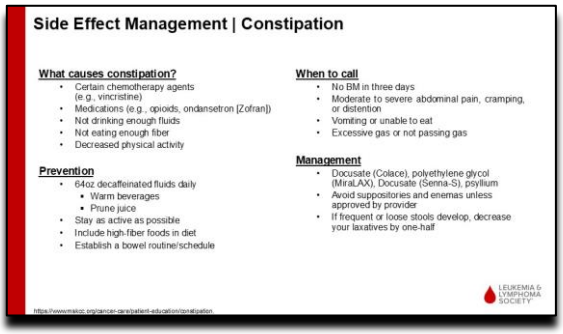

## Slide 89: Side Effect Management | Anorexia & Dysgeusia

A little bit more on dysgeusia or altered taste. This is not a life-threatening adverse effect and, therefore, is often overlooked in our clinical practice. However, the downstream effects of anorexia associated with the loss of taste may lead to the interruption or discontinuation of chemotherapy; and, therefore, I believe it should be carefully managed and not ignored. Many of our patients report that foods do not taste the same as they used to, that food and drink now taste bitter, particularly plain water, or that things just taste like plain bad, bland.

So, for patients who report bitter or metallic tasting food or drink, they can try swapping silverware for bamboo or plastic utensils. They can try adding citrus to plain water or counter that bitterness in food with the addition of a sweetener. For patients who tell us that food has no taste, they can try adding really bold flavors. Particularly tart foods can help stimulate taste and sometimes just

changing the temperature or the texture of foods can help make things more appealing. And for patients who say that food just tastes really bad, you can try recommending that they eat their foods cold or at room temperature, or just trying to stick to really low odor foods.

And for patients who love their red meat but now have an aversion to it, they can try experimenting with different marinades, other substitutions, or just hiding their meat in sauces and stews and just trying to mask those now unappealing flavors.

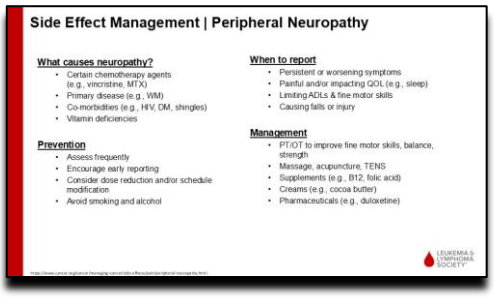



**Slide 90: Side Effect Management | Constipation**

Constipation is another frequently reported side effect in this patient population, particularly because we're getting so much vincristine (Oncovin®), though there are other contributing factors like Zofran® and opioid use and because these patients who are undergoing treatment are often not drinking enough water, they're not eating enough fiber, and they're generally less active than they once were.

I think prevention is the best strategy here. Goals include drinking at least eight cups of decaffeinated fluids a day. Warm beverages, prune juice – these can help stimulate the bowels. Educate your patient on where they can find fiber in their diet. Great sources are whole grains, beans, vegetables, fruit. Specifically prunes, unpeeled pears, and dried apricots are really great sources of fiber that naturally stimulate the bowels. It can also be helpful to try and have a bowel movement around the same time every day, particularly after a meal or after walking when bowels are most active. Sometimes prevention, diet, and lifestyle modification alone are not enough to combat these vinca alkaloids. And when that's the case, we want our patients to know when to call us.

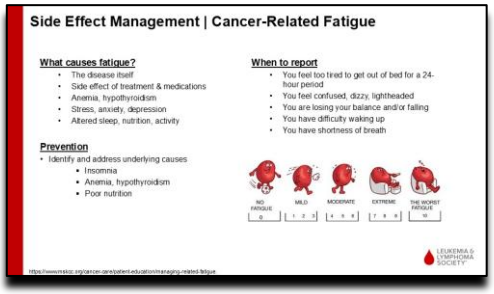
When they've gone three or more days without a bowel movement or they've developed abdominal pain, cramping, distension, vomiting, excessive or lack of gas we want to know. Management typically includes the addition of Senna-S (docusate and senna), MiraLAX (polyethylene glycol 3350), and/or Colace (docusate), and psyllium (Metamucil®) is also really helpful. For patients on active treatment, we generally discourage the use of suppositories and enemas given their risk for bleeding and infection.




**Slide 91: Side Effect Management | Peripheral Neuropathy**

Peripheral neuropathy can be caused by any treatment, by the primary disease, or by a number of comorbidities. For chemotherapy-induced peripheral neuropathy or CIPN, the best prevention is frequent assessment, early reporting, and treatment modification. Patients should feel empowered to report worsening symptoms, especially if their neuropathy becomes painful, impacts their quality of life, limits their functional ability, or risks their safety. Clinicians should assess the appropriateness of dose delaying, dose reducing, substituting or stopping chemotherapy in these patients who develop intolerable neuropathy and/or functional impairment.

Unfortunately, there are currently no medications we recommend for the prevention of CIPN. Gabapentin (Neurontin®) and pregabalin (Lyrica®) are commonly used to treat neuropathic pain, but they have not been found to be particularly useful in CIPN. Duloxetine (Cymbalta®) is the only agent that has appropriate evidence to support its use for patients with established painful CIPN, but even that has limited benefit. We do know that opioids are not recommended for the treatment of CIPN. Some helpful nonpharmaceutical management strategies include PT/OT, massage, acupuncture, TENS, and like massaging creams like cocoa butter into the affected area.



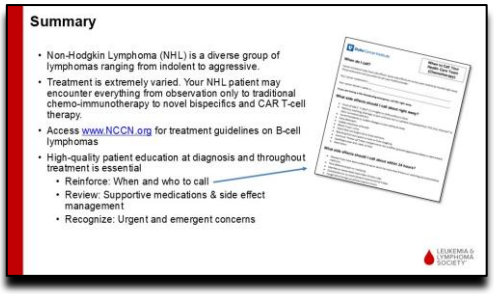

## Slide 92: Side Effect Management | Cancer-Related Fatigue

And I will end with the most frequently reported side effect of them all, fatigue, specifically cancer-related fatigue, which is described as excessive or persistent exhaustion related to cancer or cancer treatment. It interferes with daily activity and function. Symptoms include physical weakness, emotional and mental exhaustion, changes in mood, difficulty concentrating, impaired decision-making, and little interest in social activities. This can be caused by the patient's disease, by its treatment, by underlying conditions like anemia, or by psycho-social factors. Many patients find that their cancer-related fatigue is actually more distressing than even pain or nausea. And despite this degree of distress and impairment, it's often overlooked and under addressed as it's rarely life-threatening. And what's tough too is there's generally no quick fix or one single effective treatment for fatigue.

Even though this is an expected side effect, it's really important to educate patients again on when they should call us, especially if they can't get out of bed for 24 hours, if they're becoming confused, somnolent, light-headed, they're sustaining falls, having difficulty waking or catching their breath. We, obviously, want to know if that's happening.


## Slide 93: Side Effect Management | Cancer-Related Fatigue: Management

Like I said, no quick fix; but there are some strategies to reduce fatigue severity. There's really compelling evidence that exercise, cognitive behavioral therapy, mindfulness-based programs, tai chi, qigong, and American ginseng all improve fatigue during treatment. And then we have yoga, acupressure, exercise, CBT, mindfulness, and moxibustion that really help after treatment. If you're patients are at the end of their life, you can consider offering corticosteroids in addition to CBT; but evidence does not support the use of L-carnitine, antidepressants, wakefulness agents, or psychostimulants at any point in your patient's course.

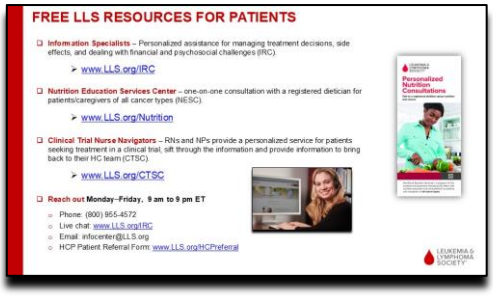



## Slide 94: Summary

So, to summarize, non-Hodgkin lymphoma or NHL is a diverse group of lymphomas ranging from indolent to aggressive. Treatment is extremely varied, and your non-Hodgkin patient may encounter everything from observation only, to traditional chemotherapy, to novel bispecific antibodies, and even CAR T-cell therapy. For all of these patients, high quality patient education at diagnosis and throughout treatment is absolutely essential. Nurses should be continually reinforcing when and who to call. They should be reviewing supportive medications and appropriate side effect management, and they should be able to recognize urgent and emergent concerns in this patient population. Thank you so much.


## Slide 95: Free LLS Resources for Healthcare Professionals

**Lauren Berger:** Ms. Reinhold, thank you for your presentation. I am now pleased to share free resources for you and your patients. The Leukemia & Lymphoma Society offers free CME & CE online webinars such as this one, in-person regional programs and a podcast channel for Healthcare Professionals, where you can listen to discussions on treatment, side-effect management and more, including strategies to support you and your patients. New and interesting topics are added every few weeks. Access these, as well as videos and fact sheets for healthcare professionals at www.LLS.org/CE




## Slide 96: Free LLS Resources for Patients

LLS Information Specialists are highly trained Oncology Social Workers and Nurses who provide accurate, up-to-date disease, treatment and support information, including financial. Patients can Contact them Directly, or you can complete a Referral form. Specialists can also help you order Free Copies of booklets To Give to your patients. LLS offers free nutrition consultation to patients with any type of cancer diagnosis in a 30-minute phone call with one of our registered dietitians. Contact them using the link or phone number here to refer a patient. Our Clinical Trial Support Center Nurse Navigators are RNs & NPs with expertise in blood cancers. They work one on one with patients, via telephone, to provide user friendly information, do a nursing assessment to provide personalized information, help find appropriate clinical trials, assist them throughout the clinical trial process and provide info for the patient to bring back to their healthcare professional.


## Slide 97: Here to Help: LLS Commitment

The Goal is NOT to enroll every patient into a trial, rather to increase opportunities for participation by facilitating informed decision making and minimizing logistical barriers for the patient. They work in collaboration with the patient's healthcare team to decide if a clinical trial is right for them. Ultimately, they educate, support, and empower patients to be active participants in and have control over their treatment decisions. This is unique service from The Leukemia & Lymphoma Society. I hope you will consider all of these specialists as an extension of your team.


## Slide 98: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, and other resources, using links in these slides.


## Slide 99: Free LLS Resources for Your Patients

Through targeted and culturally appropriate programs & services, we are committed to providing needs of minoritized and underserved communities impacted by a blood cancer and those facing barriers to optimal care. Our materials are available in English and Spanish, and our Specialists consult with patients in several languages. If you would like more information for yourself or support for your patients, contact an Information Specialist at 800.955.4572 www.LLS.org/support


## Slide 100: Thank You

Thank you to our presenters and thank you to everyone listening. I hope this information will be helpful as you care for your patients.