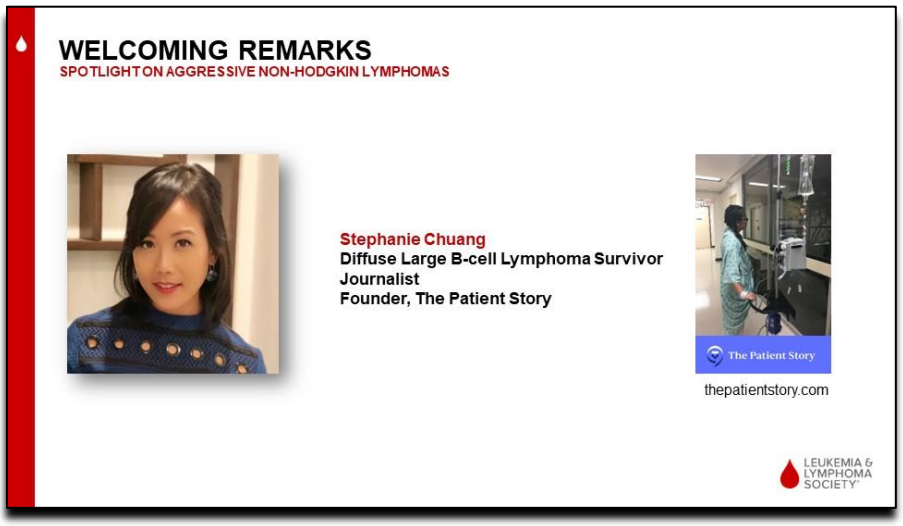
Spotlight on Aggressive Non-Hodgkin Lymphomas

Operator
Greetings. And welcome to Spotlight on Aggressive Non-Hodgkin Lymphomas, a live telephone and web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 900 people participating from across the United States as well as other countries, including Canada, Egypt, Ireland, Italy, Indonesia, Philippines, and Thailand. And, special thanks to Dr. Westin for volunteering his time and sharing his expertise with us today.



Welcoming Remarks

Before we begin, I'd like to introduce Ms. Stephanie Chuang who was diagnosed with diffuse large B-cell lymphoma at the end of 2016. Stephanie is also the founder of The Patient Story, an online resource where you can find hope, guidance, and a supportive community.

Stephanie Chuang
Hi, everyone. My name is Stephanie Chuang. And I want to first thank Lizette and The Leukemia & Lymphoma Society for inviting me on, and say hello and share what is my story, which I hope will resonate with some of you today.

So back in 2016, I started feeling a lot of symptoms that were very foreign to me. But, as many of us do, I explained them away. Being a reporter back then for the NBC in San Francisco, a schedule with news was tough. Eating on that schedule wasn't great. So, weak diet equals bad symptoms, right? There was always a reason until there wasn't.

And I was in a doctor's office, where her demeanor changed after she felt around my collarbone and below. And I remember, like that, everything, just my stomach sank. And an x-ray, and emergency CT scan, and 24 hours later, I got a phone call and heard the words: I am so sorry, Stephanie. It's lymphoma. That turned into a week of hospitalization, with countless scans; blood draws; biopsies, including a bone marrow biopsy; and, finally, after that week is when I got the official diagnosis -- diffuse large B-cell lymphoma, stage III -- so DLBCL.

And, I was 31 and two months from getting married at the time. So, I just remember feeling incredibly lost. I went through hundreds of hours of good, old-fashioned chemotherapy. And, in that experience, I realized that while the physical part of this was really tough, it was really the mental and emotional component that threw me into a very dark place. And the best light that I found was hearing from other people, in human terms. What is cancer? What does it look like day-to-day? And those were the voices that lifted me and gave me direction and help.

And that was the genesis of The Patient Story -- a platform that specializes in video stories and different pieces to really highlight the patient and care-partner voice. So, people, number one, understand they're not alone. And I'm really grateful to say we're now reaching more than a million views every month in cancer. And I'm also so grateful just to be part of this work, which is on our website thepatientstory.com and our YouTube channel.

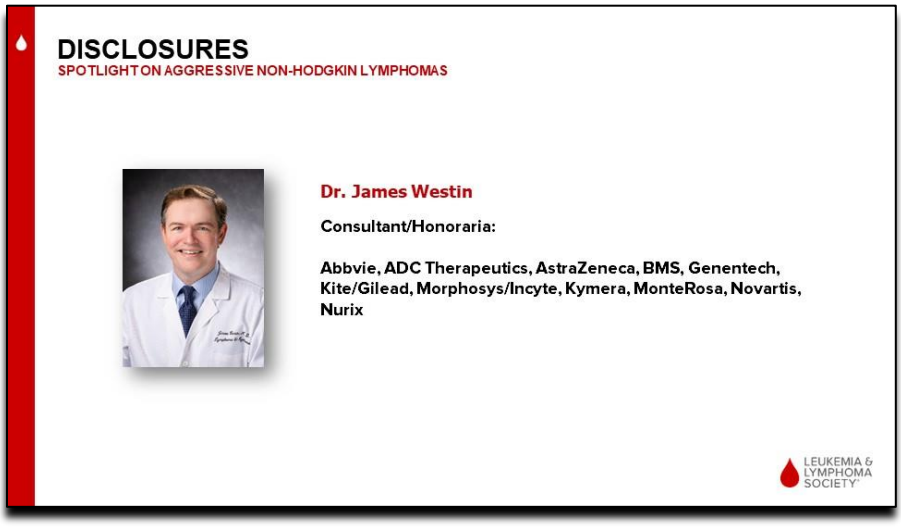
I'm also really grateful, because it's thanks to The Patient Story that I've been able to come to a place where we get to partner with an incredible organization, like The LLS, in this focus on patient voice and

experience. If you can't tell already, I'm a huge fan of The LLS. And we're collaborating now to put on programs together to really help empower patients and care partners in cancer care, share treatment decision-making, learning about clinical trials, and what are the things that really matter and will help all of us during this really difficult time.

So, I want to thank The LLS for investing in us and for investing in programs like today. Speaking of which, let's get to it. Lizette, thank you again for having me on.

Lizette Figueroa-Rivera
And, thank you so much, Stephanie. LLS is proud to collaborate with you, The Patient Story, and bring our blood cancer patients more information and support.

And for this program, we'd like to acknowledge and thank our supporters, Bristol Myers Squibb; Eli Lilly and Company; Genmab US & AbbVie Inc.; Incyte Corporation; Kite, A Gilead Company; Merck & Company; and MorphoSys US.



Disclosure Slide

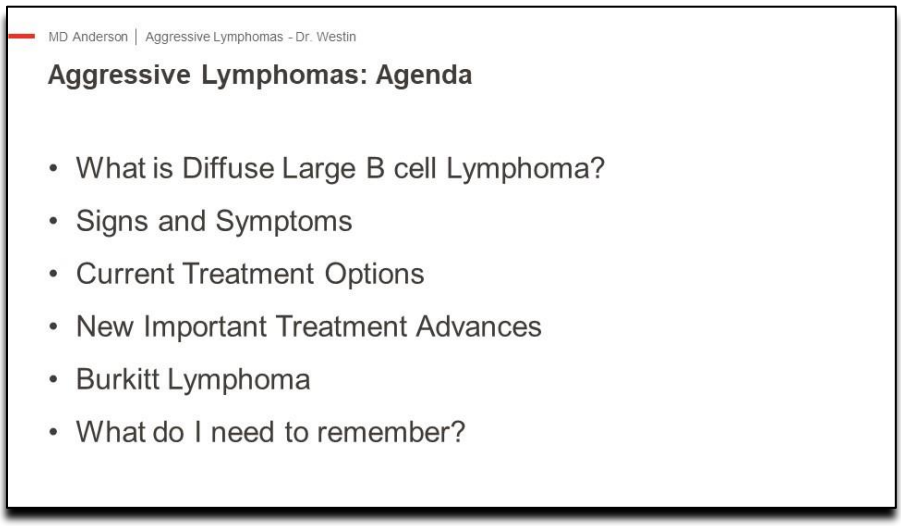
Spotlight on Aggressive Non-Hodgkin Lymphomas

I am now pleased to introduce our speaker, Dr. Jason Westin, MD, Director, Lymphoma Clinical Research, Section Chief, Aggressive Lymphoma, Department of Lymphoma and Myeloma, at the University of Texas at MD Anderson Cancer Center in Houston, Texas. Dr. Westin, I'm now privileged to turn the program over to you.

Jason Westin, MD
Thank you so much. It's my honor to be here with you today, to share this spotlight on aggressive, non-Hodgkin lymphomas. Before I dive in, I'd like to also recognize The LLS. This is a wonderful group that should be viewed by the people who are on the call today, as well as their family and their loved ones, as a trusted resource. When you're looking for information on the web about a scary diagnosis or a term that you don't know and wanting to learn more about it, sometimes there's almost too much information and it's difficult to know who to trust or what information is reputable, what information may not be that strong.

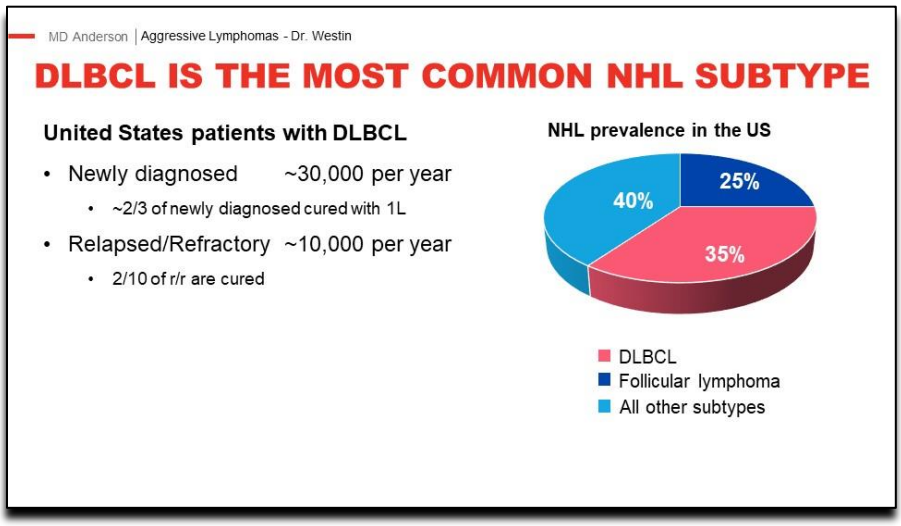
And The LLS is an excellent resource for patients and their loved ones to get more information about what's ongoing as well as to be connected to resources that can be very helpful through a difficult time. So I just wanted to start the talk off today by giving a shout-out to The LLS. Obviously, the people on the call today are already familiar with The LLS, as, because you're on the meeting with them. But just wanted to add my two cents to that, that you're at the right spot.

I also wanted to recognize Stephanie. That's a powerful and incredible story, and really taking a negative and turning it into a positive -- taking your own experience and the experience of likely many of the people on the call here today, or their loved ones, and taking that starting off feeling lost, not knowing how to connect with others, and turning that into an incredible resource, with The Patient Story website already having that many views per month. Kudos to you, Stephanie. That's a great job. So, without further ado, let's dive right in and start talking about aggressive, non-Hodgkin lymphomas.



Aggressive Lymphomas: Agenda

So, we'll go through a number of different topics today. And, briefly, the overview is on the screen here. We will talk about Burkitt lymphoma and mantle cell lymphoma, to a degree. But, most of the slides that I have in the talk today are regarding large B-cell lymphoma, as it's, by far and away, the most common subtype of the aggressive, non-Hodgkin lymphoma.



DLBCL Is the Most Common NHL Subtype

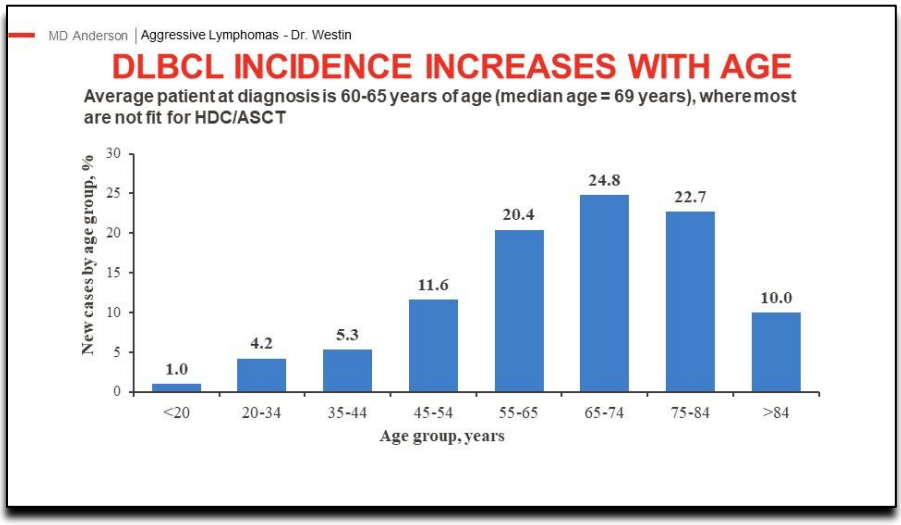
It represents about 30,000 people each year in the United States. And so, when you get that diagnosis, or your loved one gets that diagnosis -- how common is this disease?

Well, 30,000 people each year get that same piece of information and that news. And, thankfully, that number is not growing rapidly. There are changes, over time, where we do see certain cancers become more common or less common. Lymphomas have become a common cancer and are in the top 10 of cancers, which I'll show you in just a moment. But aggressive lymphomas usually represent about one-third or so of all lymphomas; non-Hodgkin lymphoma, in general, is around 80,000 people each year.

And you can see that large B-cell lymphoma makes up a sizeable chunk of that. Follicular lymphoma, a slower-growing lymphoma, is second. And then, all others added up, are equal to around 40%. Two-thirds of patients with large-cell lymphoma are cured with initial treatment, which we'll go through in

more detail. And people with relapsed, refractory disease, which means two-thirds of 30,000 -- 10,000 -- we've got more work to do. And this number has gotten better and, likely, is even improving further than what I have on this slide here.

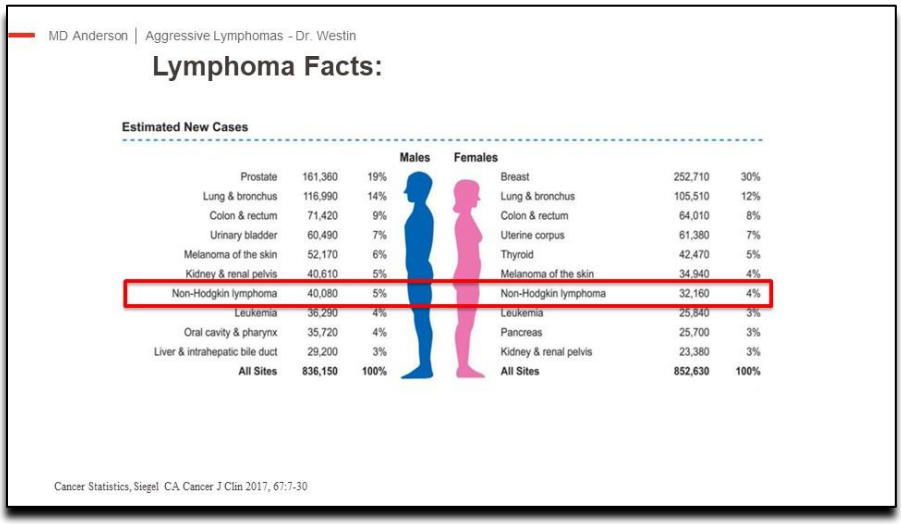
But, clearly, there is a large unmet need for -- if the disease does not go into remission, stay in remission. And, thankfully, there's lots of new treatments that are coming along.



DLBCL Incidence Increases with Age

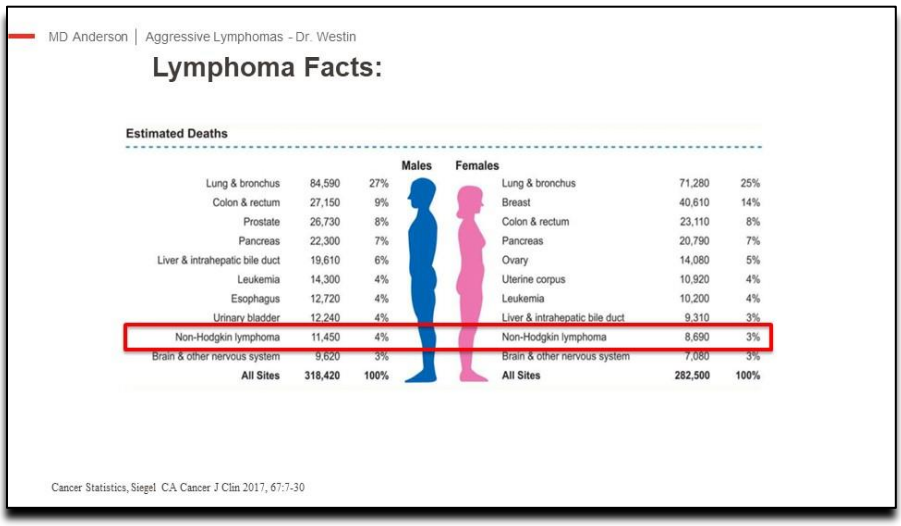
Large B-cell lymphoma is a disease that is primarily seen in patients in their 50s and 60s, but it's a disease with a median age -- it says on the slide here, 69 -- somewhere in the ballpark is correct, somewhere around 65 or so. But, as we heard from Stephanie, there are patients who are quite young that have this disease. There are patients who are the opposite of that, who have this disease.

And that spectrum runs the entire course. But many patients that I see in my clinic are in their 60s. And that is the most common age for this disease.



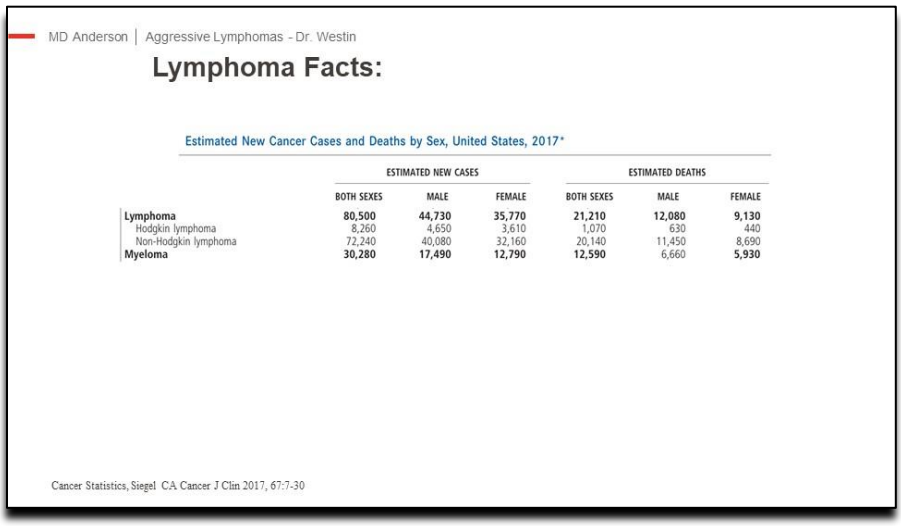
Lymphoma Facts

Looking at the incidence of all cancers, this is, by male and female, broken out. We can see non-Hodgkin lymphoma is in the top 10 for most common cancers, both for men and for women.



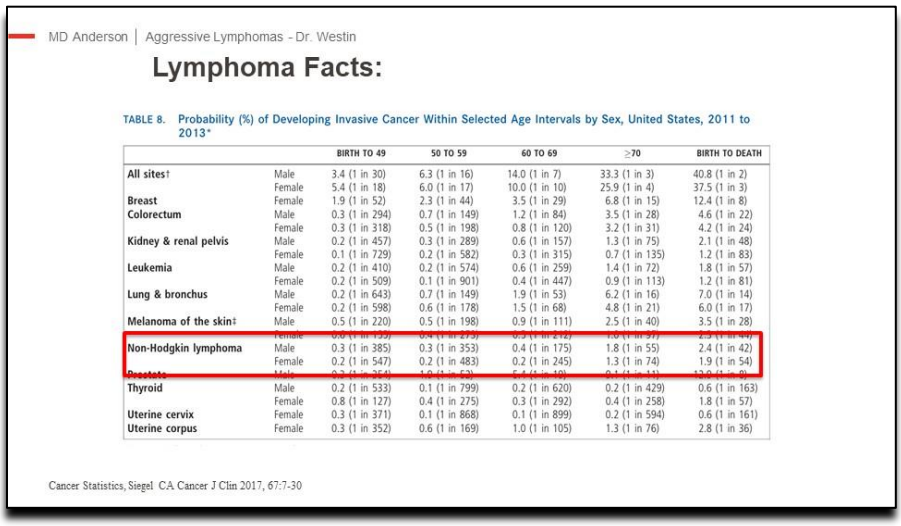
Lymphoma Facts

And in terms of deaths, it's further down the list because we have more effective treatments for lymphomas than do other cancer subtypes. But, clearly, until the number on this slide gets down to zero, we've got more work to do to help our patients and to find more ways to control the disease and go for the cure.



Lymphoma Facts

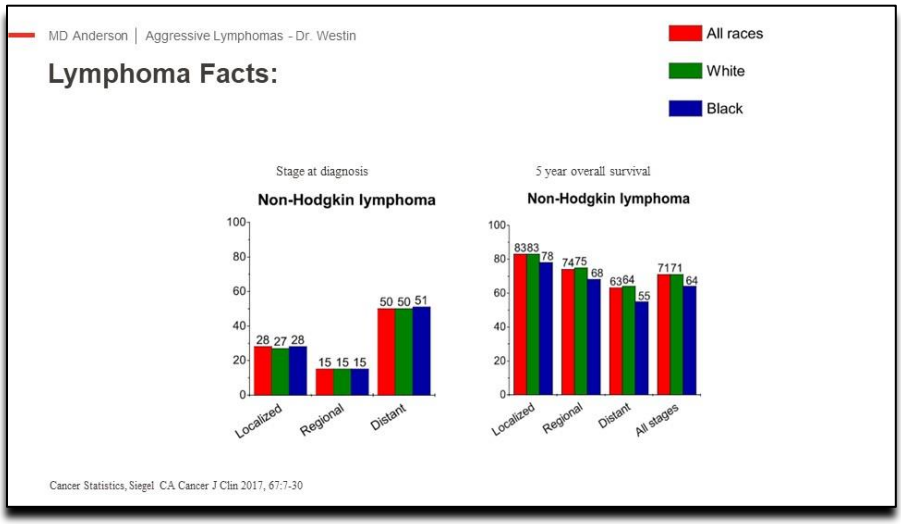
This is a cancer, which as mentioned, is seen in both sexes pretty evenly. This is not a disease that has sort of a predisposition, like a breast cancer or a prostate cancer. This is one that effects both men and women.



Lymphoma Facts

And when we look at, in terms of the incidence per age, from birth to death-- over here, I'll direct your attention, is around 2.4% chance of getting non-Hodgkin lymphoma for men: around 2% chance for women, across their entire lives.

So, say that the other way, there's a 98% chance that people don't develop lymphomas, but 2% chance is not irrelevant. So, this is a disease that is a very common disease in the cancer world and is one that clearly has a lot of work to do to make sure we can help all of those people.

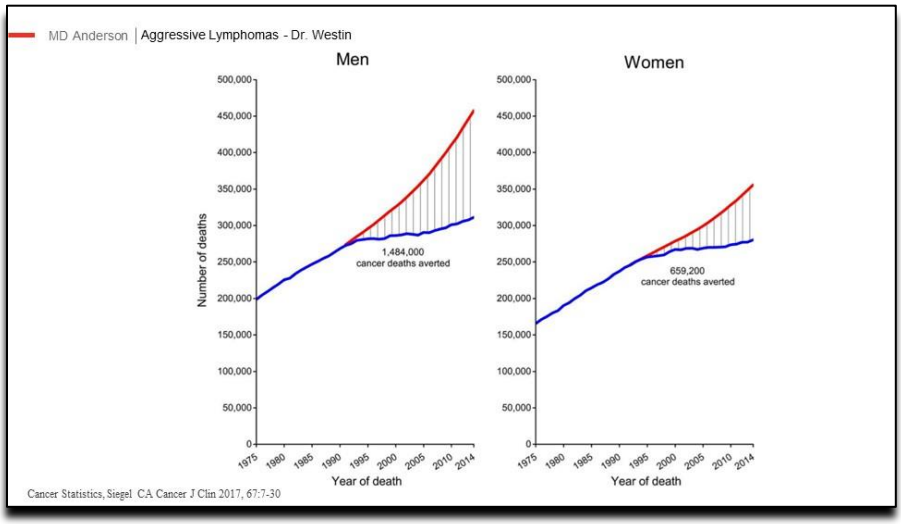


Lymphoma Facts

It's a disease that is often diagnosed at an advanced stage. Distant here, basically meaning that there is more than one site, and the sites can often be far apart.

So, we'll talk very briefly about how we stage this disease. But if your disease shows up and it's in one location, that's not the most common scenario. The most common scenario is having multiple sites of the disease, across the entire spectrum. But thankfully, regardless of the stage, the incidence of having long-term, overall survival is pretty good, across the board. So, it's not like a solid-tumor, like a lung cancer or a colon cancer. If you have metastatic disease, if you have disease that's disseminated into different parts of your body, your cure rate might go from pretty good to pretty terrible. For

lymphomas, the majority of patients are cured, where, like the aggressive lymphomas are cured regardless of their disease stage.



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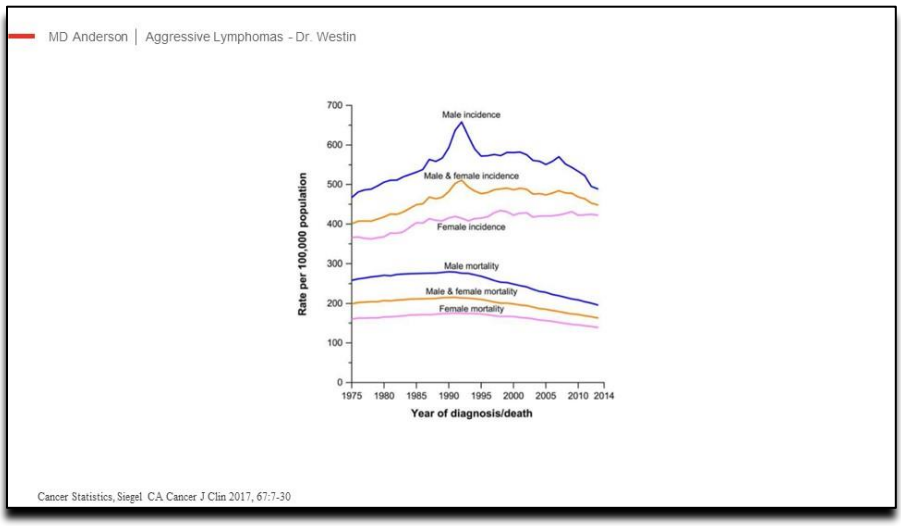
This is a brief plug for clinical research for clinical trials. This is a paper that's published every year. And I have to update this. The last time I had this updated was in 2017. But, the data are the same. Basically, the blue line here is the number of people that died of cancer. This is for men and for women. And the point I wanted to make on here is that the red line is what would have happened if that line continued, unchecked. The blue line, however, represents the reality. And we can see that line changes shape here in the 1990s, which is due to efforts of new therapies coming along from the war on cancer, from all the research that has been done, and new drugs being developed, based on the latest, cutting-edge science.

And we can see there is a huge difference between that line that would have been, versus the line that is, including more than 2 million people that would have died of cancer, that did not, because of clinical research. Clinical trials are often the best weapon against cancer. That's not just true for people that have had multiple therapies. Many times, the first treatment you get, which is often the best chance you have to have a good outcome, a clinical trial can be the best chance at a first treatment, and should always be something that's talked about.

If your doctor doesn't bring up a research or clinical trials, I think it'd be very appropriate to ask them: Should a clinical trial be something we consider? And I think if they don't want to talk about clinical trials, you might want to get a second opinion to seek out more information. Because this is changing how we manage cancers, in general, but specifically aggressive lymphomas.



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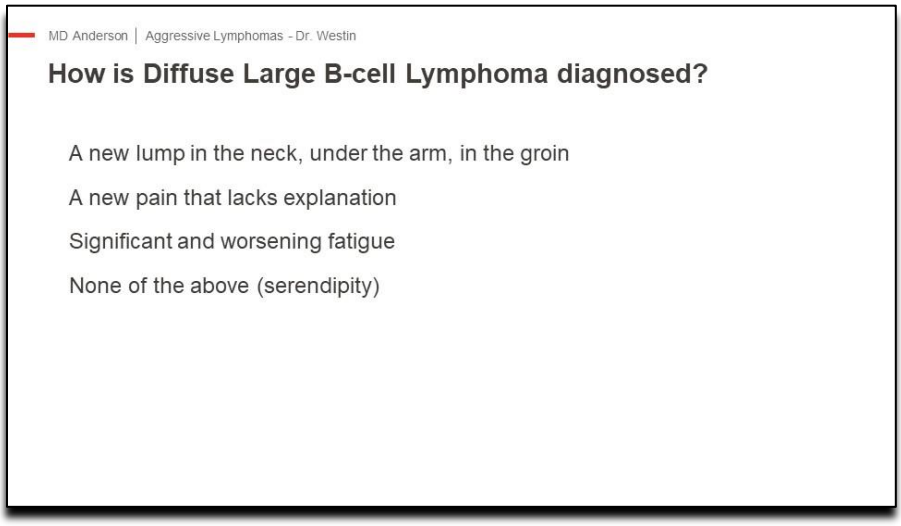
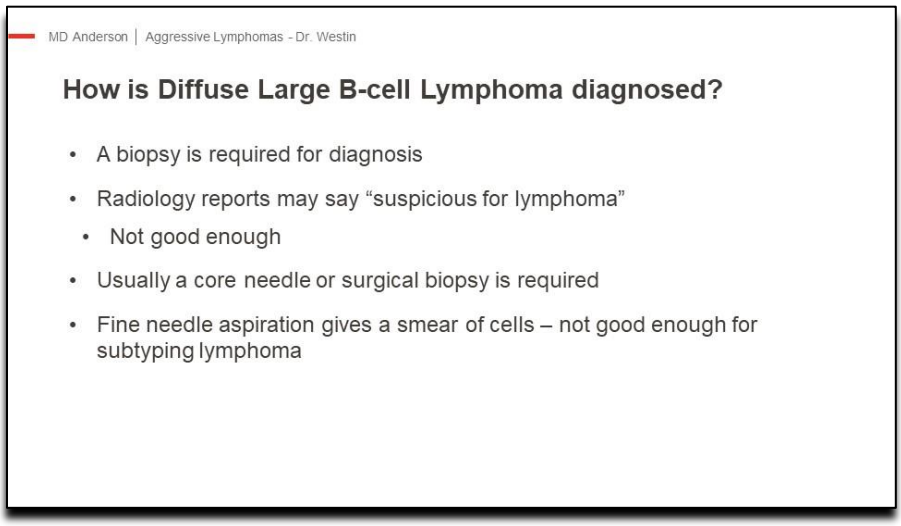
And this is the same thing -- that mortality across all cancers is declining. And that's very true in aggressive lymphomas, due in large part to research.



How Is Diffuse Large B-cell lymphoma Diagnosed?

So, let's go back to specifically talk about diffuse large B-cell lymphoma. We heard the story from Stephanie at the beginning. And the scenarios that I have on the screen here largely match up to what she described-- of having a lump, or a pain, or fatigue; sometimes not having any of the above but having a CT scan done for other reasons or being in a car accident and testing being done. But, usually, patients will tell their doctors that something is wrong. And that will prompt additional workup.



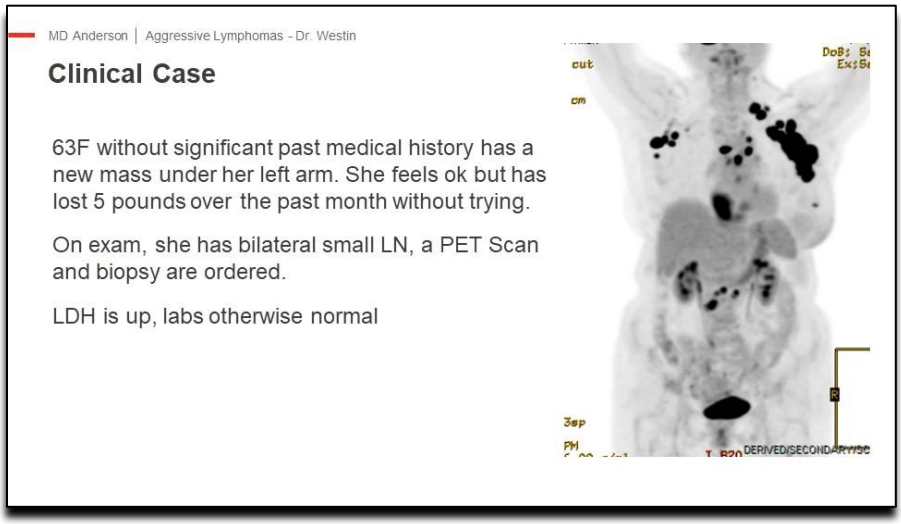
How Is Diffuse Large B-cell lymphoma Diagnosed?

Which will usually lead to the biopsy. Scans may say it's suspicious for lymphoma. That's not good enough. There are a lot of things that can be suspicious for lymphoma that may come back being benign. A biopsy is absolutely essential to make a diagnosis of lymphoma. And the type of biopsy does matter. And this is not so much for the patient to ask for, but just to be aware, if an initial biopsy is done, sometimes a second biopsy might be required.

Many times, if somebody is not sure, if a physician is not sure what's going on, they might ask for a type of biopsy called a fine-needle aspiration. That fine needle basically means a teeny, tiny, little needle. And aspiration means they pull the plunger back and kind of slurp out a slurry of cells.

Lymphomas are often diagnosed looking at the entire, abnormal area of the body. And the architecture of what cells are next to their neighbors, what cells look normal, what cells do not, is really important for the pathology doctors to make the diagnosis.

And so that's why I say a core-needle biopsy or a surgical biopsy are often required to make that diagnosis. So, if the biopsy comes back and the doctor says, we have to get a second biopsy, that's wise. It's really important to get the right biopsy to get the right diagnosis. Everything else comes downstream from getting that biopsy.



Clinical Case

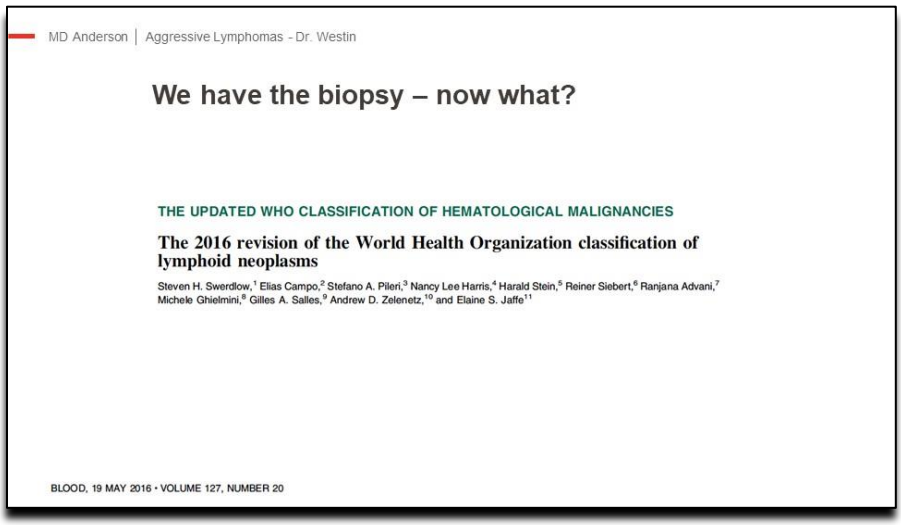
So, let's talk about a clinical case to kind of make this more real and less abstract.

This is a patient of mine who was a 63-year-old female at the time, didn't have any major medical history, but showed up in my clinic after noticing that she'd had a new mass develop under her left arm. She felt okay, but she had lost a little bit of weight, in hindsight, and noted that she really wasn't doing anything different, diet- or exercise-wise. And, yeah, actually, that was kind of weird. She didn't think of it at the time, but when we asked her about it, she noted she had lost a little bit of weight.

She has bilateral, both sides, small lymph nodes. And a PET scan and biopsy are ordered. On a blood test, a test called LDH (or lactate dehydrogenase) is elevated, it's above normal. Otherwise, her labs are within normal limits. And this is what the PET scan showed. So, when you look at a PET scan, this is the view, I like to call the across-the-room view, where you can basically see the patient's arms are up above her head.

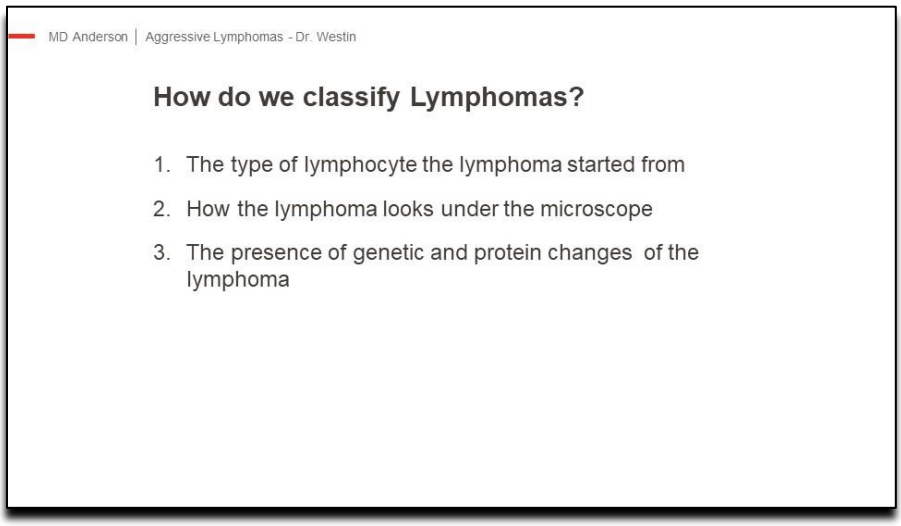
And these dark areas in her chest represent abnormal lymph nodes. We can see her kidneys and her abdomen; they're filtering the contrast out. So those are actually supposed to have the contrast. We can see her bladder, where the contrast is being collected before she gets rid of it into the bathroom. But there are some lymph nodes in the abdomen that look abnormal, as well. So, this patient has advanced-stage disease, having disease both above and below the diaphragm.

If you have lymph nodes that are one side of the diaphragm, the muscle that splits the chest from the abdomen -- so in your neck and under your arm and that's it -- that could be stage II disease. If it's on both sides, that's at least stage III disease. And the way that we look at it, it's kind of either stage I, stage II, or stage III, stage IV, in terms of our prognostic systems. So, having disease on both sides means she'll have at least stage III disease.



We Have the Biopsy – Now What?

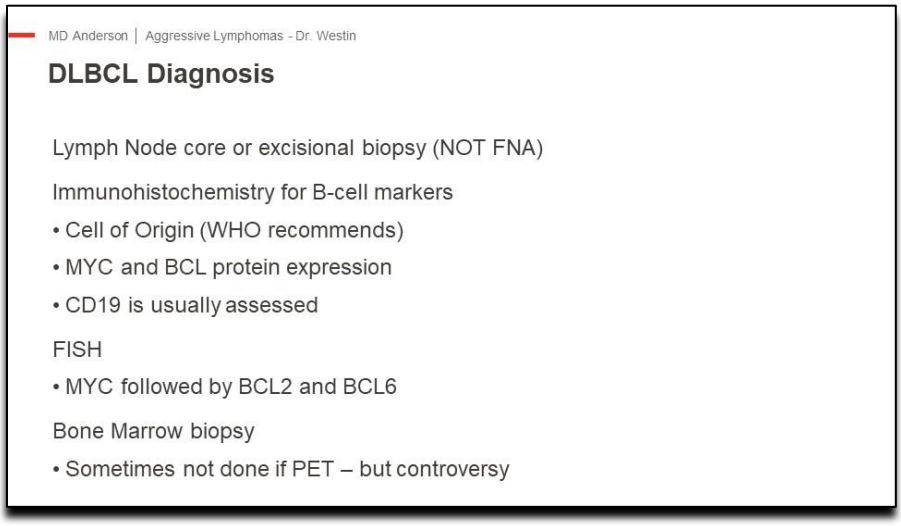
All right, the biopsy comes back and what do we do with those answers?



How Do We Classify Lymphomas?

The type of lymphoma comes from what type of immune cell went wrong. So, when see the pathology report that comes back and says diffuse large B-cell lymphoma, what exactly does that mean? Well, the pathology doctors don't look for a name tag on these cells. They look at what type of immune cell--based upon different proteins that are expressed, different markers that are expressed on the cells, the size of the cells. Large cell lymphoma comes from large cells.

These are all things that can help the pathology doctors make a diagnosis. And often using more modern technology, there can be changes in genetics or in proteins that can be informative for the pathology doctors.



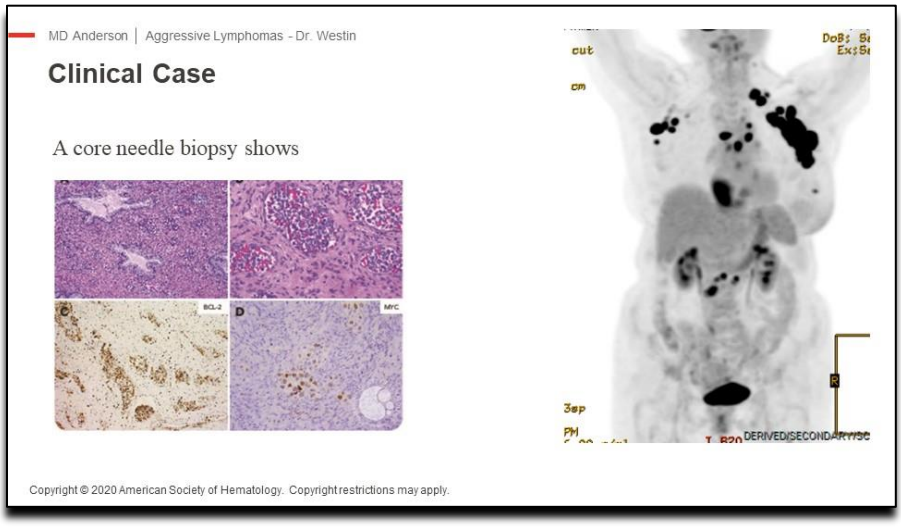
DLBCL Diagnosis

So, there are markers and tests that are usually required of the pathology doctor to look at. And these are not things that the patient needs to ask for, but are often assessed by the pathology doctor, looking for something called the cell of origin. What cell did the cancer originate from? What type of immune cell?

Certain proteins that we can then look for, called MYC, M-Y-C, or BCL2, or BCL6 protein expression; a test called FISH, which does not stand for something you might catch with a worm and a hook but stands for fluorescent in situ hybridization. That's a special, genetic test to see if any

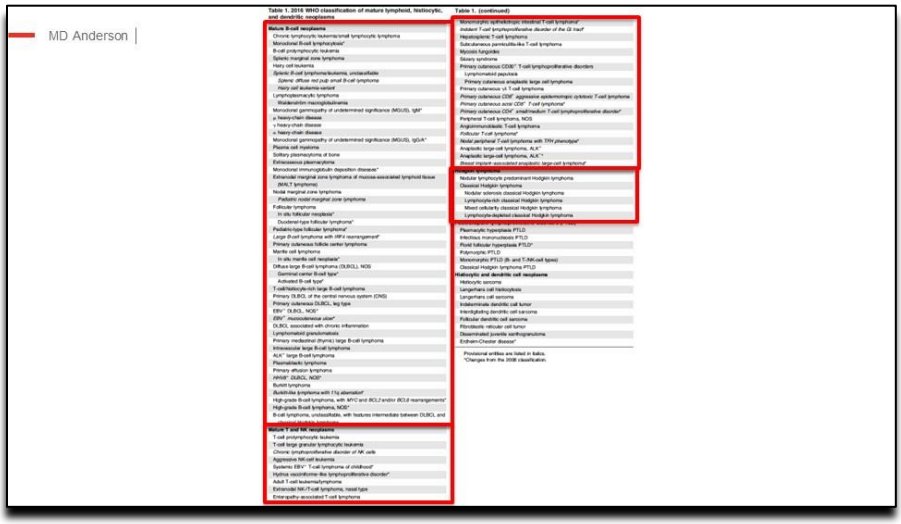
information from chromosome -- and chromosome have swapped places, basically have a genetic abnormality that can occur from a change within the chromosomes that can sometimes cause a gene to be overexpressed.

And then, sometimes, a bone marrow biopsy may be requested. We heard from Stephanie that, in her case, that was done. Sometimes, that may not be done, although that is a bit controversial. And I would refer you to your doctor if they recommend you get one or don't. It depends a little bit upon the PET scan and upon their treatment plan that they're being looked at.



Clinical Case

So, for our patient that I had mentioned, that had lost a little bit of weight and had the lymph nodes under her left arm, her core-needle biopsy comes back showing abnormal B-cells, sheets of large B-cells that do have overexpression of these proteins BCL2 and MYC. I don't need to give you a complete pathology course today but, nonetheless, this kind of what your pathology doctor looks at, to see these abnormal cells and look at different proteins that are expressed.



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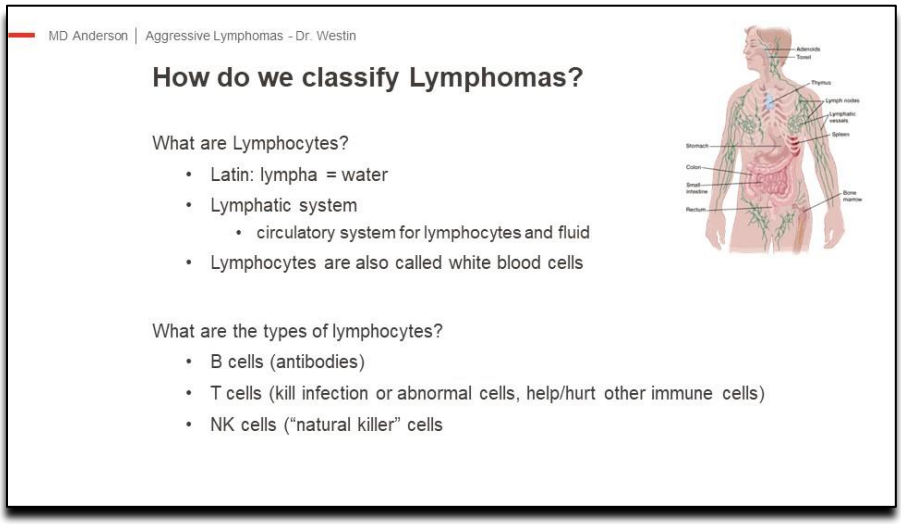
And this is not for us to go through each and every one of these. These are all the different types in the 2016 World Health Organization, WHO, classification system for mature, B-cell lymphomas; mature, T-cell lymphomas. There's a lot of subtypes of non-Hodgkin lymphoma. And so, getting the accurate diagnosis from the pathology doctor -- if they're not sure, if the biopsy comes back suspicious for (or possibly consistent with), getting a second opinion from a pathology doctor or sending those slides out to a different place-- like to MD Anderson or to the Mayo Clinic or to the NIH-- that's something that doctors will often consider to do, to make sure that the right label is put onto the biopsy.

Because treatments are often quite different if you have lymphoma subtype A versus B, I'm not going to go through all these.



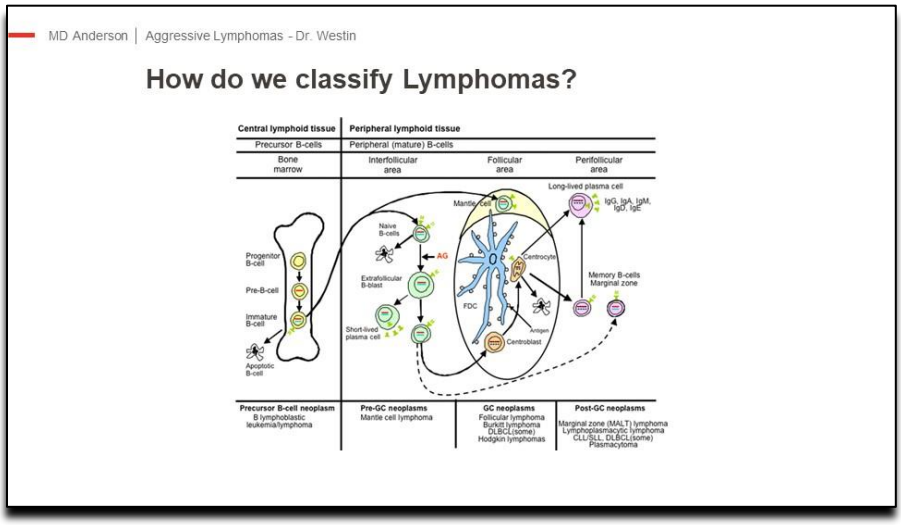
How Do We Classify Lymphomas?

How do we classify lymphomas? Well, first off, where did that term come from -- lymph system or the lymphatic system? Sometimes, people may have heard of that, that their cousin had surgery for breast cancer and had a bunch of lymph nodes removed and now they've got lymphedema in their arm.

The lymphatic system is a type of circulatory system we have in our bodies. We know about the blood circulatory system that has arteries that pump blood out and veins that bring it back in. We actually have another circulatory system called the lymphatic system. And this is where lymphocytes can go out to see if there is any invading bacteria or fungus or virus, and then go back to the lymph nodes to report and call for reinforcements. In Latin, lympha means water. And these lymphatic systems often have a fluid in them that looks like water.

It doesn't have blood. It's got kind of a clear, serous fluid. And lymphocytes are often called white blood cells. They're not called water cells, because that sounds weird. But they're often called white blood cells. And that's the term lymphocytes. If you look at your blood test and see the absolute lymphocyte count, that's a subtype of white blood cells—so B-cells, T-cells, and NK cells (or natural killer cells). Those are different subtypes of lymphocytes.

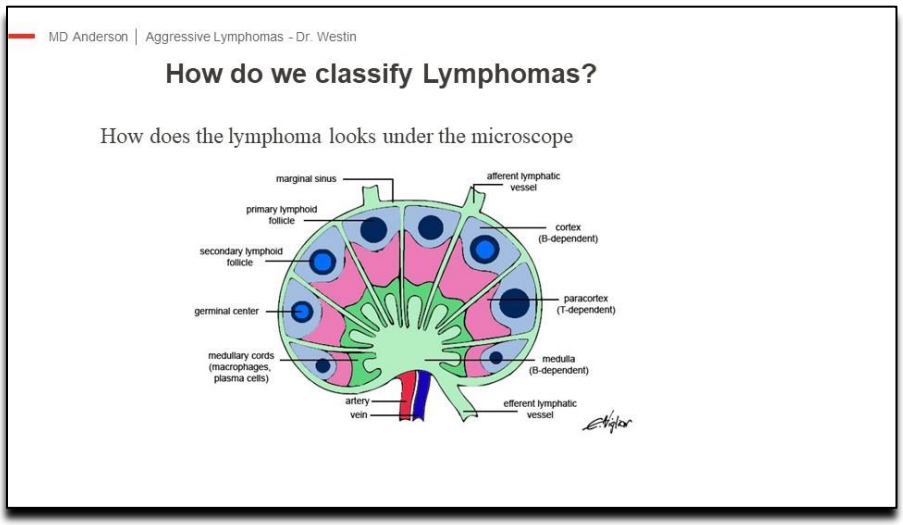
And, obviously, B-cell lymphomas come from the normal, healthy B-cells that make antibodies against infections or against vaccines.



How Do We Classify Lymphomas?

Why do we care about this -- where do these cells come from? Well, the type of immune cell that went wrong -- effectively, which cell in our body turned into cancer and went wrong has a lot to do with what type of lymphoma we get. And, so different stages of maturity, from cells that are coming from the bone and going out into the blood, to other cells that have already gone to a lymph node and seen a protein from an invading bacteria, or invading virus, or some target, and have now left that area of the lymph node to go out into the blood to make antibodies or seek and destroy, these make different types of immune cancers, lymphomas.

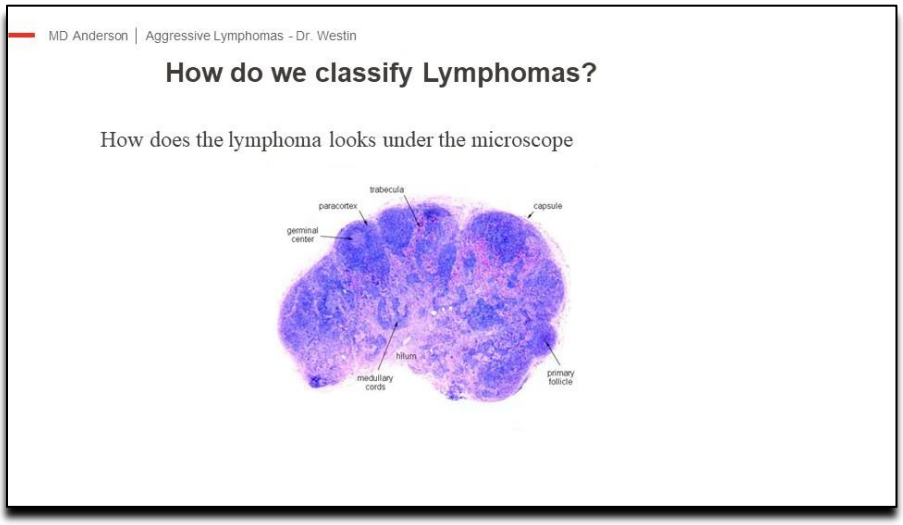
And large-cell lymphoma usually comes from immune cells that have come from either in the lymph nodes or outside the lymph nodes. They're relatively mature immune cells. These are not very immature cells. And many leukemias will be -- most immature cells that come from the bone marrow.



How Do We Classify Lymphomas?

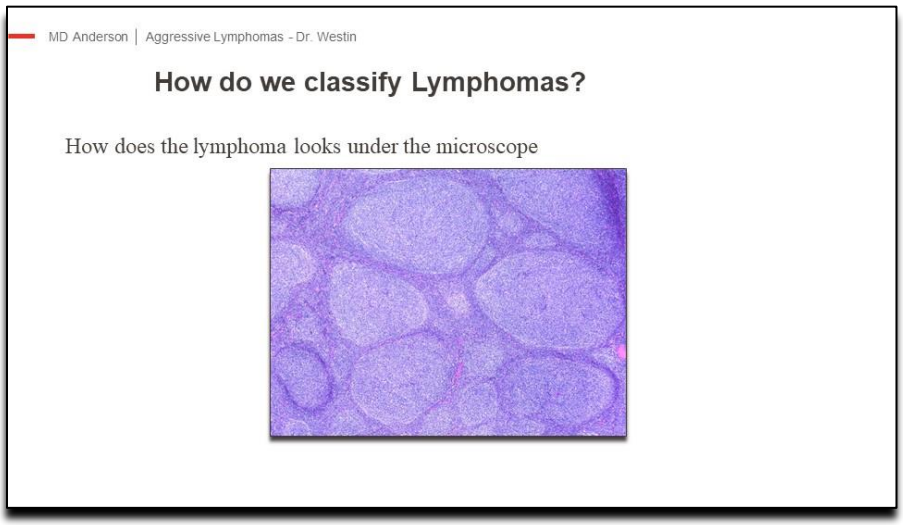
How do we look under the microscope? Well, just as brief primer, because I know some of you may have not heard all this before, but this is what a lymph node looks like. This is a cartoon to show the different types of a lymph node.

As mentioned, there is this circulatory system. In-flow of lymphatic fluid from the circulatory system, as well as blood and arteries and veins, go into a lymph node. And within the lymph node, these immune cells come in, interact with other immune cells, and then go back out into the tissue to effectively look for the target that they were instructed to watch out for. If they had a wanted poster saying, “If you see this type of bacteria, go get them,” they then go back out there and stay on high-alert for whatever target they’re looking for.



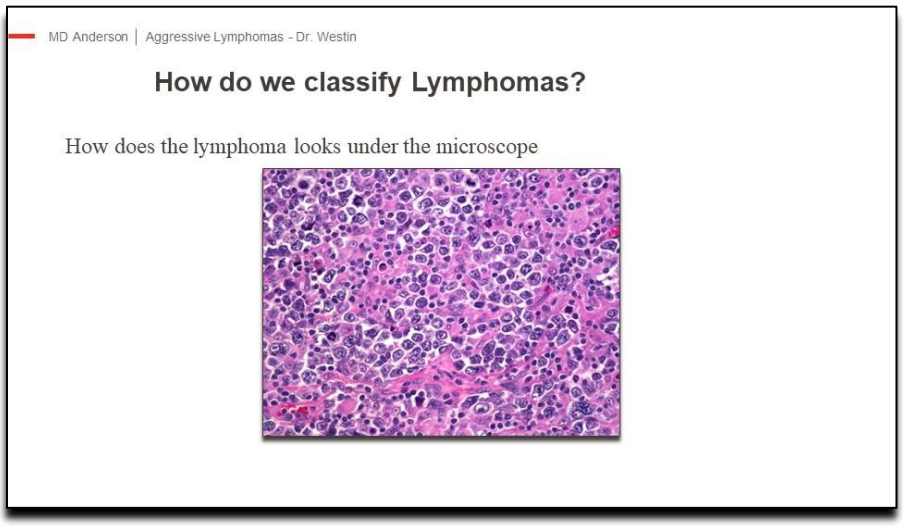
How Do We Classify Lymphomas?

Under the microscope -- this is not a cartoon, this is an actual lymph node that’s cut in half, a healthy one with different types of areas called follicles. Follicular lymphoma comes from the follicles. They also have germinal centers. Some of you might have heard of germinal center subtype of large B-cell or non-germinal center subtype of large B-cell. That’s what it looks like under the microscope.



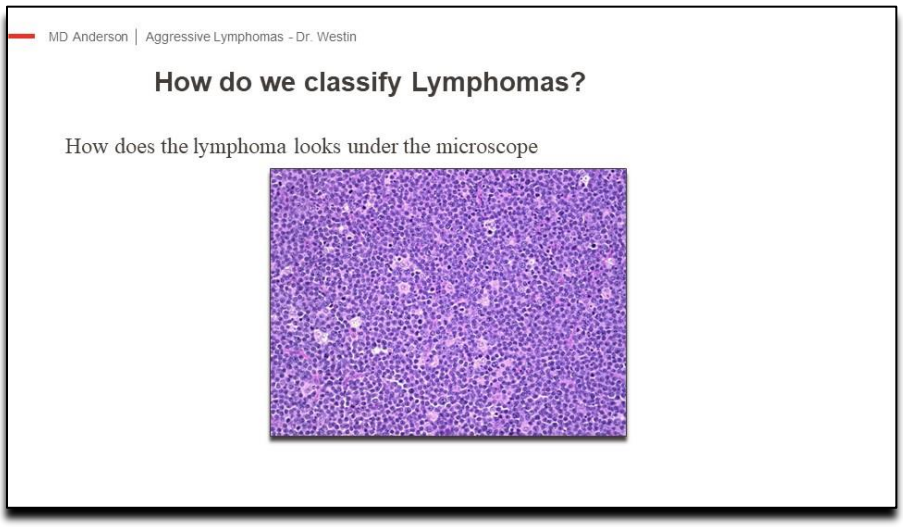
How Do We Classify Lymphomas?

Here's more of a zoomed-in part of a germinal center, with each of these little tiny dots actually being an individual immune cell.



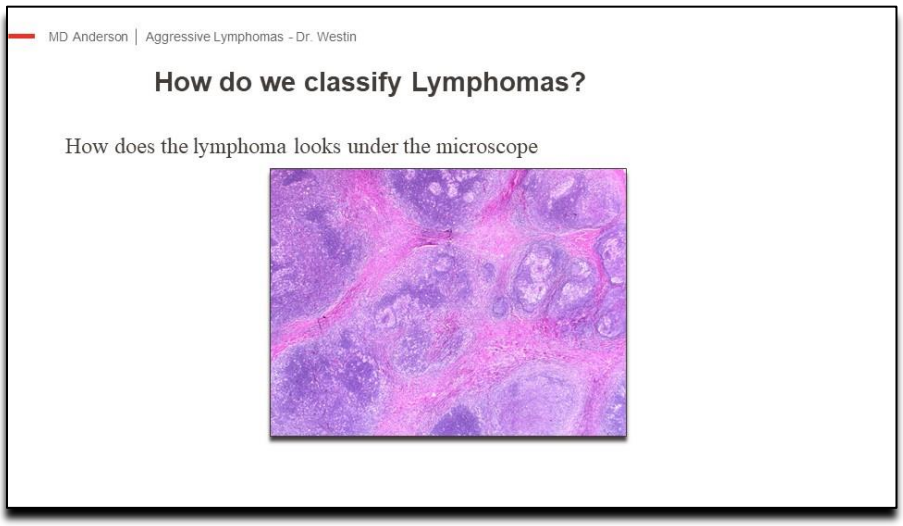
How Do We Classify Lymphomas?

And then, if we zoom way in, we can see some of these cells are larger than others. Some of them represent normal, structural tissue called stroma. Others are actually lymphocytes. And some of these can be actually cancerous lymphocytes on this image here.



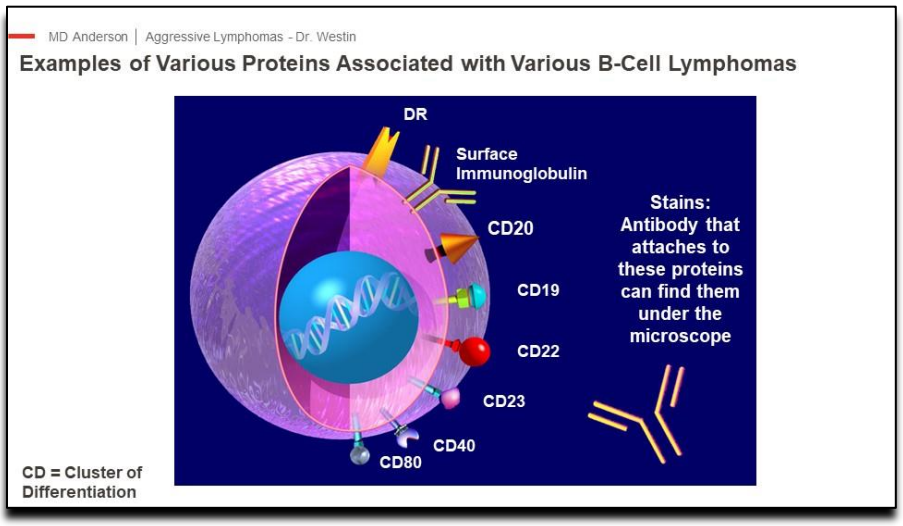
How Do We Classify Lymphomas?

And then, zooming even further, we can see different types of immune cells.



How Do We Classify Lymphomas?

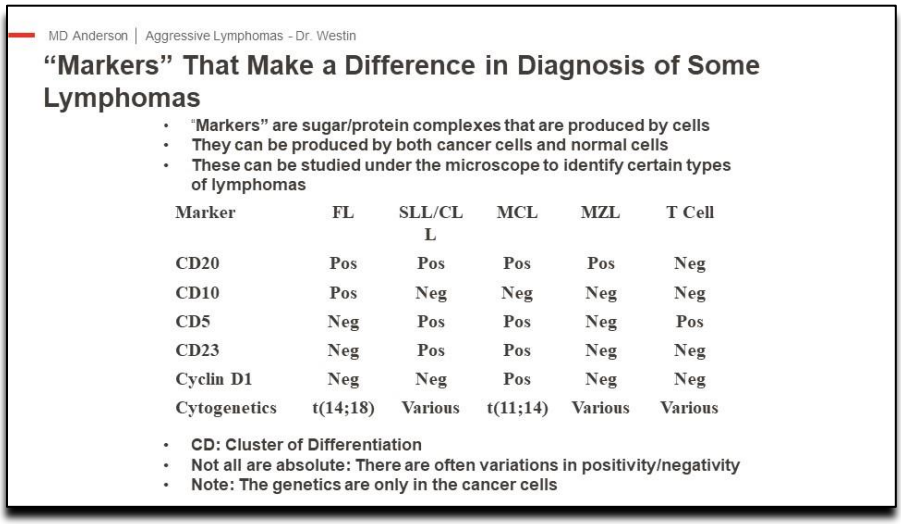
So, there are a lot of things that could be seen under the microscope. And this why you need a talented hematopathologist to review your biopsy, because some of these can be quite tricky. These cells do not have labels on them saying large cell, or follicular, or Burkitt, or mantle cell. There's a lot of art to this, as well as science, to make a classification.



Examples of Various Proteins Associated with Various B-Cell Lymphomas

One of the parts of the science of it, though, is protein expression on the outside.

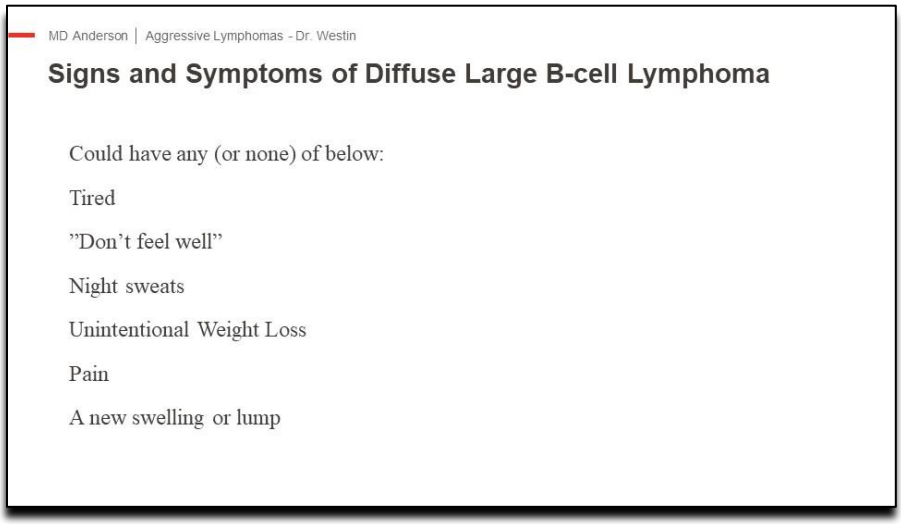
And, so, we've heard of drugs like rituximab (Rituxan®). We've heard of therapies like CAR T-cell therapy. Rituximab targets the CD20. And it's not shaped like a little cone on the outside. This is just kind of a cute figure that was made. But, it targets a protein on the outside called CD20. CAR T-cells target CD19. Other therapies target different things. That's what those terms mean, it's basically a little marker on the outside that the pathology doctors can stain with an antibody that's labeled with a color. And when they look under the microscope -- if I go back one slide -- it would look like a different color than its neighbors. And you can basically check to see if these cells in question express the protein of interest by checking for these markers.



"Markers" That Make a Difference in Diagnosis of Some Lymphomas

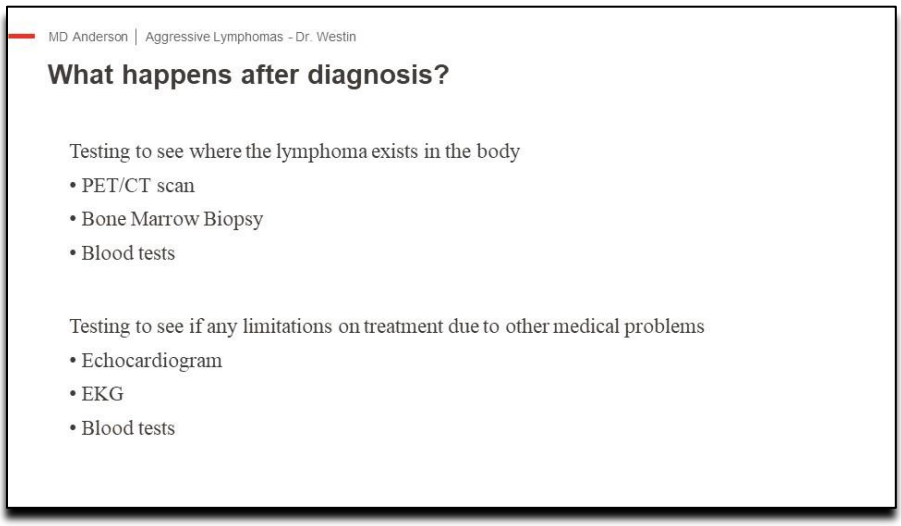
Okay, let's keep moving on to finish out the part on pathology here. This is an example of different types of lymphoma having different markers that are expressed. And the pathology doctors have lots and lots more things they look at.

But, just as an example -- it's almost like a puzzle, but you see, okay, my slide in front of me, from this patient has this, this, this marker expressed; does not have that one, does not have that one. How does that match up with the table? That helps the pathology doctors to make the diagnosis, in addition to what it looks like with their eyes.



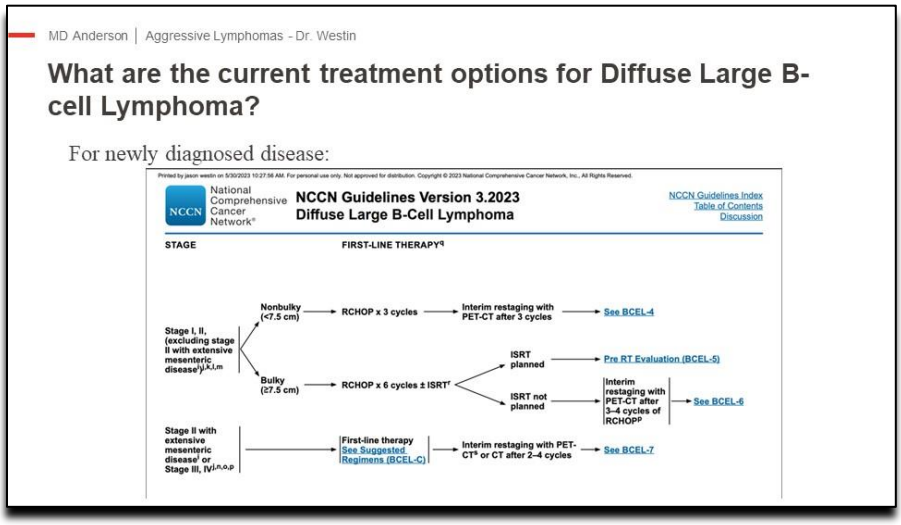
Signs and Symptoms of Diffuse Large B-cell Lymphoma

So patients, as mentioned, will show up with some complaints. Some of these could be complaints related to lymphoma. These are all pretty non-descript. Biopsy is the way we make the diagnosis, not just because of the symptoms.



What Happens after Diagnosis?

I think we already went over some of this; but, a PET-CT scan, the image I showed you is really important because sometimes we can have lymph nodes that are enlarged. Other times, we can have non-lymph node sites, like bone or liver or spleen, that may not change in size but are really important to see if there is uptake of that nuclear medicine contrast to see if that's something that could be useful, and for your doctor knowing the full extent of your disease.

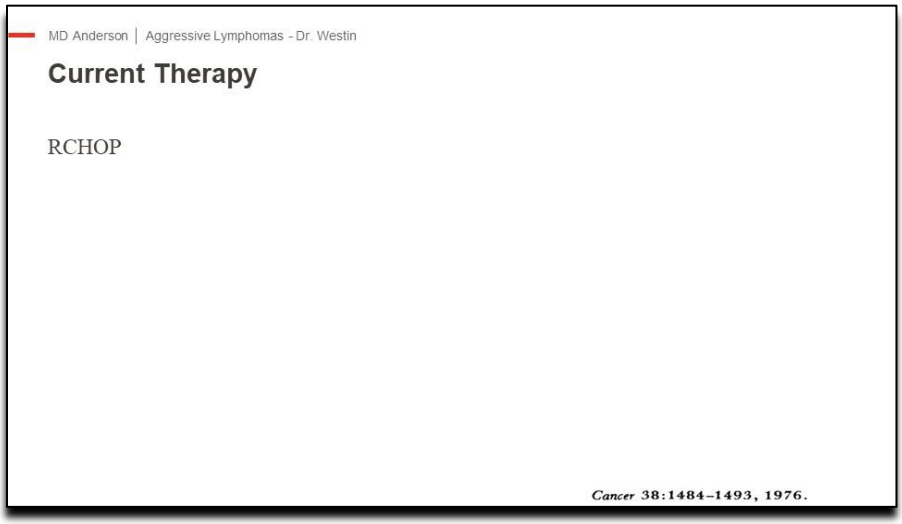


What Are the Current Treatment Options for Diffuse Large B-cell Lymphoma?

So now that we've got the diagnosis of aggressive lymphoma, what do we do with it? Now that we've got the report in hand, saying this is what the biopsy shows, how do we manage that disease? There is a publicly available database called the National Comprehensive Cancer Network that works with experts to effectively come up with treatment recommendations based upon the best evidence possible. So, I mentioned at the beginning, LLS -- thumbs up, great resource.

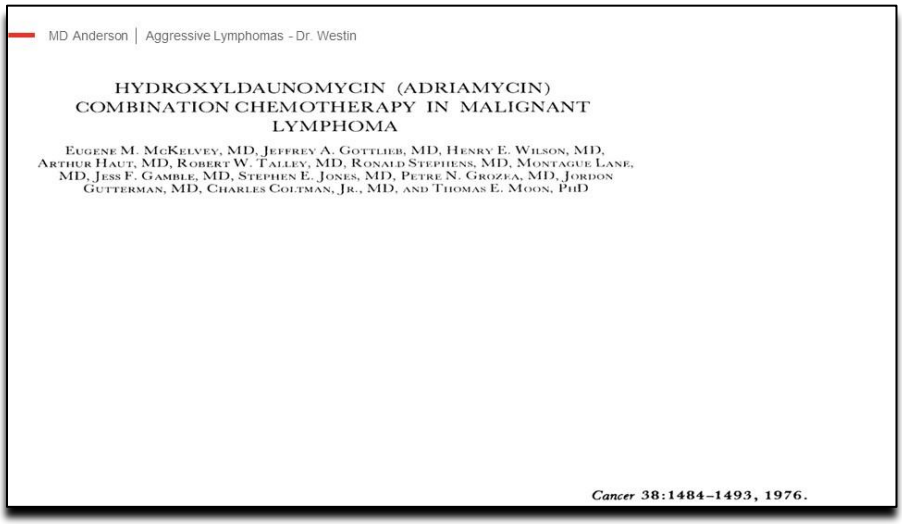
This is another one that you can, if you're interested, can go and see what algorithms are out there for treating different diseases. And this is the most recent update for the guidelines for diffuse large B-cell lymphoma. This is broken out by stage. So, a patient with diffuse large B-cell lymphoma, if the disease is localized, stage I or stage II, there is a question about if there is any bulk to the disease. If the disease is larger than 7.5 centimeters in one direction, that would be considered bulky. And if so, consideration of radiation.

If not, sometimes a shorter course of chemotherapy could be considered. The standard chemotherapy, some of you may have already gone through this treatment, would be a treatment called R-CHOP, C-H-O-P, each letter representing a different drug.



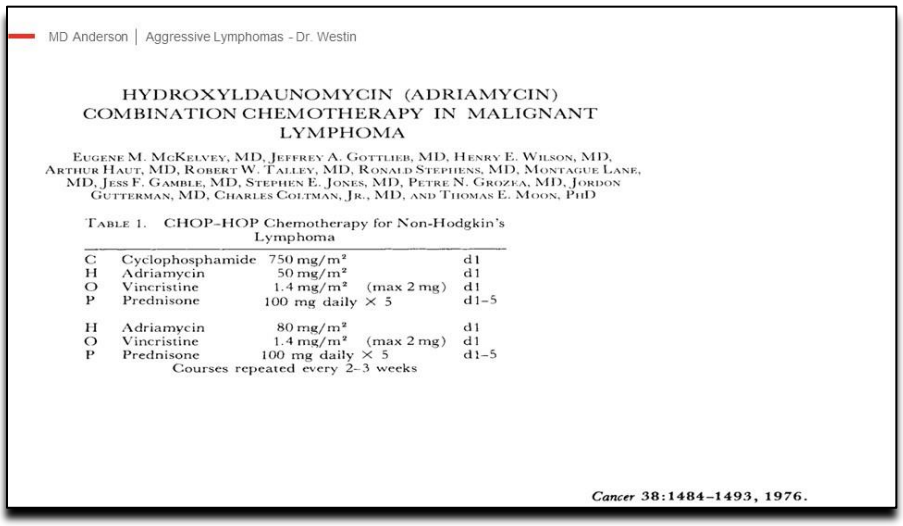
What Are the Current Treatment Options for Diffuse Large B-cell Lymphoma?

So, let's talk about R-CHOP. Where do we get the therapy R-CHOP? R-CHOP -- each letter represents a different drug. But it's been around for quite a while. And the bottom of my slide here shows what journal this is from. That's 1976, the year.



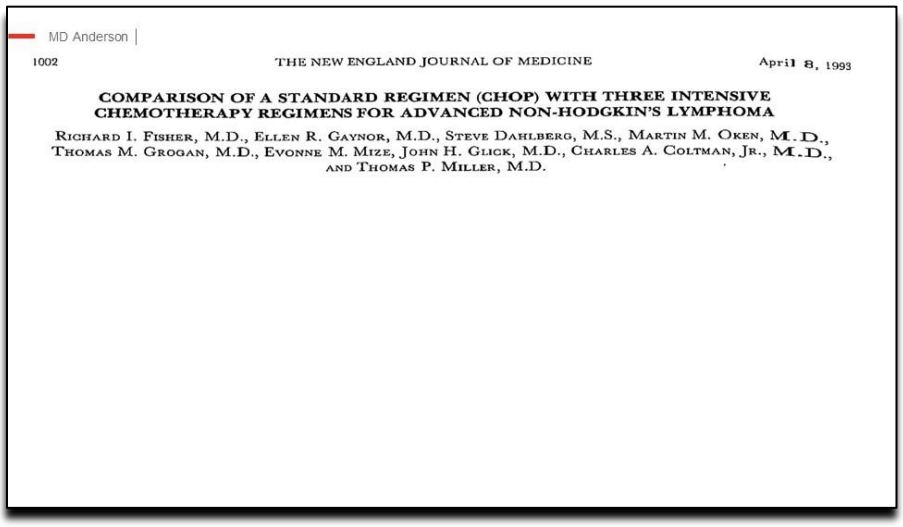
What Are the Current Treatment Options for Diffuse Large B-cell Lymphoma?

That this paper was actually published. This is not a mistake. This is not a typo. Do not adjust your speakers at home. This is actually where the therapy CHOP came from 1976. Two doctors from MD Anderson were the lead authors here. And at the term hydroxyldaunomycin, this is the drug now known as doxorubicin (Adriamycin®)-- the Red Devil sometimes not so affectionately referred to.



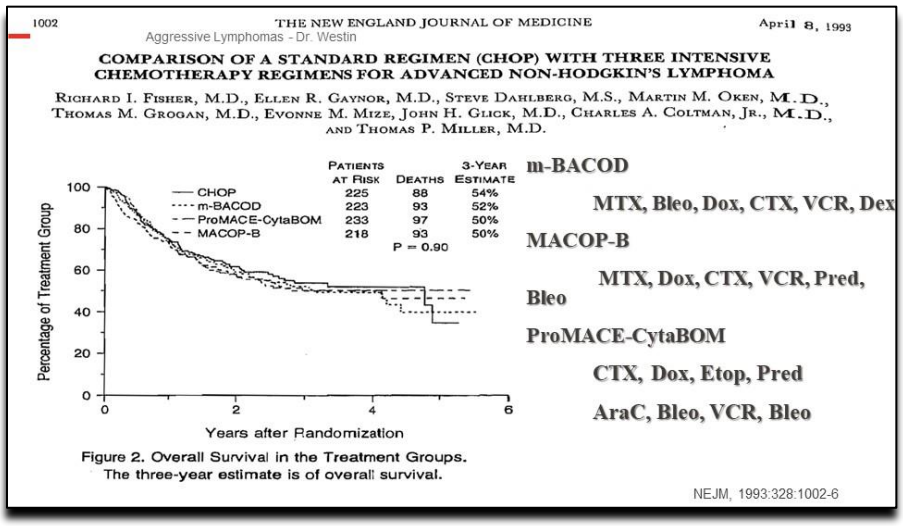
What Are the Current Treatment Options for Diffuse Large B-cell Lymphoma?

This treatment, CHOP, was described in the doses we still use today in the clinic. So in 1976, this was first described. And Rituxan® (rituximab) was added about 20 years later -- a little bit more than 20 years later. So this therapy has been around for quite a while.



Journal

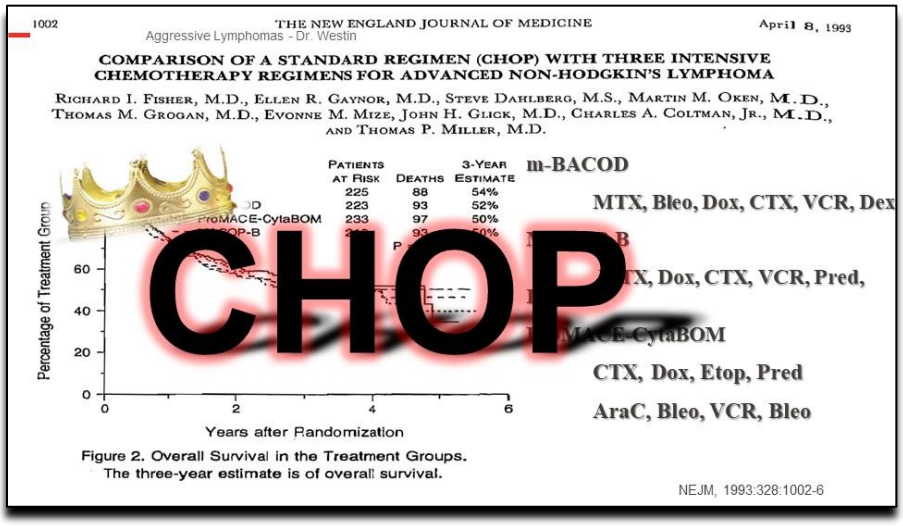
Obviously, we've tried to improve upon that many times. Here is a very large, randomized, phase III study conducted and published in *The New England Journal* in 1993.



Journal

Looking at four different versions of CHOP, different chemotherapy drugs that were studied. And effectively, the take-home point was they were all about equally good.

But, there were a few -- fewer patients who had died receiving the CHOP regimen. And so CHOP continued on as the standard. I wish I could say CHOP was, by far and away, superior. It was not. But it was also less toxic than these other regimens. And back in the 1990s, we didn't have very effective anti-nausea medications. And so this was something that was quite important, of looking at toxicities. Clearly, that's a key part of a patient's journey, of how do they feel on the treatments.



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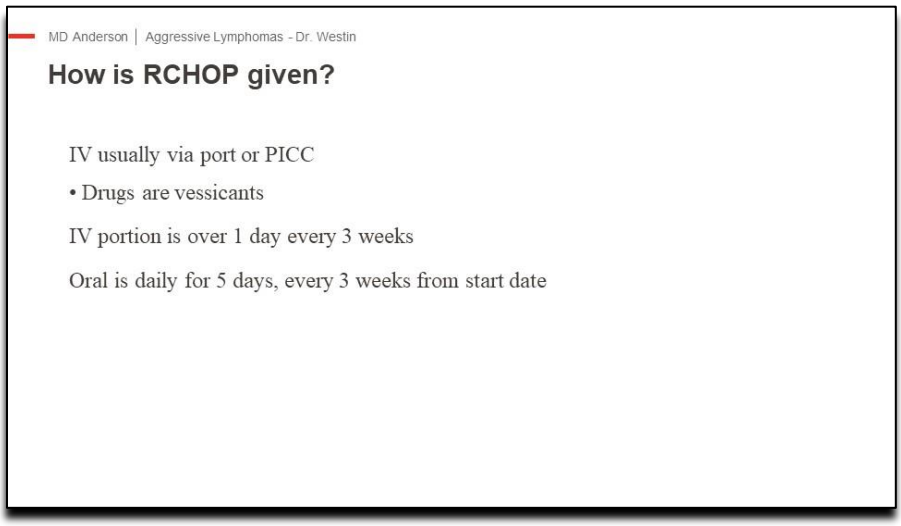
CHOP was deemed to be the king because it was about as good, but not quite as bad, as some of the other therapies. It worked fairly well but didn't have as many side effects. And it still is given today.

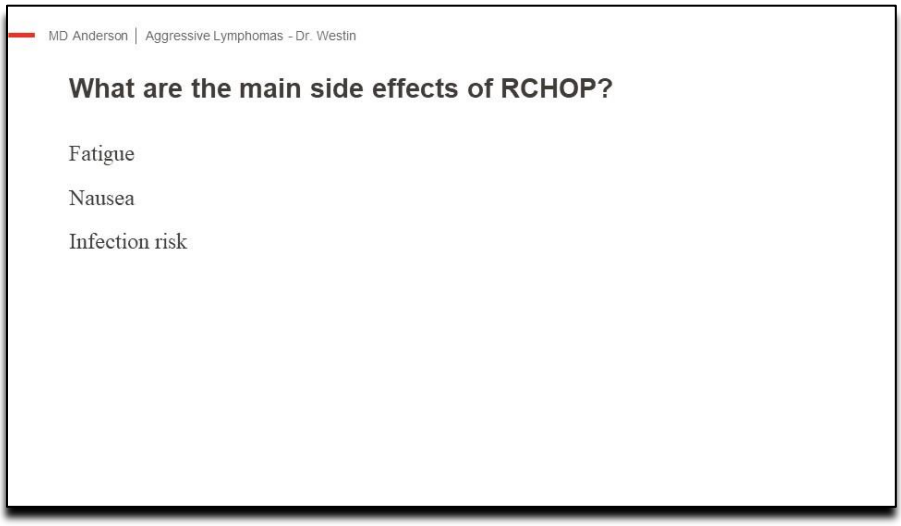


How Is RCHOP Given?

I'll talk about our new option on the scene in the past few months; but CHOP, by and large, is the standard for many of our patients.

How is it given? It's given through an IV. All the letters, except for P, are IV medications. P stands for prednisone. The other ones are all IV medications. Usually, we recommend this be given by some type of large IV, either a port-a-cath or a PICC. PICC stands for peripherally inserted central catheter. The reason for that is these drugs are bad drugs. That's kind of a no-brainer. But they can be bad not just for side effects. They could also cause a chemical burn in your skin if the IV -- a small, little IV in the back of your hand-- were to leak.

Those chemicals are not ones you want to have, in a concentrated fashion, in one part of your body. We want them to disseminate out to the entire body. And so having a good, reliable IV, like a port-a-cath or a PICC line is often very important. Usually, chemotherapy like R-CHOP is given through the IV once every three weeks. And the prednisone part, the P, is given by mouth every five days, also every three weeks.



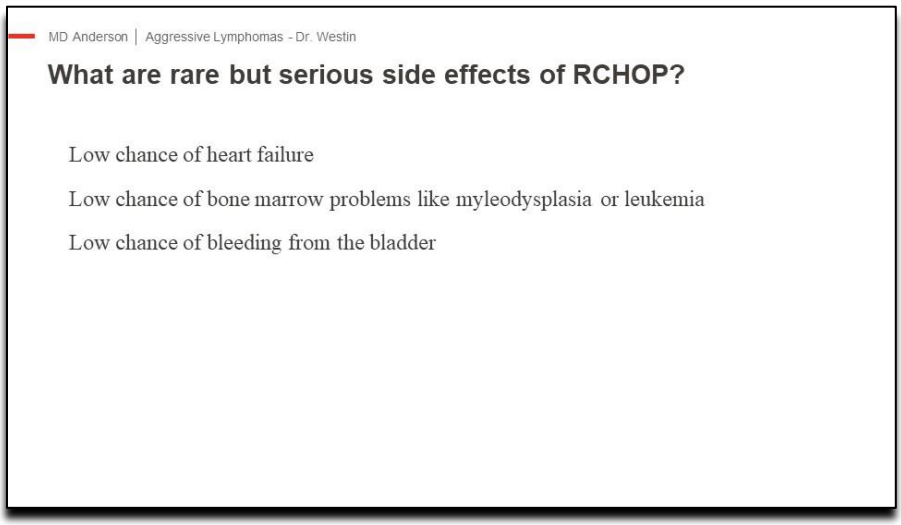
What Are the Main Side Effects of R-CHOP?

The main side effects-- for those that have gone through R-CHOP, you could speak to this more than I can-- but the main thing my patients tell me about, are feeling tired, usually not when they're on the

prednisone but after the prednisone wears off, for about a week. There's a pretty good fatigue that can set in; nausea, although the anti-nausea medications we give are often quite effective to control the nausea; and risk of infection.

This is an issue when your blood counts are decreased from chemotherapy. You're more vulnerable to pick up infections. And there's a type of infection called neutropenic fever. Neutrophils are the blood cells that are most important to fight against bacteria. If neutrophils are low, it's called neutropenia; hence, the term neutropenic fever is having a fever with low blood counts. If you get a fever and you're on R-CHOP, that is a trip to the ER. Do not pass go, do not collect $200. Go straight to the ER.

It doesn't matter if you feel great or if you're going to go see your doctor in clinic in two days. That could be an emergency. And so it's best to get that checked out and go to the ER so they can draw labs to see what your white blood cell count is and potentially start antibiotics. Sometimes, that's a couple days in the hospital to make sure there's not a serious infection. Thankfully, neutropenic fever is relatively rare. Maybe one out of five people who are getting R-CHOP will experience that toxicity. So, say it the other way, four out of five don't. But if it happens to you or to your loved one, don't take Tylenol® (acetaminophen) and try and sleep on it and tough it out. That could let the infection get worse, if there is an infection.

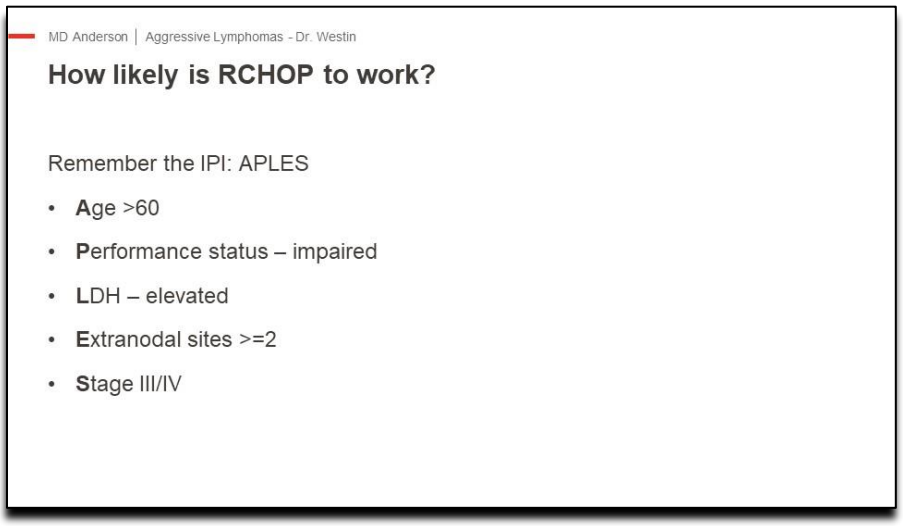


What Are Rare but Serious Side Effects of R-CHOP?

What about rare or serious side effects? There is a very low chance, but not zero chance, of developing heart failure. Often, this is years after the CHOP has completed, which means that you're doing well enough to be around to have that problem occur. But, nonetheless, it could occur.

This is often why an echocardiogram, or a heart test is done, prior to starting the R-CHOP therapy. I'd say this is around 1% or lower, and it's due to the red Red drug that I mentioned before, doxorubicin, that's usually the culprit. But clearly, that is a rare occurrence for a drug that has been a staple for 40-plus years to fight this disease. Same low chance of 1% or less of bone marrow problems, like myelodysplasia or leukemia. This is five to seven years after chemotherapy.

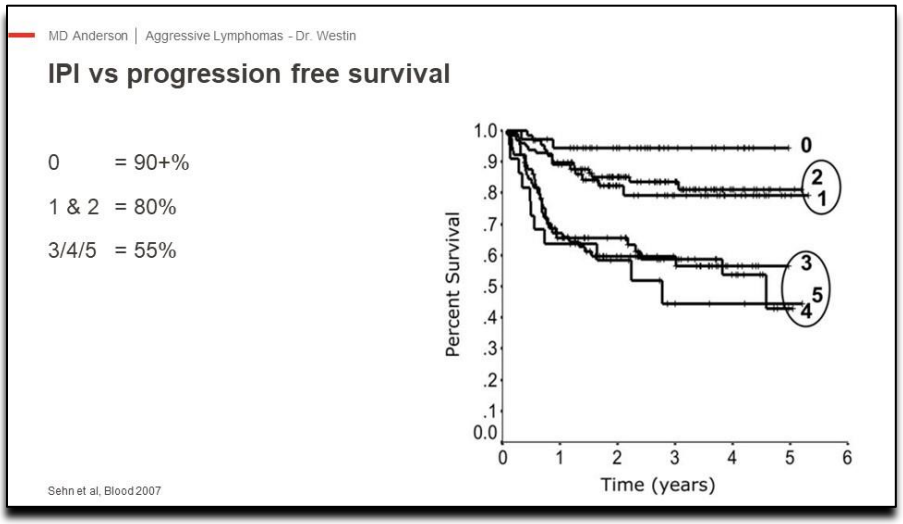
Patients could have blood counts that begin to drop for no good reason -- anemia, low platelets, low white blood cells, and a bone marrow [biopsy] should be done to evaluate if there is something serious going on. And then, lastly, the drug Cytoxan® (cyclophosphamide), the C drug in CHOP, rarely could cause irritation of the bladder. So if someone was receiving the CHOP-based chemotherapy and noticed, when they went to the bathroom there was some blood in the toilet when they urinated, they should tell their doctor that right away. That could be a side effect of the chemotherapy. That's also quite rare.



How Likely Is R-CHOP to Work?

How likely is R-CHOP to work? There is a mnemonic that doctors will use called APLES. A mnemonic is kind of a rhetorical device that helps you remember things. -- APLES -- and it's spelled wrong. There's only one P. But, nonetheless, this is for a prognostic system called the IPI, International Prognostic Index.

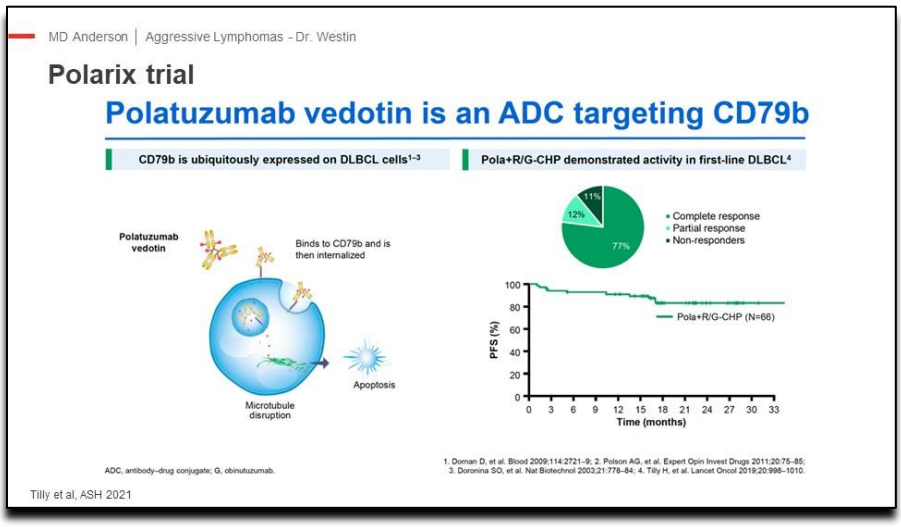
Age 60 or greater, performance status, normal or abnormal, or, I should say, abnormal or normal. So basically, the conditions that are on the screen here, give you a point. And points are bad. We don't want to have points on this prognostic system. So the adverse features on here: if your age is above 60; if you have an inability to do your normal activity, if you're bedbound or you're significantly knocked down by the cancer, you've got a poor performance status; if your LDH is elevated -- that blood test I mentioned from the case of my patient; if you have two or more sites of disease that are not lymph nodes -- extranodal sites; and if you have advanced-stage disease.
Each one of these independently counts as a point.



IPI vs Progression free Survival

And so, what does that mean for our patients? Well, if we have zero points on this scale, we have an excellent chance of being treated with a treatment like R-CHOP therapy, an excellent chance of having long-term survival. If we have all of those five points, we still have a pretty good chance, but it's closer

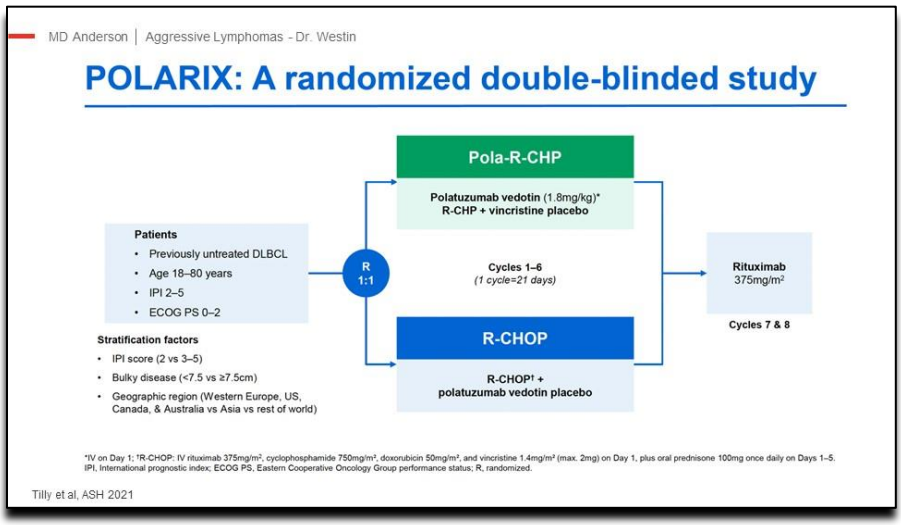
to 50 to 60% with that. So these are kind of useful tools that the doctors will often consider when thinking about what treatment to give for their patient, thinking if this something we have high confidence, we've got it. Or, perhaps, if having less confidence, a clinical trial might be preferred than standard treatments.



Polarix Trial

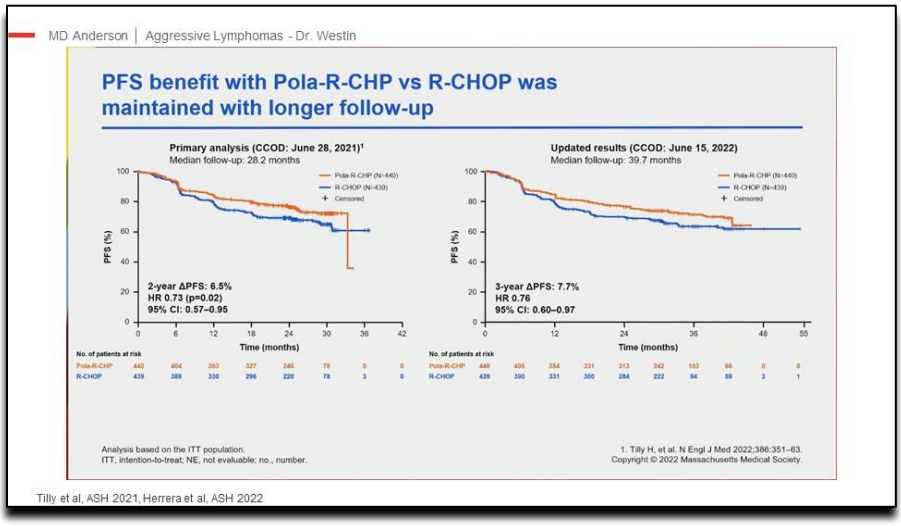
Now, I mentioned there is a new kid on the block. For those that watch the news and pay attention to large B-cell lymphoma developments, just in the past couple of months, this drug, polatuzumab vedotin (Polivy®), was recently approved for patients with newly diagnosed, diffuse large B-cell lymphoma, based upon the trial I'm going to show you in a moment.

I want to show you this slide because polatuzumab vedotin is an antibody. It has chemotherapy tacked on the back-end of it. It's an antibody that targets a protein like CD19 or CD20, we talked about earlier, targeting CD79b. CD79b is a very common protein on the outside of B cells, including large B-cell lymphoma. And when it binds to the surface, the cell says something is going on, and it pulls that in and, basically, takes the chemotherapy inside the cancer cell -- thank you very much -- and the cancer cell is killed by that process.



Polarix: A Randomized Double-Blinded Study

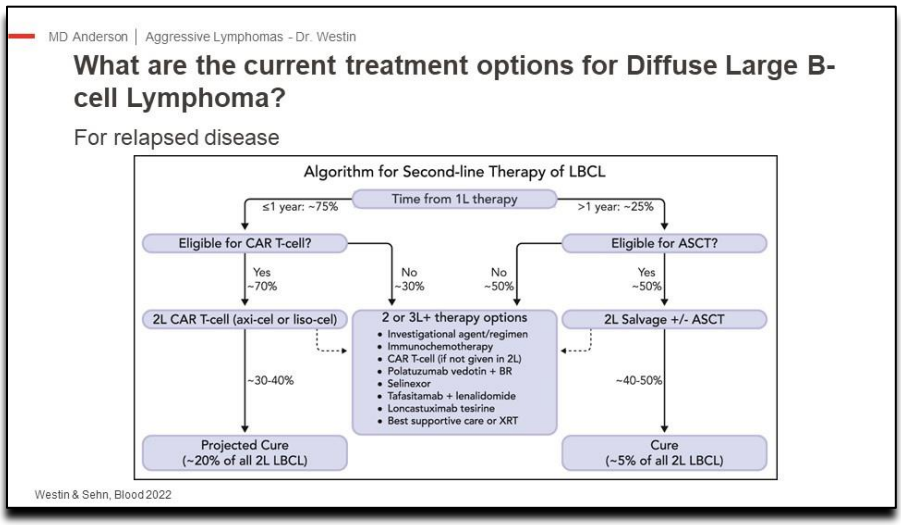
A clinical trial, called the Polarix trial, was conducted, targeting adults with large B-cell lymphoma who had an IPI score -- we just talked about the APLES, five-point score -- patients with two to five points on that scale. And patients were randomized to receive R-CHOP or pola-R-CHP, basically taking the O drug, vincristine (Oncovin®), out of R-CHOP and replacing it with polatuzumab. And these patients were randomized to receive one or the other.



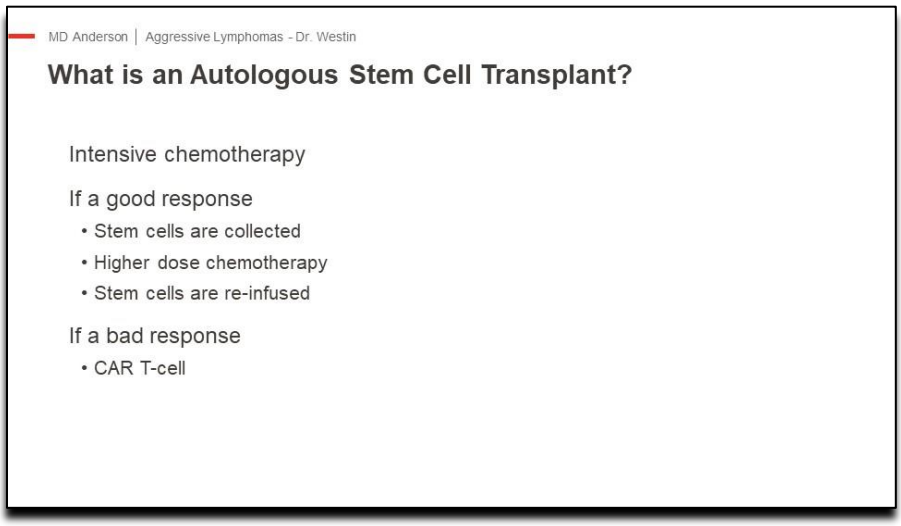
PSF Benefit Pola-R-CHP vs R-CHOP was Maintained with Longer Follow-Up

And the results -- in the orange curve, shown in the higher, orange curve versus the lower, blue curve -- on the left-hand side is the initial difference, showing a statistically significant improvement in what's called progression-free survival, not having cancer progress or grow. And then, an updated result from last summer, showing that this was further evidence of more time, showed that the benefit continued, long-term.

So based upon this improvement at three years of nearly 8% difference between R-CHOP versus pola-R-CHP, the FDA approved this for therapy for patients with an IPI of two to five, as a potential option for standard of care. So that is something, that basically, concludes the part about newly diagnosed, large B-cell lymphoma. R-CHOP, pola-R-CHP -- I'm not going to go today into a controversial subject about dose-adjusted R-EPOCH. But that is something used for more aggressive lymphomas, like Burkitt lymphoma or high-grade lymphoma, with translocations, such as double hit.



What Are the Current Treatment Options for Diffuse Large B-cell Lymphoma?



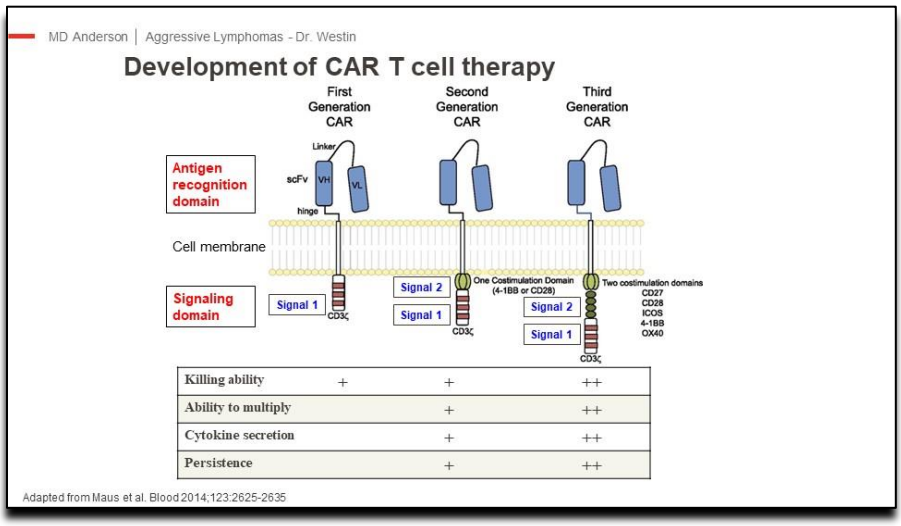
What Is an Autologous Stem Cell Transplant?

What I will talk about instead is what do we do in second-line therapy? Well, for patients that have R-CHOP or pola-R-CHP or dose-adjusted EPOCH and the cancer comes back, here's what we can see as an algorithm for an option to treat. In the past, we used to talk about if the patient was fit for autostem cell transplant, yes or no. And the dogma was that about half the patients were eligible for that, half were not.

We have now some new developments hot off the presses, which say that is no longer the paradigm. This is a brand-new paradigm that Dr. Laurie Sehn and I proposed last year, where we now think that CAR T-cell therapy may be the preferred option for patients that relapse within one year of first-line treatment. Autologous stem-cell transplant is a good option for people that relapse later.

So, let's first take on autologous stem-cell transplant and say what does that look like for our patients? What is an autologous stem-cell transplant? This is high-dose chemotherapy. If that works, then patients will go through a procedure where, via a blood draw, stem cells are collected, an even higher dose of chemotherapy is given, and, then, those stem cells that were collected are reinfused to help the patient recover from the high-dose chemotherapy and, hopefully, be cured.

This was the standard of treatment for patients, from second line, for diffuse large B-cell lymphoma for nearly 30 years, up until around last year when there were some new developments, which argued that there should be consideration of a new treatment, which is CAR T-cell therapy. Because autologous transplant has been around for a while and it's not likely to be the preferred option for the majority of patients going forward, I'm not going to spend much more time talking about that. But that is something, historically, which has been considered.



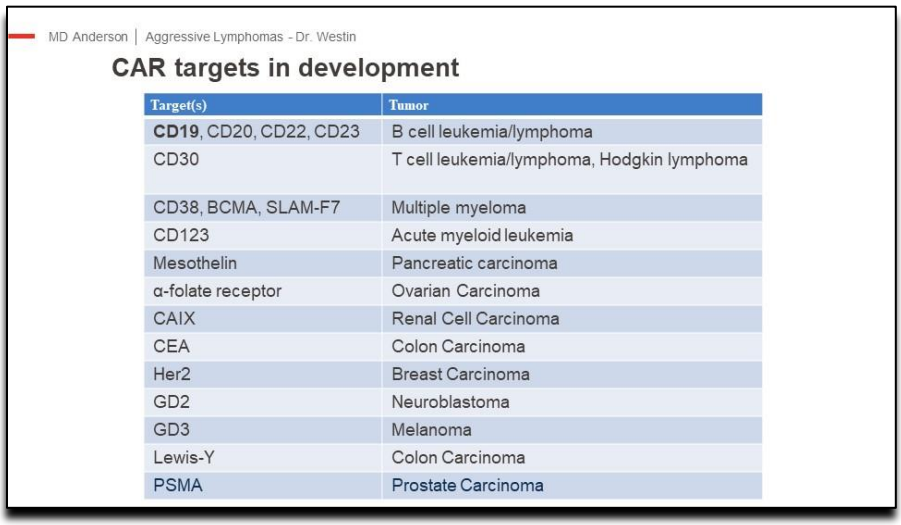
Development of CAR T-cell Therapy

Let's talk about what I said should be considered as a new option for second-line treatment, and that's CAR T-cell therapy.

CAR T-cell stands for chimeric antigen receptor, not driving a car, but chimeric antigen receptor T-cells. What does that mean -- chimeric antigen receptor? Now chimera, from your Greek, is basically a fusion animal. It was a Griffin or another unusual animal that was like a lion and an eagle fused together-- some type of fantasy thing.

Well, fantasies sometimes come to life and chimera like this can actually be created in the lab and used as drugs. This is what a CAR T-cell actually looks like, in terms of the structure. The ones that are used in the clinic right now are the second-generation CAR T-cells. There's an external part. This is the cell surface of the T-cell, this yellow with the lines pointing down. This is the outside part. And these blue things are basically binding domains that will grab onto an antigen in question. CD19 is the one that we use most commonly.

And then, on the inside of the cell membrane, there are stimulatory domains, which basically allow the T-cells to become active. And that's what a CAR T-cell looks like, in terms of what's actually put on the surface of the CAR molecule on the T-cells.

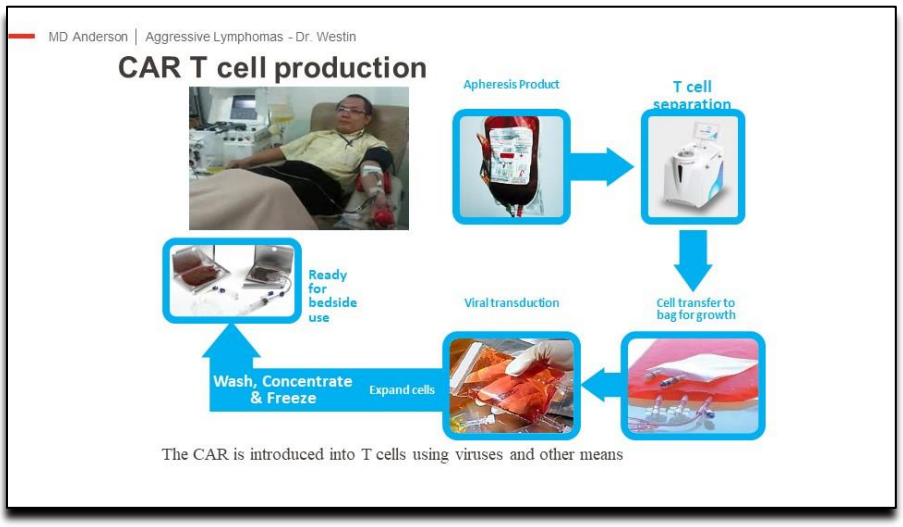


Target(s)	Tumor
CD19, CD20, CD22, CD23	B cell leukemia/lymphoma
CD30	T cell leukemia/lymphoma, Hodgkin lymphoma
CD38, BCMA, SLAM-F7	Multiple myeloma
CD123	Acute myeloid leukemia
Mesothelin	Pancreatic carcinoma
α-folate receptor	Ovarian Carcinoma
CAIX	Renal Cell Carcinoma
CEA	Colon Carcinoma
Her2	Breast Carcinoma
GD2	Neuroblastoma
GD3	Melanoma
Lewis-Y	Colon Carcinoma
PSMA	Prostate Carcinoma

CAR Targets in Development

So those signaling domains can help turn those on. CAR T-cells are an incredible advance and are being looked in all of these different types of cancers.

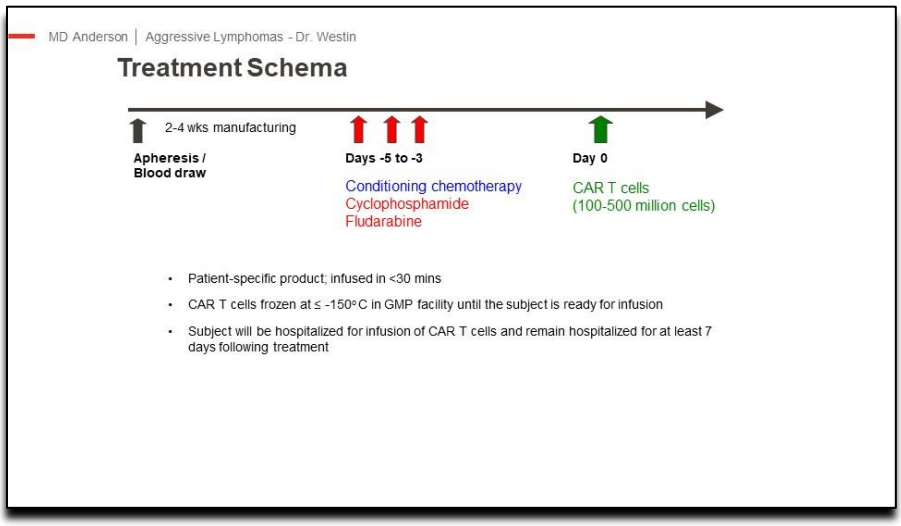
So this is not a therapy that's likely to stay only in aggressive lymphomas. But, it is something that's worked best, thus far, in aggressive lymphomas.



CAR T-cell Production

How exactly does this work? Well, a patient who is a candidate for CAR T-cell will have a blood collection, something called apheresis, where their blood is filtered to capture special cells, these T-cells. Those T-cells are then shipped to a facility that makes CAR T-cells. And basically, there is a procedure to enrich for T-cells and to sort of take out cells that we don't want. T-cell separation can often be done.

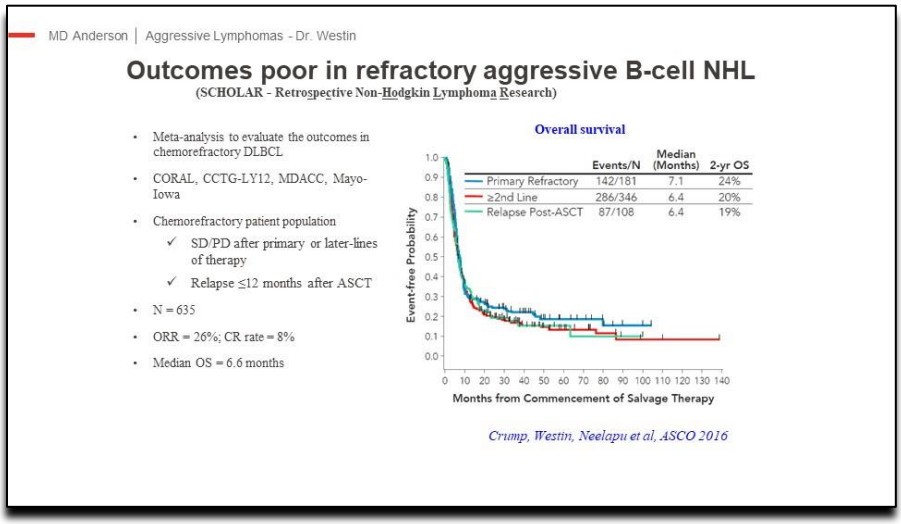
Those are then put into a special medium that allows these cells to grow, temporarily, outside the body. And then, a mechanism to get new, genetic information into the cells-- a viral transduction using a benign, non-infectious virus, to insert that genetic material, to put that CAR molecule on the surface of the T-cells-- is done. Those cells are then expanded, they're watched to make sure that there's no bacteria or other infectious agents that could be harmful. And then they're shipped back to our patients. And that whole process usually takes about three weeks, sometimes four weeks, to get the cells back.



Treatment Schema

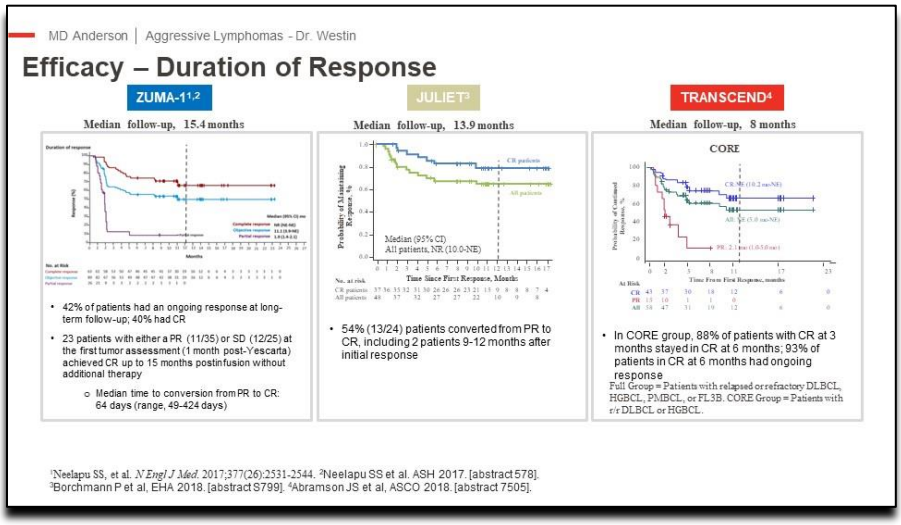
So as mentioned, the apheresis occurs, two to four weeks for manufacturing, and then a countdown chemotherapy is started. It's called lympho-depleting chemotherapy, using often these two drugs, fludarabine (Fludara®) and cyclophosphamide (Cytoxan®), over three days -- days minus five, four, and three. And then there's two days of some antibiotics or some white blood cell shots, booster shots.

And then, the CAR T-cells are infused on day zero. And then, those cells, when they get back home to the patient that they originally came from, they grow and expand and multiply many, many times over.



Outcomes Poor in Refractory Aggressive B-cell NHL

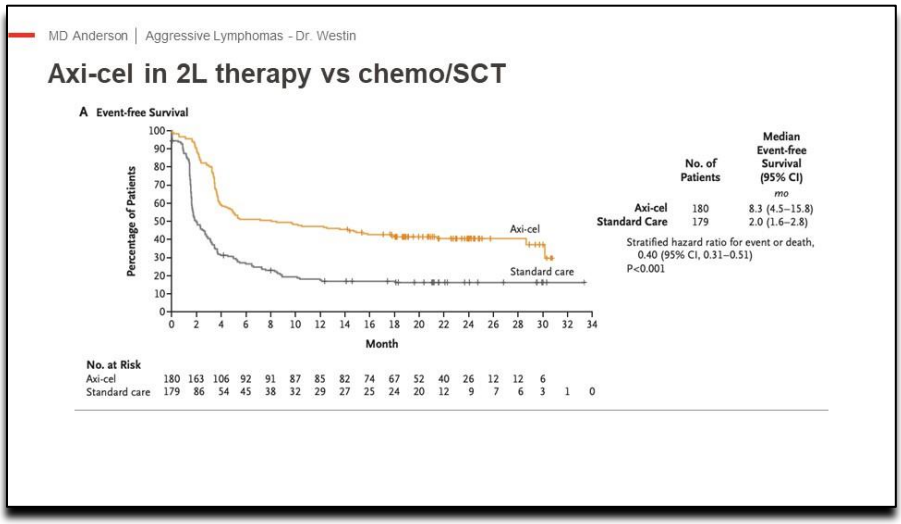
Before we had CAR T-cells, patients that had disease that was either completely resistant to chemotherapy or came back after autologous transplant, had not very good outcomes with additional chemotherapy and what was called event-free survival. Did the patient have long-term, durable benefit or not? That line drops very quickly, in terms of percentage of patients who don't have a problem over time. And so, we were hoping maybe a quarter of our patients with additional chemotherapy ...



Efficacy – Duration of Response

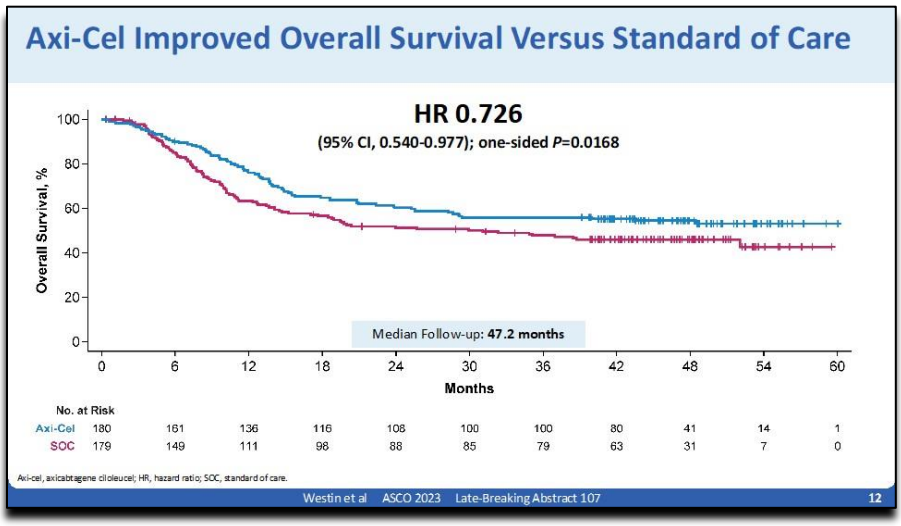
Enter CAR T-cells and the early response information for CAR T-cells in the first trials that were done, the ZUMA-1 trial, the TRANSCEND trial, and the JULIET trial showed that, in patients who had a complete response to CAR T-cells, it was giving very long-term disease control and potentially cure for what previously was a very difficult situation. So CAR T-cells look way better than what we'd seen in the past, with further chemotherapy.

Well, instead of waiting for a patient to have resistant disease, why not take this into a situation where patients newly diagnosed with relapsed disease, second-line treatment?



Axi-cel in 2L Therapy vs Chemo/SCT

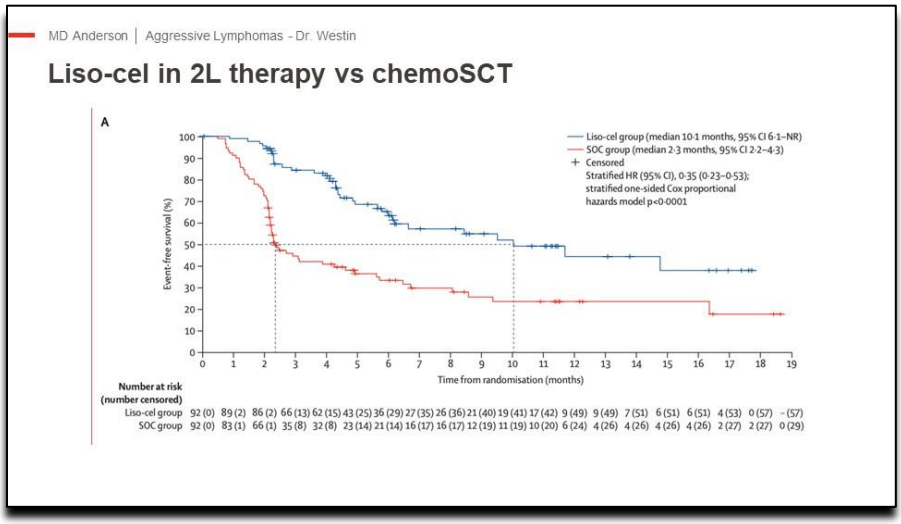
And so there were three clinical trials done that showed the CAR T-cells compared with chemotherapy and autologous transplant. This is from a trial called the ZUMA-7 trial that we published in *The New England Journal of Medicine* last year. I actually saw much better than the standard approach of chemotherapy, high-dose therapy, and autologous stem-cell transplant.



Axi-Cel (Yescarta®) Improved Overall Survival vs Standard of Care

This is a slide from a talk that I gave at the ASCO meeting two days ago, on Monday. And it was actually published in *The New England Journal of Medicine* on Monday, as well, showing that survival-- overall survival, where people alive or not alive-- was actually also improved with the CAR T-cell therapy, even though a lot of patients on this standard arm went on to receive CAR T-cell therapy as an additional treatment, if chemo or transplant didn't work. More people lived longer if they received a CAR T-cell therapy, here specifically Axi-Cel [axicabtagene ciloleucel], in second-line, over the old approach.

So, this is something that is, I think, effectively ending the debate of should we try chemo first and save CAR T-cell for a later day? If you have relapsed large B-cell lymphoma after R-CHOP or pola-R-CHP, or other initial treatments, and you are within one year of your treatment ending from first-line treatment, CAR T-cell therapy has a better chance of curing you than anything else as a second-line treatment.

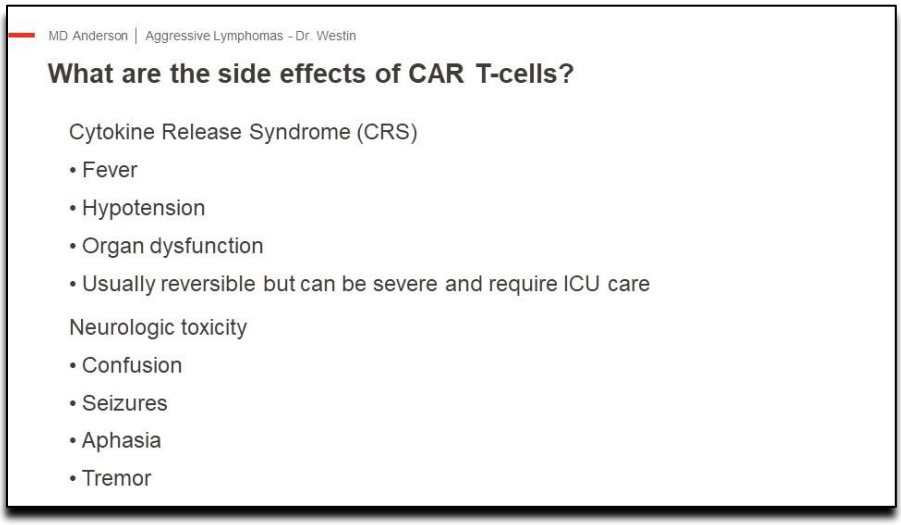


Liso-Cel (Breyanzi®) in 2L Therapy vs ChemoSCT

There was also a second trial, which showed great results using a CAR T-cell called Liso-cel [lisocabtagene maraleucel]. And the initial publication for this showed a dramatic improvement of Liso-cel over the chemotherapy approach. And Liso-cel is also approved for second-line treatment for patients with large B-cell lymphoma in the U.S. who are within one year, or who are not eligible for a

standard chemotherapy-based approach. So two options in second line -- Axi-Cel or Liso-cel. Those are both products that have been approved for second-line treatment with CAR T-cell.

Axi-Cel, the one that I mentioned first, is also being looked at now in a clinical trial of newly diagnosed patients with high IPI scores, four or five. So, if you or your loved one just got the diagnosis this week and are getting ready to start a treatment, there's a clinical trial called ZUMA-23 that's looking at CAR T-cells as a new treatment option, potentially, for patients with newly diagnosed, aggressive lymphomas.



What Are the Side Effects of CAR T-cells?

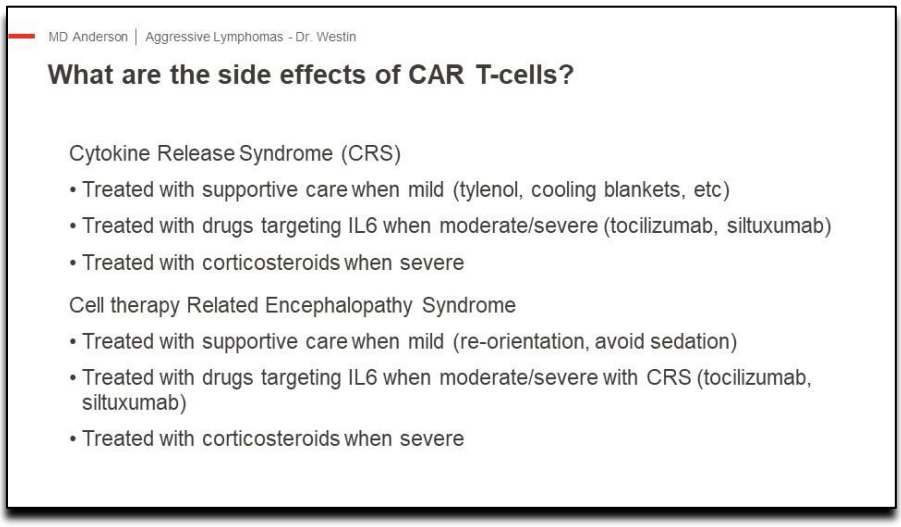
Let's talk about the side effects, though. CAR T-cells are great, but they do not come without a trouble of side effects. The things we worry about most commonly, and most people talk about, are two side effects of CAR T-cells called cytokine release syndrome (CRS), number one, and number two, neurologic toxicities.

Cytokine release syndrome looks a lot like an infection. Cytokines are effectively chemicals that our body uses to signal they need a help from the immune system. They need reinforcements from those lymph nodes, kick out all the blood cells that are in the fort, and send them out into battle because there's something bad happening. So when we get a fever, or when our blood pressure goes low, or when we have some organ dysfunction-- those things that go along with sepsis or infection, that's because of the chemicals that are secreted by our immune system saying, "Red alert! Something bad is happening."

That can happen with CAR T-cells if they're overactive and growing very quickly. Sometimes, that can cause this syndrome, cytokine release syndrome. It's usually reversible; but rarely, it can be severe and can require ICU care. And for this reason, CAR T-cell therapy is not available all over the place. It's available at specialized centers that can handle this toxicity. So, they're usually is a CAR T-cell center, relatively near you.

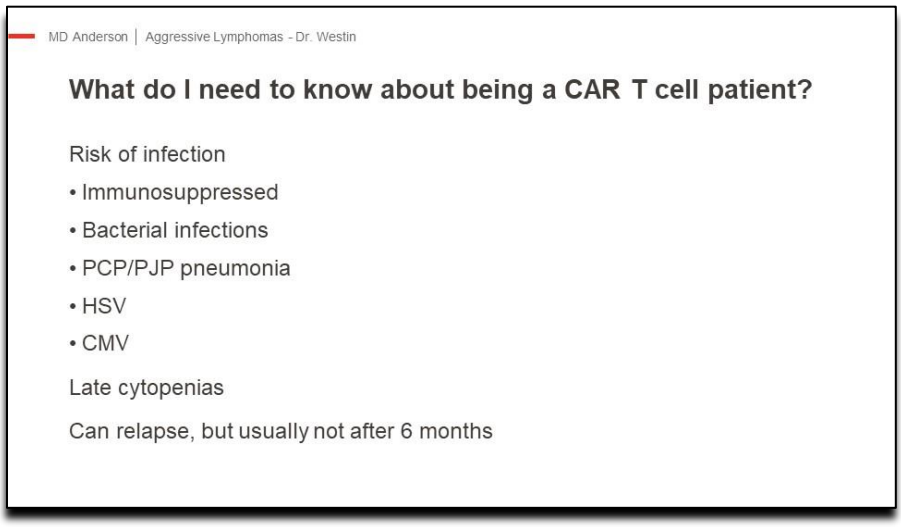
I'm sure The LLS has information about which centers potentially could help administer this. But, if you have newly diagnosed large B-cell lymphoma, these side effects, although they sound scary, you have a better chance of being alive. And so, therefore, I still would consider CAR T-cells to be the standard approach. I mentioned, too -- I talked about cytokine release syndrome and neurologic toxicity. This is something that we often will admit people to the hospital for, if it occurs. But, thankfully, this is something that is not a toxicity that everybody deals with.

With the Axi-Cel CAR T-cell, this can occur in around 60% of patients. But, thankfully, the higher-grade versions are in a small minority of patients. With the Liso-cel CAR T-cell, this is often less common, with a much lower percentage of people having significant neurotoxicity with that product. But when it happens, it can look like confusion, rarely people can have seizures, or aphasia, or tremors. But this is almost always reversible and happens right after the infusion, within the first week or so.



What Are the Side Effects of CAR T-cells?

This is something that -- just for your information, there are treatments for these conditions, if they occur – Tylenol®. There are rarely uses of other drugs, like tocilizumab (Actemra®), to try and target some cytokines and knock them down. Or, sometimes, steroids might be used to try and knock this back.

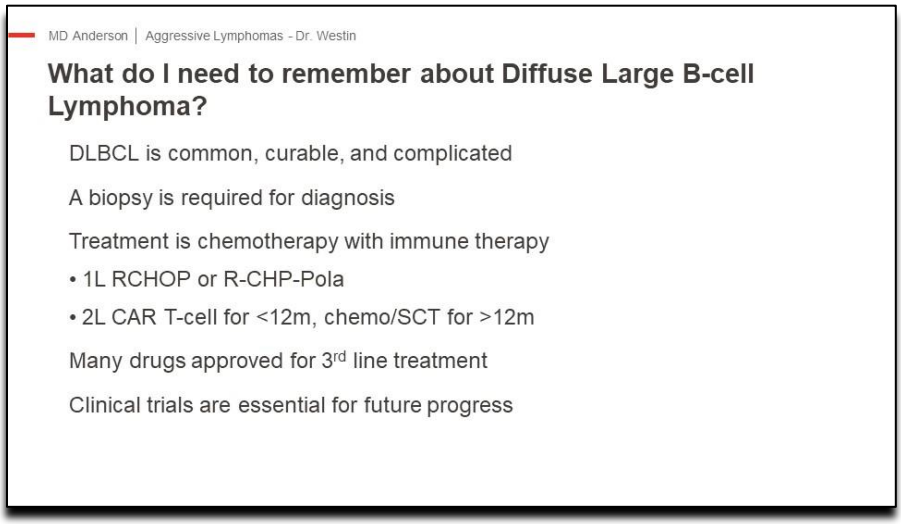


What Do I Need to Know about Being a CAR T-cell Patient?

What about if I'm a CAR T-cell patient? What do I need to know? Well, there's a risk of infection that goes along with messing around with the immune system and, often, we'll have our patients on a regimen to suppress potential infections, looking at a type of pneumonia called PJP. Often, a treatment, like an antibiotic like Bactrim™ (trimethoprim/sulfamethoxazole), will be given.

Suppression for having shingles or HSV [herpes simplex virus] infections. So, Valtrex® (valacyclovir) is often given. But this is something that can occur for patients after CAR T-cells. There can also be low

blood counts that can sometimes linger. So these are things that we have to watch out for our patients that are receiving CAR T-cell therapy.

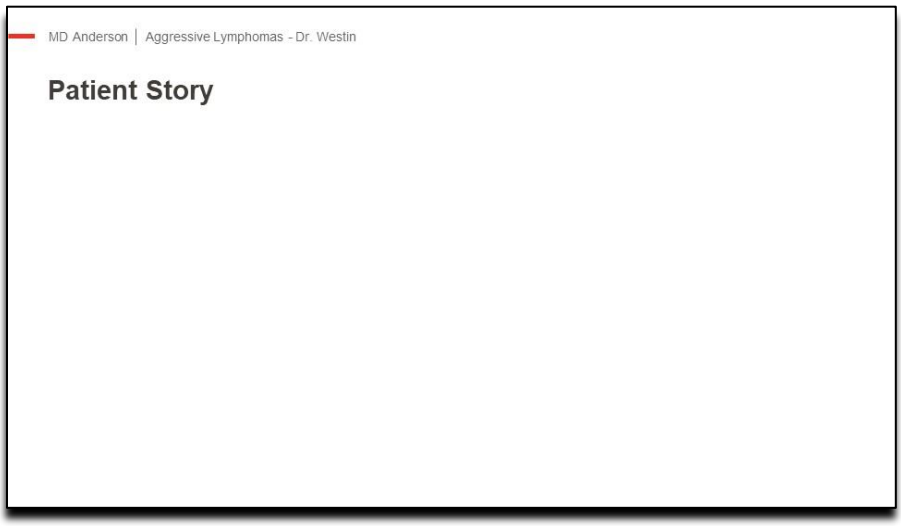


What Do I Need to Remember about Diffuse Large B-cell Lymphoma?

All right, so as we're getting closer to the end of the talk about large B-cell lymphoma, what do I need to remember? It's common; it's curable; and it's complicated.

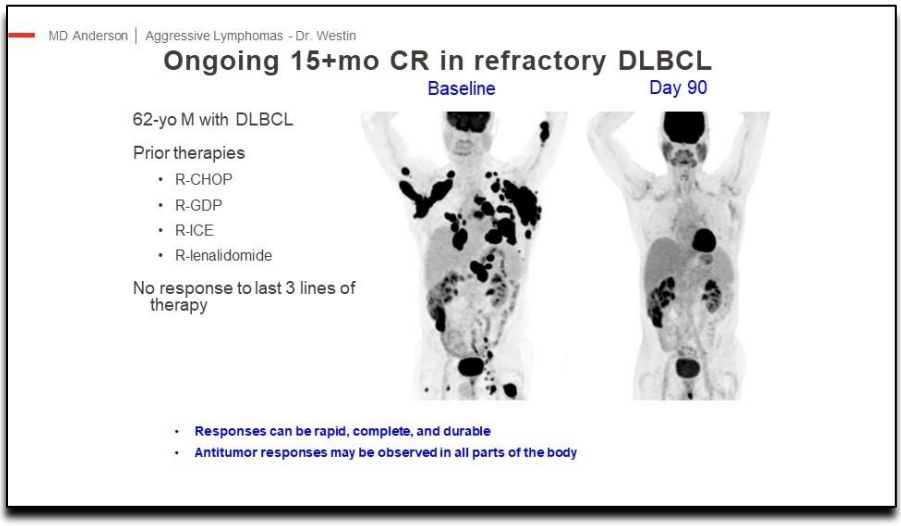
So being seen at a facility that can offer and consider clinical trials, if that's possible for you or your loved one, it is often a good idea. A biopsy is required for diagnosis. If somebody says your PET scan shows you've got lymphoma, that is not how PET scans work. They can say something is abnormal, but the biopsy is required, and a good biopsy, at that. Treatments-- for first-line therapy, right now, the standard in the U.S. is either R-CHOP or R-CHP-pola.

And second-line: For patients that have early relapsed disease, the vast majority will be considered for CAR T-cell therapy. For people that are more than 12 months, most patients will be considered for chemotherapy and stem cell transplant. There are other options, which we'll briefly touch on here in the remaining time, before we open up for questions. For people that are not eligible for those or that have additional disease and third-plus line -- and I would highlight, again, that clinical trials are often the best weapon for you to help fight your disease as well as to help others who may be dealing with this disease in the future.



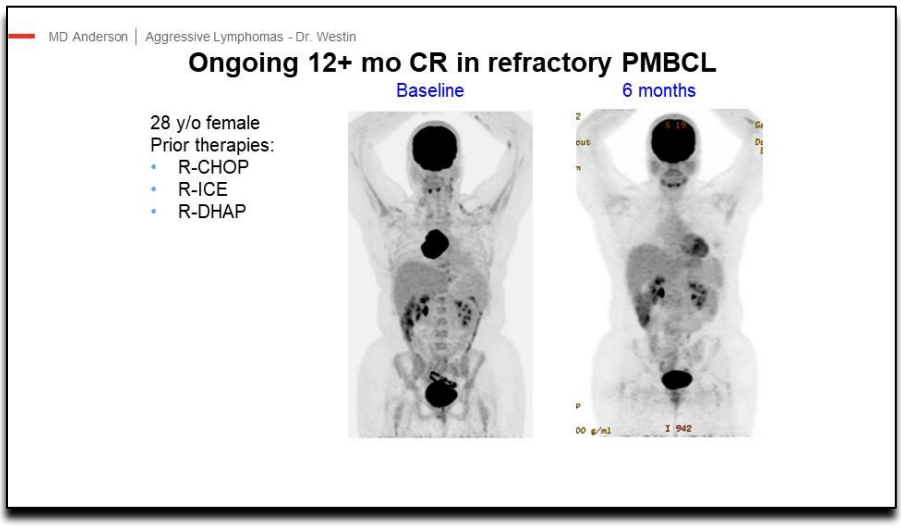
Patient Story

So, let's briefly go over a couple of patients of mine who went through a clinical trial and had an excellent result.



Ongoing 15+-mo CR in Refractory DLBCL

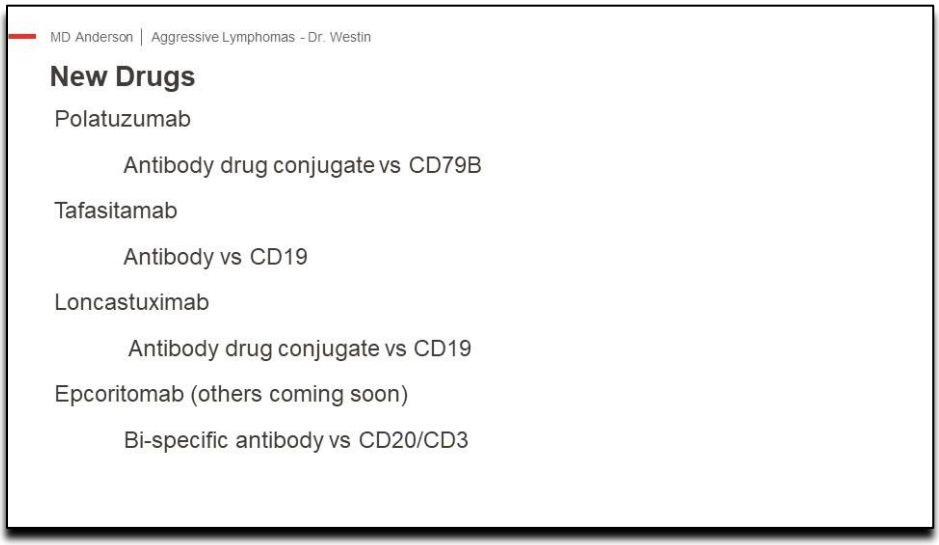
Here's a patient who had large B-cell lymphoma -- 62-year-old male with a PET scan on the left showing a lot of dark areas, lots of disease. Had treatments with the chemo, shown here -- R-CHOP, a chemo called GDP, a chemo called ICE, and then a drug called lenalidomide (Revlimid®). He did not respond to any of those treatments in a durable fashion. And then, received a CAR T-cell therapy, and now is well into a long-term remission, with no evidence of disease. So being able to overcome resistance, obviously, a great thing for CAR T-cells.



Ongoing 12+-mo CR in Refractory PMBCL

Here's another patient of mine: a young, 28-year-old mother of three. She'd had R-CHOP, R-ICE, and R-DHAP. Did not respond at all to those chemotherapies and was in a bad way, with a tumor in the middle of her chest beginning to compromise some of her organ function in her chest. And she's now so healthy she won't come back to see me in clinic. She says, "Save that appointment for somebody that's actually sick. I'm back to normal after a CAR T-cell therapy."

Obviously, that can happen with R-CHOP. Not everybody goes through having disease that doesn't respond to those. But just pointing out that if therapies don't work, sometimes homeruns can occur even in the later line settings. And CAR T-cells are certainly an example of that.



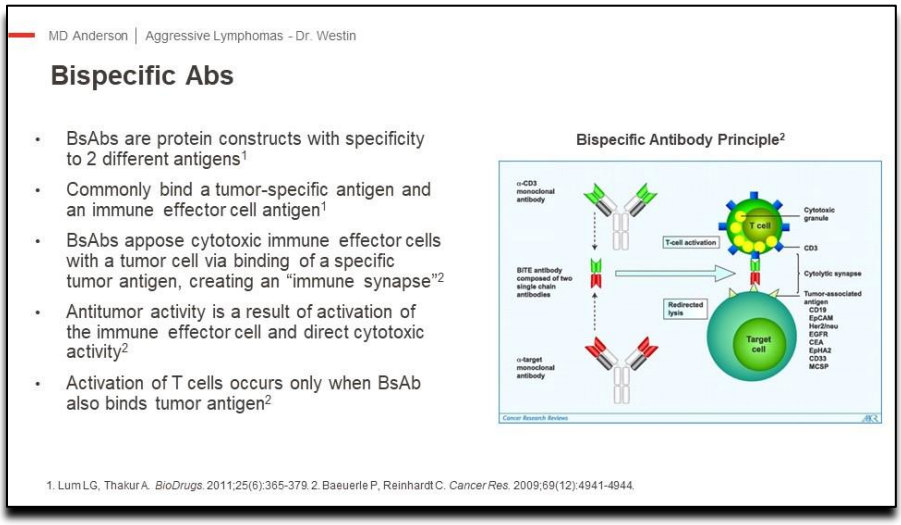
New Drugs

But these other drugs are also great ones that can sometimes help our patients who have disease that doesn't respond to initial treatment. There's a drug called polatuzumab, which I mentioned is now approved in first-line. It's also approved for patients with relapsed disease.

So that's a drug that sometimes might be considered if your cancer comes back after initial treatments. Another antibody called tafasitamab (Monjuvi®)-- this is an antibody similar to rituximab (Rituxan®) or to polatuzumab. This is targeting CD19. And it's usually combined with lenalidomide, an oral agent. And

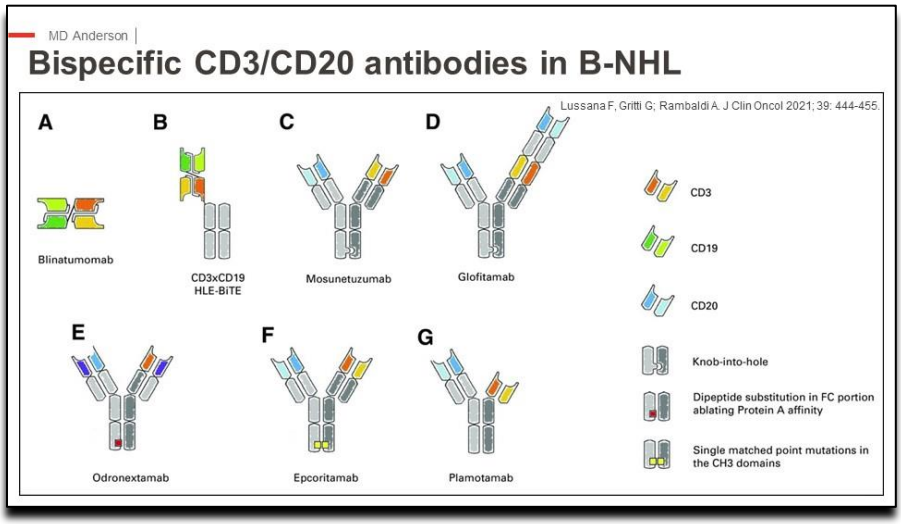
that's approved for patients with second- or third-line disease and can have complete responses, which can be quite durable. Loncastuximab (Zynlonta®) is an antibody drug conjugate, so another antibody with chemo tacked on the back end of it, targeting CD19.

And, just approved about a week and a half ago, was a drug called epcoritamab (Epkinly™), which is a bi-specific antibody targeting both CD20 and CD3. I'm going to show you a couple slides on that, because that's a really cool subject.



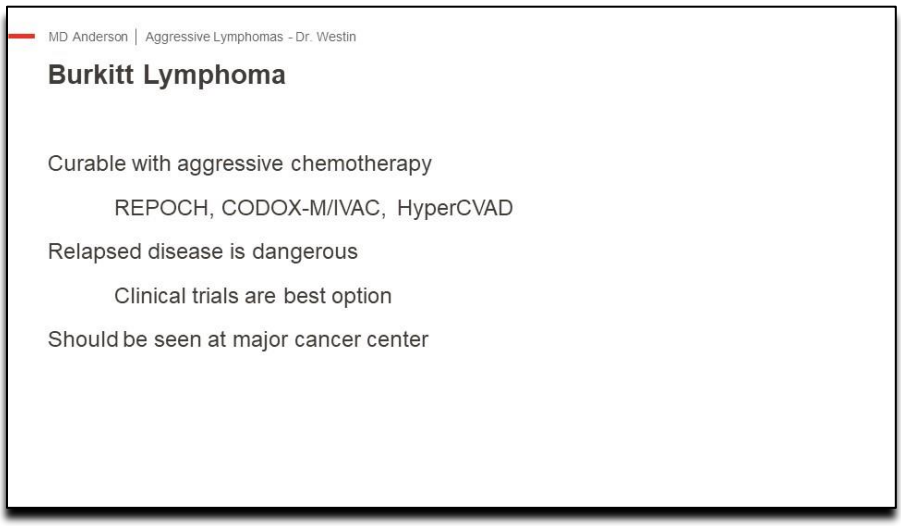
Bi-specific Abs

Bi-specific -- we know bi, like bicycle, having two wheels -- bi-specific is an antibody that targets two different things. And so, basically, it's taking an antibody from grabbing onto this type of cell, and then an antibody that grabs onto that cell, and then, basically, hooking those together. So now you have an antibody that can grab onto two different cells.



Bispecific CD3/CD20 antibodies in B-NHL

And there are a lot of these that are coming through the clinical research pathway. So the one I mentioned that was FDA approved last week, epcoritamab -- stay tuned, because there might be a number of other of these that may be approved very soon. But these are very active in clinical trials. And leading to the approval of epcoritamab, showing high response rates, which can be quite durable in our patients. So another weapon fighting against aggressive lymphomas.

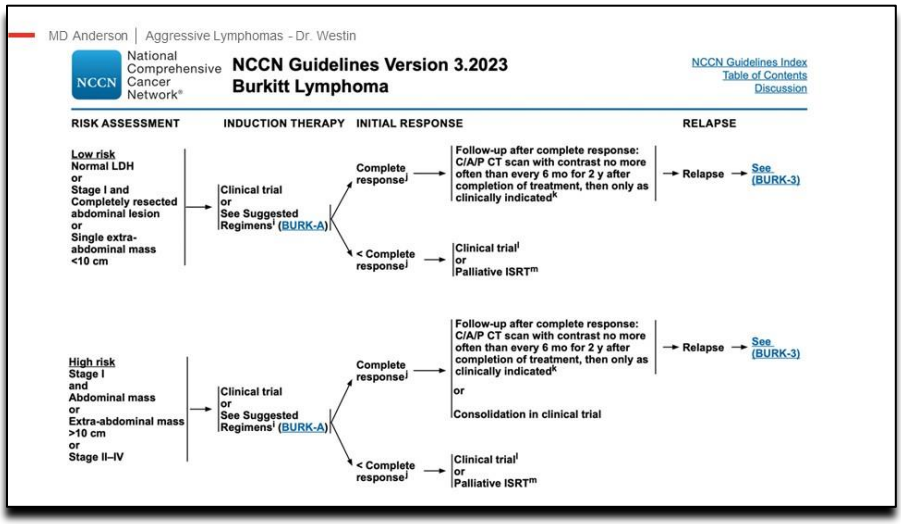


Burkitt Lymphoma

And the last few slides -- I'm going to touch briefly on Burkitt and mantle cell. And then I want to save us time for going through some questions. So Burkitt lymphoma is a very, very, very aggressive, large B-cell lymphoma. It's a separate category than diffuse large B-cell lymphoma, but it's a cancer of B-cells. It is curable. And usually used chemotherapy -- I mentioned R-EPOCH, a five-day infusional version of R-CHOP, adding in the drug etoposide (Etopophos®, Toposar®).

There are other chemo cocktails that are sometimes tried -- CODOX-M/IVAC or Hyper-CVAD. Those are often considered to be standard options for treating newly diagnosed patients with Burkitt lymphoma. If the cancer does not go into or stay into remission -- if the cancer comes back-- it can be very dangerous. And a clinical trial is the best option. So, for patients with Burkitt lymphoma, I would recommend being seen at a relatively large cancer center because this is a rare disease.

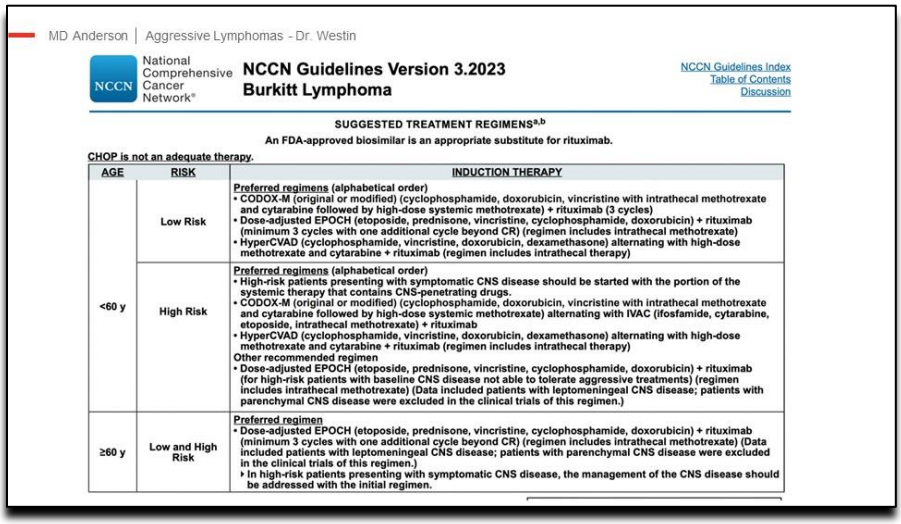
And if your doctor is not somebody who treats lymphomas on a regular basis, it could be quite complicated.



NCCN Guidelines Burkitt lymphoma

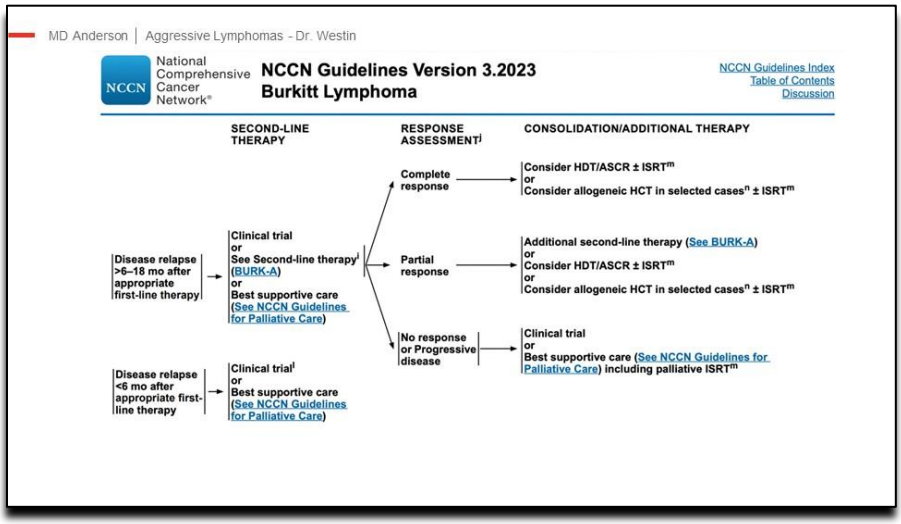
Here are the NCCN guidelines I showed earlier for large B-cell lymphoma. This is for Burkitt lymphoma. And both of -- for localized disease and high-risk disease-- clinical trial is the preferred option. So

again, please do seek out a second opinion if this is a diagnosis that you or your loved one is dealing with.



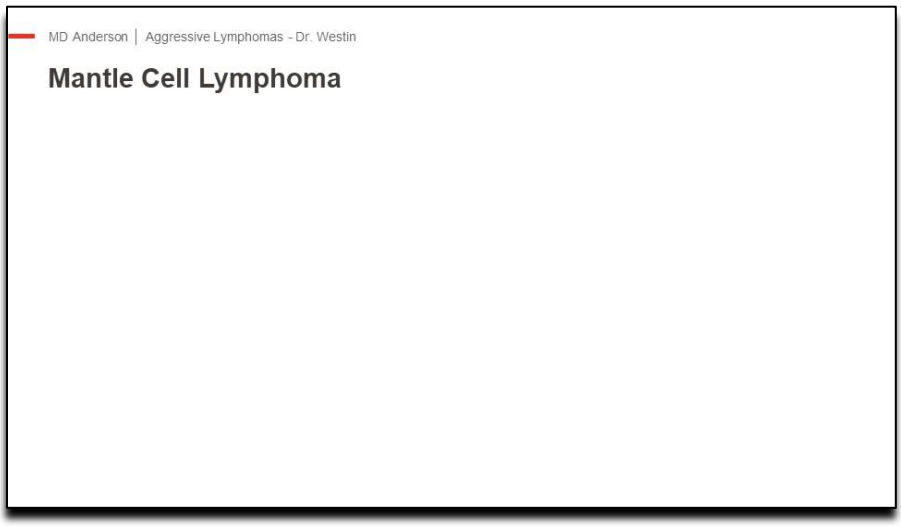
NCCN Guidelines Version 3.2023 Burkitt lymphoma

What does low-risk mean for this disease? Low-risk basically means: you have low tumor burden; you do not have any bulky disease; your LDH is normal; and you don't have any other high-risk features. These regimens here can be considered. And sometimes, patients can even have a shorter course of chemotherapy, only three cycles, if they're low risk. Somebody with higher risk certainly would not want to have an abbreviated course and would want to receive the full course of chemotherapy.



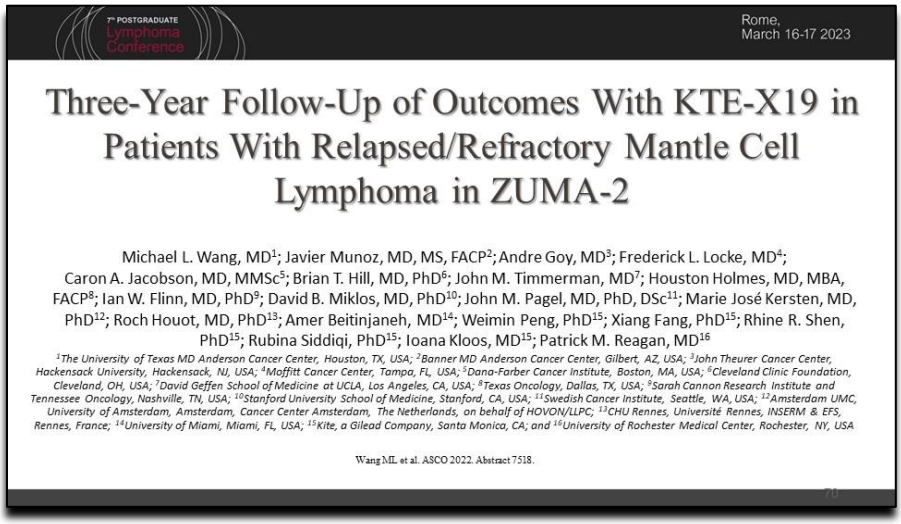
NCCN Guidelines Version 3.2023 Burkitt lymphoma

If the cancer comes back, if somebody has six cycles of dose-adjusted R-EPOCH or CODOX-M/IVAC or R-Hyper-CVAD and the cancer comes back, again, clinical trials are the preferred option. So please do consider that, if you or your loved ones deal with Burkitt.



Mantle Cell Lymphoma

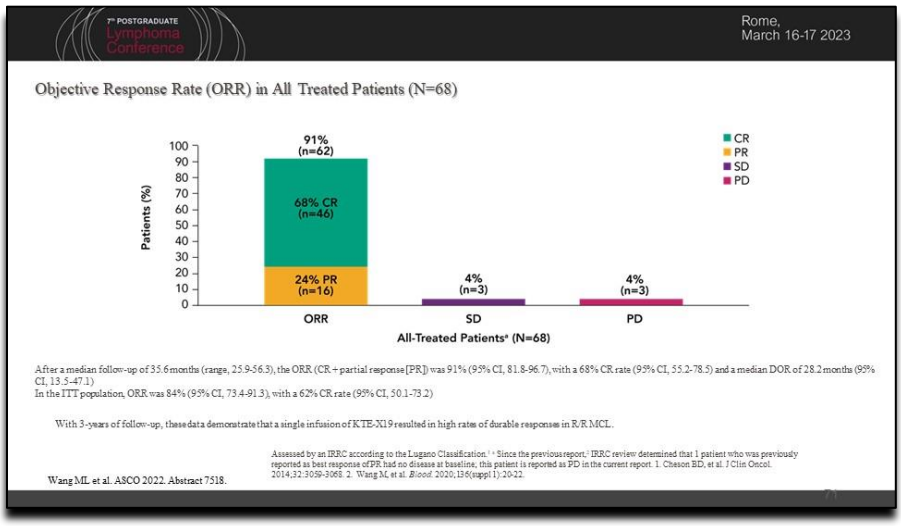
Mantle cell lymphoma is another more rare subtype of non-Hodgkin lymphoma.



Three-Year Follow-Up of Outcomes with KTE-X19 in Patients with Relapsed/Refractory Mantle Cell Lymphoma in ZUMA-2

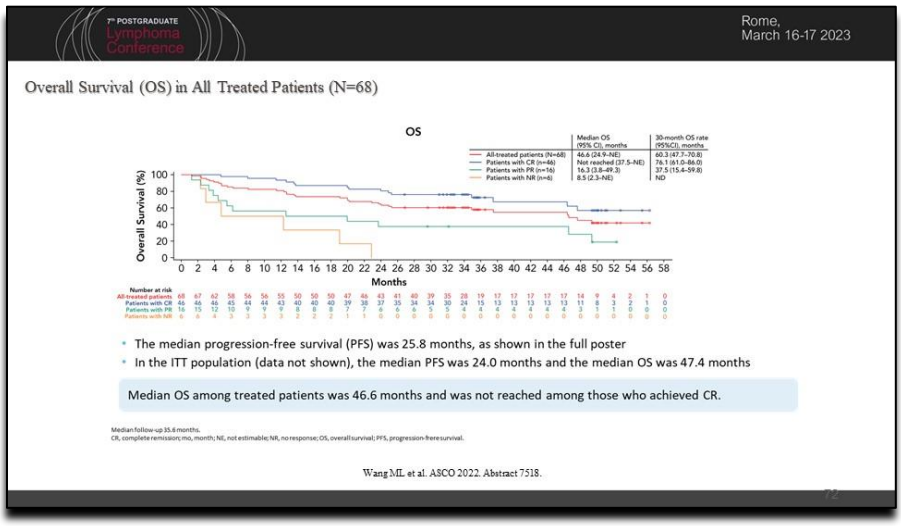
It kind of straddles the line of aggressive and slow-growing. Sometimes, it has features of slow growing disease, other times as aggressive disease.

Mantle cell lymphoma, if it keeps coming back, over time, has approval for CAR T-cell therapy. Slightly different than the CAR T-cells I showed you before, in that there's an extra step to basically filter the blood to make sure there's no mantle cells within the apheresis immune cell product that's being used as the seed to make CAR T-cells.



Objective Response Rate (ORR) in All Treated Patients (N=68)

Here's a presentation from my colleague, Dr. Michael Wang, looking at a CAR T-cell that's now called brexucabtagene (Tecartus®), but at the time was called KTE-X19. And in patients with relapsed mantle cell lymphoma, it gave excellent responses. Ninety-one percent of patients had complete responses.



Overall Survival (OS) in All Treated Patients (N=68)

In patients who had a complete response, the blue line here had very good overall survival. For patients that had less than a complete response, we still have more work to do. But, thankfully, there are a large number of new drugs, including the bi-specific antibodies that I mentioned. Those are also being looked at for mantle cell. And stay tuned for more great things to come for treating this disease.

Question & Answer

So, with that, I'm going to conclude my part of the talk. And I think we'll move back to our moderators, who are going to help us to take on some questions.

Lizette Figueroa-Rivera
Well, thank you so much, Dr. Westin, for your very informative presentation. Like you said, it's time for the question-and-answer portion of our program. For everyone's benefit, please keep your questions general in nature, without many personal details.

Doctor, since you were speaking in regards to mantle cell lymphoma, Nadine is asking, what distinguishes indolent, or slow-growing, mantle cell lymphoma from its more aggressive version? And will the indolent mantle cell lymphoma always transform into a more aggressive version?

Dr. Jason Westin
Great question. The second question first -- no, not always. Many cancers do get meaner and more aggressive, over time, and can certainly sort of pick-up speed as time goes on, getting new mutations or more aggressiveness. But not always. Not every lymphoma is created equal, in terms of its aggressiveness or its chance of causing death. Some lymphomas, for reasons that we don't fully understand, behave in a very slow-growing or less-aggressive fashion.

So there are some features under the microscope -- they can suggest that the cancer is going to be aggressive or not. So for mantle cell lymphoma, one of them is a marker called KI-67 -- KI-67. That is, basically, staining to see which cells in the biopsy sample were actively growing at the time the biopsy was taken. And the lower that number is, the lower percentage of cells that were growing, usually the lower aggressiveness of the disease.

Soif somebody's biopsy at diagnosis shows they already had a biopsy where two-thirds of the cells were actively growing and dividing, that's usually a red flag to their doctor that, look out, this is not likely to be a slow-moving disease. This may grow very quickly. If, on the other hand, it was 5% of the cells were growing and dividing, sometimes observation could potentially even be an option for a patient with mantle cell.

There're also a few other genetic tests. There's a mutation looked at in the gene called TP53 that can sometimes be consistent, if it's there, with high-risk disease and aggressive disease. So, it's more of a microscope discussion than a clinical discussion, in terms of how likely the disease is to be aggressive.

Lizette Figueroa-Rivera
Thank you so much. And we'll take the next question from our telephone audience, please.

Operator
Thank you. This question comes from Dean, calling from North Carolina. Please state your question.

Dean
Yes, I am trying to get a doctor to perform MRD testing for my mantle cell. The FDA hasn't approved it. They approved it for other lymphomas. Is that not helpful in seeing what my next treatment and how it will act? I just can't get anybody to do it. Can you comment on that, please?

Dr. Jason Westin
Yeah, absolutely. Thanks, Dean. So, the MRD testing you mentioned -- for those that don't know that term, MRD stands for minimal residual disease. Basically, a short-hand for-- can you measure the amount of cancer in the body from a blood test? And the answer for many cancers, surprisingly, is yes, that we can use blood tests to see if somebody still has residual, leftover lymphoma in their body, if their CT scans or PET scans show a clean response.

Well, that's only meaning that there's nothing big enough that a PET scan or a CT scan can pick up. It doesn't guarantee that there's not lymphoma that's still present. MRD testing is not something that is yet incorporated in a lot of our treatment guidelines. It is a test that has great promise. It has not lived up to that promise, as of yet. And that's largely due, in part, to the assays that are used. The tests that are used, they are not as good as we'd like them to be.

There still is a risk of having false positives, showing that the cancer is there when, in fact, it's not. And perhaps an even greater risk of having false negatives, saying that is everything is fine when, in a reality, there is lymphoma there. And using tests like that, when the CT scan or PET scan is normal, to make a treatment decision, you really want to have a very reliable test that you can take to the bank and put your money on it. That's something that you're using that test -- and if it's potentially inaccurate, you could be getting a treatment, or not a treatment, in an inappropriate fashion.

So that's a long answer to a short question. But the reasons that your doctor may not be wanting to do that testing could be related to that. It could also be related to reimbursement. Many times, payers will say what are you using this test for? It's not on the algorithms. And, therefore, they will not want -- the insurance company will not want to pay for it. Sometimes, these tests can be very expensive.

So, Dean, I can't speak specifically to why your doctor doesn't like that test. But those are some of the challenges that go into MRD testing. I do think, as we work the kinks out with these tests, that these will become a part of our standard management. But we really do need prospective, clinical trials for a patient that has a completely clean scan, nothing on the scan, and if a blood test says that there is something amiss, how do we know for sure that acting now is better than waiting until something gets worse? How do we know that that advantage of time actually is going to change a response to treatment or prolong a patient's survival? The way we would do that is through a clinical trial, where we would treat some people and then observe others closely and start treatment as soon as something had occurred. But basically, do the test to figure out, is that lead time actually providing an advantage? Or, is it just starting somebody on treatment a couple months earlier and still the same result? So, it's a complicated subject matter about minimal residual disease testing.

I do think it's going to be something that, in the future, may even be able to replace staging scans, those, "Come back and see me in every six months to do scans to see if your cancer is in remission." I do think that it may be able to be used during treatment to see if the treatments are working well. And if they are, potentially even stopping them sooner. Or, if they're not, changing treatments. But, for the time being, they are often not used as part of standard of care.

Lizette Figueroa-Rivera
Thank you, Dean, for the question. And, Doctor, you just mentioned scans. So, Carol is asking is annual check with CT scans frequent enough to catch an aggressive NHL? She's been in remission for seven years.

Dr. Jason Westin
Great question. So, the frequency of scans is a little bit operator dependent. And what I mean by that is-- there is not a right or wrong answer to how often scans are done. There is significant variability in the way follow-up is conducted after somebody completes therapy for an aggressive lymphoma. The reason for that is that the timing of scans, if it's somewhat arbitrarily based upon a calendar, doesn't mean that the lymphoma could not have a relapse not on the calendar.

Basically, you could have a relapse a couple days after a scan was conducted, and then have a clean scan, but come back into the doctor's office a month later and say, "What is this lump?" Cancers don't always follow a schedule. But what I would say, is that aggressive lymphomas, if they do come back, usually do so within the first year, maybe within the second year. And so, in my practice, I will do more scans in that first year, and then as time goes on, kind of ramp down the frequency of my scans, eventually moving out to annual scans. And then, stopping scans altogether. It's a subject matter that, it depends on who you ask, how often they do scans. Some centers in the U.S. -- good, academic, strong, rigorous centers -- do one scan at the end of treatment. And, they basically say, "If you have any symptoms, let me know." They see you back for follow-up, but they don't necessarily do scans because of not wanting to spend the money, or have the radiation exposure, or a condition that the patient, more often, will tell the doctor, than the doctor will tell the patient that the cancer has come back. Symptoms, often, are the trigger. Do a work-up, not serendipity. But other centers do scans as the questions are asked. Surveillance scans to follow-up. In my own practice, I often stop doing scans altogether if somebody is five years or more removed. So, specifically, to answer this person's question, is annual scan sufficient to catch if there is a relapse? Yes, it is. If you're 7-plus years out, I think it'd be reasonable to consider that you may not need scans anymore, as the chance of relapse at the timepoint is very, very low.

Lizette Figueroa-Rivera
Thank you. And, Doctor, Aaron and Valerie are asking about anaplastic large-cell lymphoma. How far along has treatment plans and research come in the past three years?

Dr. Jason Westin
Anaplastic large-cell lymphoma can be a disease that's under two different categories. So, there's an anaplastic large B-cell lymphoma. And that often has a translocation from a gene called ALK, A-L-K. That is a disease that is very aggressive and often very resistant to treatments. Anaplastic large B-cell lymphoma sometimes might benefit from standard therapies. But, it can often come back. And clinical trials are usually a good option.

There are drugs that specifically target that ALK, or A-L-K, gene abnormality. And this, surprisingly, that's an abnormality, even though the L in that gene stands for lymphoma, it can also be seen in lung cancers. And there are some treatments that work well in lung cancers that can work in patients with that gene abnormality with anaplastic large B-cell lymphoma. There is also a T-cell subset of lymphoma, called anaplastic large T-cell lymphoma. That is a disease that affects not the B-cells but, in fact, the T-cells.

And can be something that it's also difficult to treat with standard, front-line chemotherapy options. And sometimes those patients will need to have a stem cell transplant. There are lots of new drugs coming out for both of these. And so, I would say for these two people who asked the questions, please make sure you're being seen at a center that has clinical trials, to be considered for the anaplastic large cell lymphoma subtypes.

Lizette Figueroa-Rivera
Thank you. And actually, Micki was asking how equipped are local cancer centers in successfully administrating the newest procedures versus a research facility like MD Anderson?

Dr. Jason Westin
That's a great question. And it's difficult to speak, in general terms, about specific things. What I'd say is that local cancer centers can often do incredible things. But sometimes, there are new advances that might be a little bit outside of their scope or what they're able or willing to administer. A good example to that is CAR T-cell therapy. This is a treatment that has revolutionized, for many patients, their disease course, and to patients that would not be alive today, are thriving and doing well.

The young soccer mom that I showed -- she traveled to see us in Texas, from Florida, because her local team didn't have access to CAR T-cells at the time. But some small cancer centers can do CAR T-cells. So I think it depends upon the actual specific center that this questioner is at. I think what I'd say is that it often is a good idea to consider getting a second opinion, or a third opinion, at a large center. And if a large center, like MD Anderson or other large centers-- there is a number of great centers out there-- if they basically reiterate what your local doctor said, or if they say, "Yeah, that's great," now you've got confidence that your local team is doing the absolute best for you for fighting this disease.

If they say, "Oh, that's a good option. However, there might be a better one," well, now, you've potentially got a better treatment as a result of that second opinion. So, if you're able to, if you have the ability to get a second opinion or a third opinion at a big cancer center, I'd encourage you to consider doing that. But for those that don't, The LLS and others are a great resource for you to learn more about what's new and what's great. And if your doctor is not singing from the same sheet of music as what you see on those resources, then it may be a better idea to see about getting a different opinion.

Lizette Figueroa-Rivera
Thank you. And yes, Micki, we are equipped to assist you here at LLS with finding information about second opinions as well as other treatment centers.

We'll take the next question from our telephone audience, please.

Operator
Our next question comes from William, calling from New York. Please state your question.

William
I was diagnosed with non-Hodgkin's lymphoma, subtype follicular. Tumor was removed, pressing against my spine. I was wondering about reoccurrence and what form?

Dr. Jason Westin
Yes. Thank you for the question. So, the subtype that you mentioned of non-Hodgkin lymphoma, follicular lymphoma, that's a disease that can often recur at a later timepoint. That's usually thought to be not as an aggressive subtype of large B-cell lymphoma. Sometimes, it can show up in bad spots, though. And having disease-- like you mentioned, near your spine-- that obviously is a scary place to have something, a cancer, pressing upon to cause damage or injury to the spine.

But that disease, often, is very sensitive to treatments and will go into remission, commonly, but has a nasty habit of hiding in the weeds. And sometimes, years and years and years later can come back. So the treatments for follicular lymphoma can be a little different than what I mentioned for large B-cell lymphoma, with the idea that that disease is often considered more of-- as a marathon and less of a sprint. Lower-toxicity therapies are often an option for patients with that disease.

But I would, again, say that clinical trials are often a great weapon. And many of the newer treatments for follicular lymphoma are actually not chemotherapy-based but are targeting the immune system. The bi-specific antibodies that I mentioned -- one of those was recently approved, back in December of last year, for patients with relapsed follicular lymphoma. There are also CAR T-cells out there. So, there's a lot of great new things coming along. But chance of relapse with that disease is, unfortunately, still high.

Lizette Figueroa-Rivera
Thank you. And I do see that a lot of slow-growing lymphoma patients are on the line and wondering if their type of slowing-growing lymphoma will advance to an aggressive lymphoma?

Dr. Jason Westin
Yes. Great question. That term, advanced to large-cell lymphoma -- the way we often phrase it in my neck of the woods is-- we will often say, "Did it transform into large B-cell lymphoma?" So, we know that Saturday morning cartoon, the *Transformers*, where the semi-tractor trailer transforms into the robot. That word transform is always the word we know what it means.

Transforming, here, is from a slow-growing lymphoma into an aggressive lymphoma. Thankfully, that's a relatively rare condition. So, transformation of a slow-growing lymphoma occurs on the order of around 3% of the time. But that 3% is for each year. And so, it doesn't mean that 3% this year, and 6% next year, and nine the year after. It's 3% each year. So, at -- if you have that disease, odds are, this year, are -- it's very, very low that that would happen to you.

If somebody tells you it's only a 3% chance of rain today, you're going to go out to your picnic and not think twice about it. But over time, rare things can occur. And so, 3%, give or take that number, I wouldn't say is a firm number, but it's that neighborhood, a very low chance. If you have this disease, and you're treated, and you're in remission, and it comes back, and you're treated, and you're in remission, and it comes back, and you've had this disease now for 15 years, the chance of, over time that that disease could transform-- sometimes that rare roll of the dice could go the wrong direction.

And if it did happen, that disease would usually be managed as diffuse large B-cell. And the aggressive component, the transformed component, could be cured with a chemotherapy-based approach, like R-CHOP or R-CHP-polatuzumab. So there are treatments, if it happens. But, thankfully, it's a rare situation.

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

Operator
Our next question comes from Renee, calling from Texas. Please state your question.

Renee
Yeah, good afternoon. Thank you for taking my call. I'm 61 and diagnosed with diffuse large B-cell lymphoma at the left acetabulum [part of the hip bone]. I know I'm not saying that right. Anyway, I've went through six sessions of R-CHOP. And in December, I was told that I was in remission. And I just had my check-up again with my oncologist.

I'm having a lot of pain in the same hip where all of this originally started. Plus, I've got compression fractures in my back, which I had one little surgery for on L1 and 3. I'm still needing L2 and 4 taken care of. But I'm trying to hold off on this, just because I'm having a lot of hip pain again. The last PET scan has stated that there are no foci, F-O-C-I, of abnormal traits or activities suggest FDG-avid lymphoma, which obviously, is good news.

So, my question is, because this was aggressive, it was just a matter of months after a full hip replacement on the opposite side, it was found. I'm just obviously very skeptical of this -- keep it

staying at bay. I am anemic. I've been anemic for a long time. And I'm just trying to figure out -- I did request from my oncologist for another PET scan, which I'll have next week. And so, I am curious, with this CAR T-cell, if it has returned, if that's an option for me in Dallas, Texas.

Dr. Jason Westin
Yeah. Great questions. So, taking on the idea of bone troubles after a diagnosis of lymphoma and a treatment like R-CHOP -- the prednisone part of R-CHOP, the P drug, does have a chance to cause weakening of bones. And sometimes people could be at risk of having bones that are frail and weak, independent of having lymphoma -- osteoporosis or osteopenia are terms that we hear sometimes from doctors doing studies of bone density.

That can be sometimes worsened if somebody has a predilection to that and receives chemotherapy, including prednisone. So, I think getting a bone density test is, like, a great idea. And considering if that bone density shows to be low, to be on an agent that helps maintain bone's density, such as a bisphosphonate or other agents. There are drugs that can help improve bone health.

Regarding your pain in the hip, the acetabulum is a bone in the pelvis. That pain is potentially due to scar tissue or to damage done from the cancer, when there was cancer. That does not imply that there's not -- there's necessarily relapse of the disease. If a PET scan shows no evidence of anything lighting up, FDG-avid disease, then that pain would be consistent with just damage done to the bone from the cancer and from, potentially, the chemotherapy.

But if there were a disease that were present, a biopsy to see for sure if this is lymphoma, if it's the same lymphoma you had before. And if it did show the same darn thing, then CAR T-cell therapy would certainly be an option to consider. And it would be available in the Dallas area, yes.

Lizette Figueroa-Rivera
Thank you. And the next question, Doctor, John is asking: What evidence is there for cardiovascular side effects, such as atrial fibrillation, of chemotherapy and other treatments for NHL?

Dr. Jason Westin
Yes. Great question. So, these drugs-- the chemotherapy drugs we use often have lots of side effects. And cardiovascular ones are not the most common, but they can occur. It's sometimes difficult to know when something goes wrong. Is it the chemo that did it? Or was it something that was potentially kind of brewing under the surface and the chemo just kind of lowered the water a little bit and let something come out that was already right there?

Atrial fibrillation is not a common side effect of chemotherapy, but people who get chemotherapy are often in the age group that could get atrial fibrillation. And so, it's sometimes-- we don't do tests of giving chemotherapy to people to see if it gives them atrial fibrillation. We only find out when somebody gets chemo what side effects they see. And things like that would be in the low, single digits or even lower than that occurrence. There are also other treatments that we give for lymphomas, such as some inhibitors of special proteins.

There's a class of drugs called BTK inhibitors that are commonly used for patients with mantle cell lymphoma and chronic lymphocytic leukemia. Those agents can cause atrial fibrillation. That's a relatively common side effect of some of those drugs, and sometimes leads to pausing the drug or holding it. The management of atrial fibrillation, if it's due to or related to cancer treatment, would be the same.

The cardiology doctors would do the same thing, in terms of getting treatments to help control the heart rate, to consider using blood thinners. So, there's not a prevention strategy; but, if it occurs, it's managed largely the same as somebody -- your neighbor, who never even heard of lymphoma or chemotherapy and had atrial fibrillation.

Lizette Figueroa-Rivera
Thank you so much, Doctor. And the next question, from Carol. So Carol is in remission from DLBCL, after CHOP. She was diagnosed at 59, and has two siblings who also have a lymphoma diagnosis, one with DLBCL and one with follicular. So, out of seven children, three have lymphoma. Just asking what's the latest perspective on any genetic aspect of this?

Dr. Jason Westin
Yeah, this is a great question. And this comes up a lot in my clinic. When somebody is newly diagnosed and they're thinking of their kid at home or their sisters, brothers, and like--how worried do they need to be for somebody else? The scenario that our questioner is describing, thankfully, is relatively rare one. This is not a disease that is often considered to be genetic-- in that your grandma had it, your uncle had it, and you've got it.

It's not something like certain types of cancers, like breast cancer syndromes, the BRCA mutations, Lynch syndromes, colon cancer. There are some diseases where half the family has that disease. Lymphomas, that's rare. So, this particular questioner-- it certainly sounds like there is something that was going on, whether it was a genetic abnormality, or some chemical exposure in the house when they were younger, they lived too near a water stream that was contaminated or near power lines or -- who knows?

Unfortunately, for many patients, we don't have a smoking gun as to what caused lymphoma. But there are rare exceptions, where genetic abnormalities seem to run in the family and could help trigger lymphomas. I would suggest that this person and their siblings that have the lymphoma, consider to see a genetic counselor who could consider doing genetic testing to see-- is there any mutation that could be detected that could be looked at for this, as the potential, heritable condition?

If that was the case, that's not a preventative treatment. There's not some lifestyle modification or something else to be done. But certainly, a curiosity and a, likely, some common thread for three out of seven siblings to have lymphoma, with this not being the cancer that's happening in half the population of the United States. It's a rarer condition than that. But for everybody else on the call, what I'd say is, the chance that your first-degree relative-- be it your sibling, or your child, or your parent-- would develop non-Hodgkin lymphoma, it's a little bit higher than the average population.

But if I make up a number and say that there is a 1% chance of getting lymphomas, the chance that your child would get it might be something like 1.5% or 1.1% -- still not 50%, still not something very high. So, for this questioner, there is potentially something going on and maybe you would want to see a genetic counselor. For most people, lymphomas are sporadic and not genetic.

LLS Education & Support Resources

Lizette Figueroa-Rivera
Well, thank you. And thank you, Carol, for your question, which was our final question today. Again, a special thanks for Dr. Westin for sharing his experience, his expertise with us, and for his continued dedication to our blood cancer patients as well as their caregivers and families.

If we weren't able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572, from 9 a.m. to 9 p.m., Eastern Time. Or go to lls.org/informationspecialist, to chat online. Or, you can email us at lls.org/contactus.

LLS also has a Clinical Trial Support Center, where Clinical Trial Nurse Navigators will personally assist you throughout the entire clinical trial process. And you can reach them at lls.org/navigation.

LLS Education & Support Resources
Again, we'd like to acknowledge and thank: Bristol Myers Squibb; Eli Lilly and Company; Genmab US & AbbVie, Inc; Incyte Corporation; Kite, A Gilead Company; Merck and Company; and MorphoSys US, for their support.

LLS Education & Support Resources

Thank You
On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program, and take good care. Thank you.