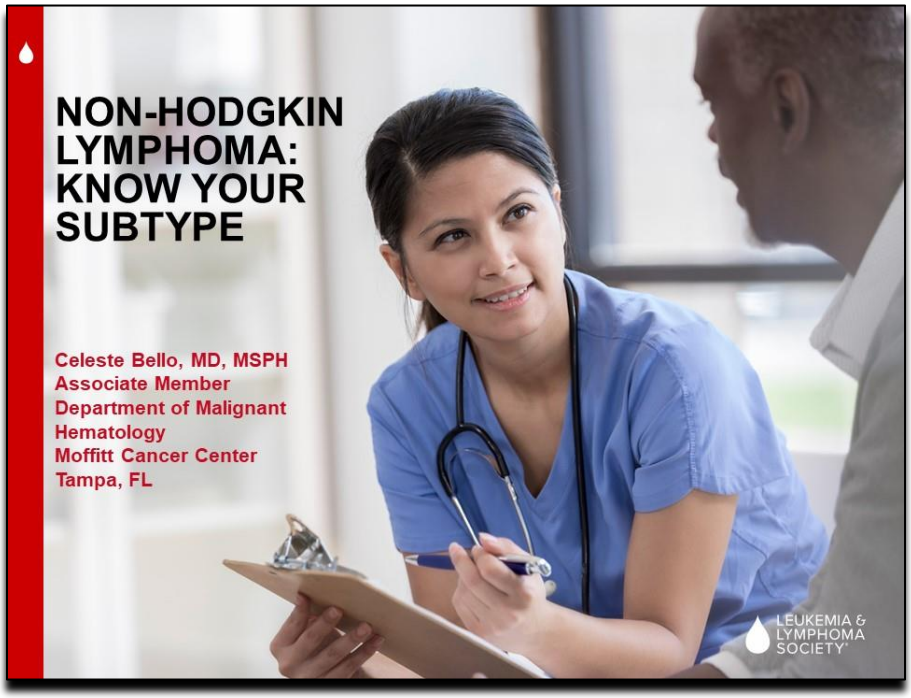
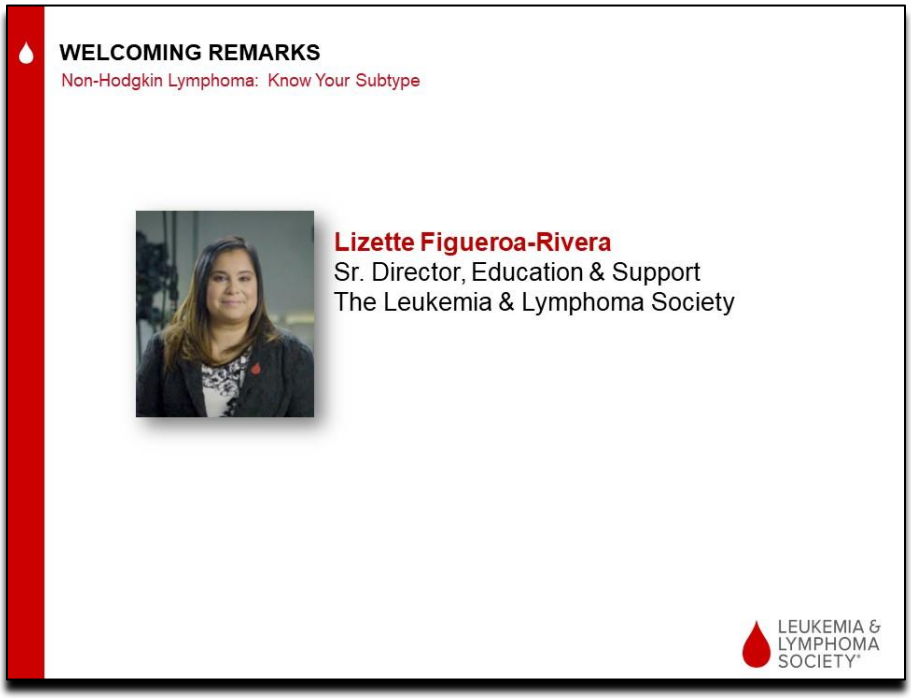


Non-Hodgkin Lymphoma: Know Your Subtype

Operator
Greetings and welcome to "Non-Hodgkin Lymphoma, Know Your Subtype," 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.

Special thanks to Dr. Celeste Bello, MD, MSPH for sharing her time and expertise with us today. Before we begin, I would like to introduce Lyneshia Johnson-Woodland, an NHL survivor. Lyneshia will share a few words. Lyneshia, please go ahead.

Welcoming Remarks

Lyneshia Johnson-Woodland
My name is Lyneshia Johnson-Woodland. I was diagnosed with NHL in September of 2020. Yes, during the pandemic. I am an Internet radio show host, actress, and comedian, and I just taped a podcast on The Bloodline with LLS titled, “A New You: You Made It Through.”

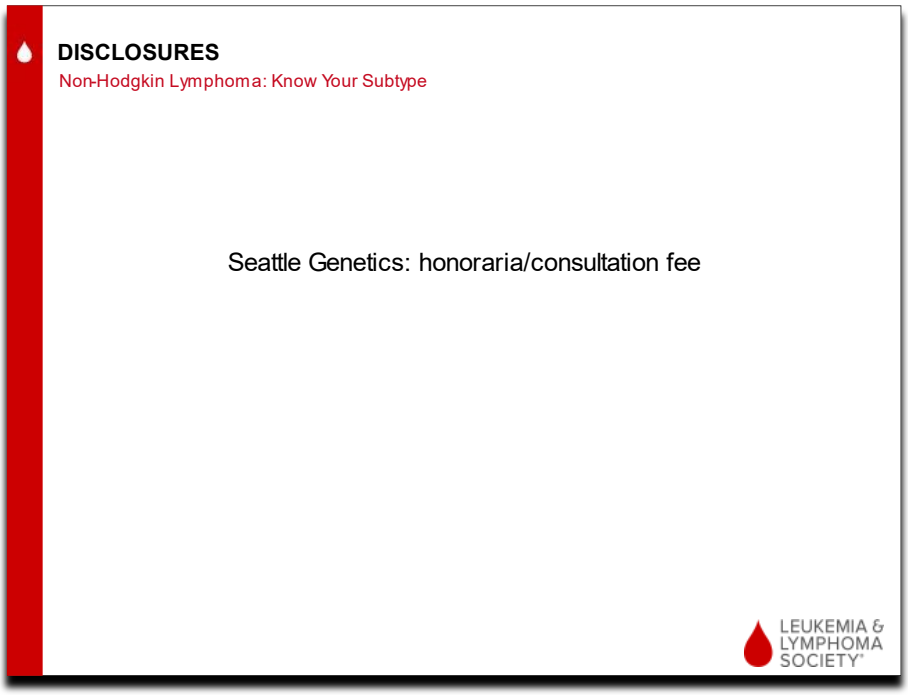
As of March 2021, I am in remission. I know this type of cancer, along with many other types, can be discouraging. But you will enjoy the new you because you will make it through. Thanks to the wonderful doctors, nurses, amazing faith-filled family and friends, and the support of LLS for the opportunity to share my journey, who also gave me encouraging words that motivate me to stay in the fight. I am grateful for this opportunity, which allows me to help, encourage others and give hope.

Remember, be intentional, be consistent, be present. The Leukemia & Lymphoma Society (LLS) is a champion for lymphoma patients, caregivers, survivors, and families. LLS, together with their volunteers, patients, researchers, healthcare professionals, and supporters, they are determined to change the future of lymphoma treatment and care.

Their vision centers in driving new breakthroughs and cures, helping all lymphoma patients access the care they need to survive and thrive and addressing healthcare disparities that, disproportionately, impact underserved populations. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

Today, we are fortunate to be able to learn more about how our particular NHL subtype directs our treatment and treatment goals. We appreciate Dr. Bello’s dedication to supporting our mission. I’d like to thank her for providing us today with this important information on NHL. Thank you to all. And for now, I’ll turn the program back to Lizette.

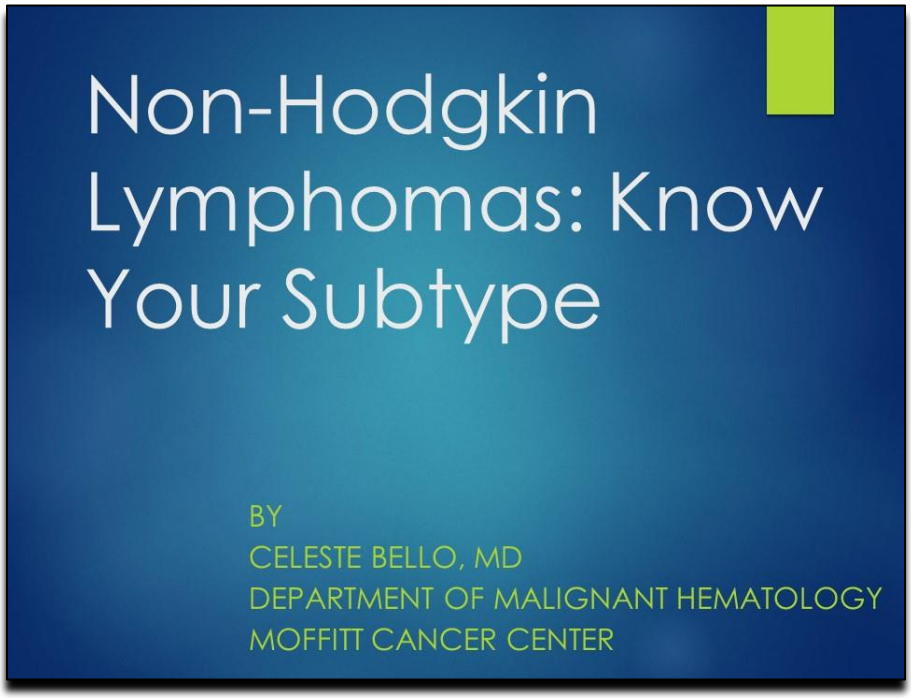
Lizette Figueroa-Rivera
Thank you so much, Lyneshia, for your welcoming remarks and for your encouragement.



Disclosures

As Lyneshia said, you can find her story on our patient podcast, *The Bloodline*, by visiting TheBloodline.org.

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



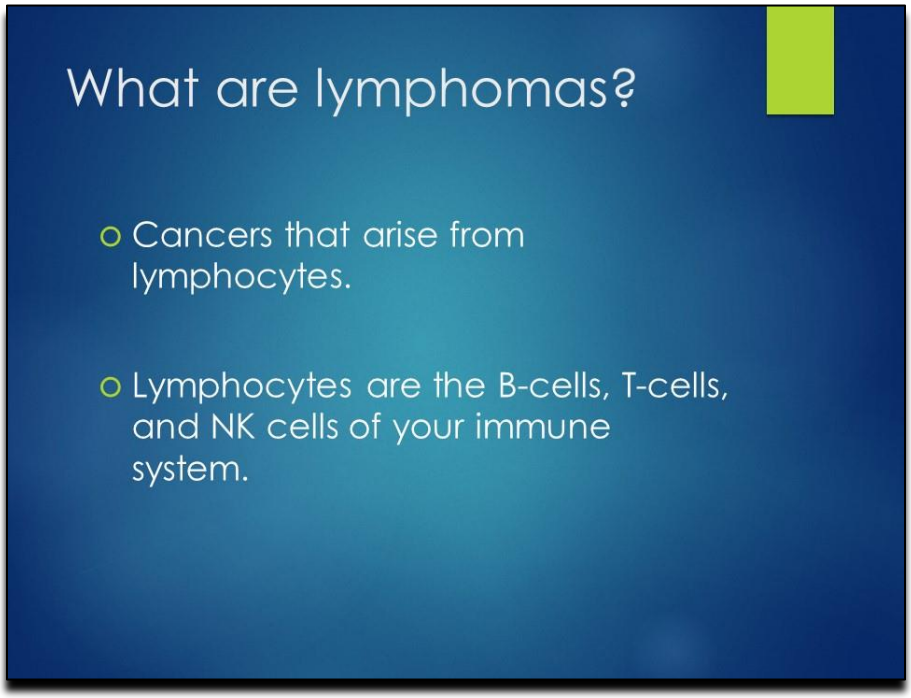
Non-Hodgkin Lymphomas: Know Your Subtype

I'm now pleased to introduce Dr. Celeste Bello, Associate Member, Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida.

On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time and expertise with us today. Dr. Bello, I'm now privileged to turn the program over to you.

Celeste Bello, MD, MSPH
Thank you, Lizette, and thank you—*thank you*—everybody at LLS for all the work that you guys do. I mean really, it's a great, great organization in putting on these multiple patient education seminars and webinars. And we really appreciate it. You guys do a great job.

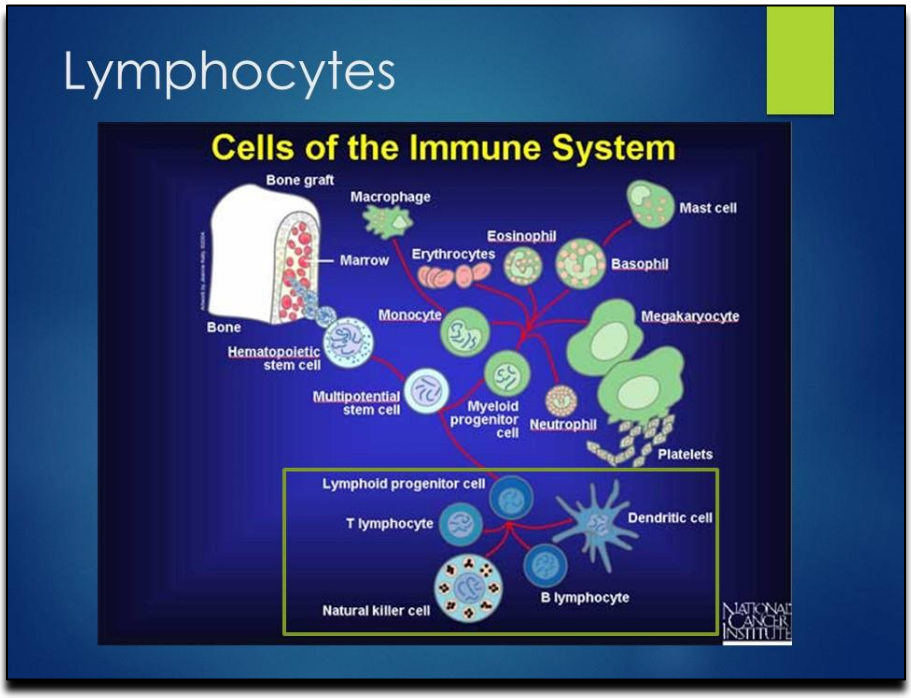
So, thanks again for inviting me. I consider it a privilege to be here. So, with that I'll get on to the talk, which is "*Non-Hodgkin's Lymphomas: Know Your Subtype*."



What are lymphomas?

And so, basically, I like to start kind of simple here and kind of answer a simple question, "What are lymphomas?"

Well, basically, lymphomas are cancers that arise from lymphocytes. And lymphocytes are the B cells, T cells, and natural killer cells of your immune system.

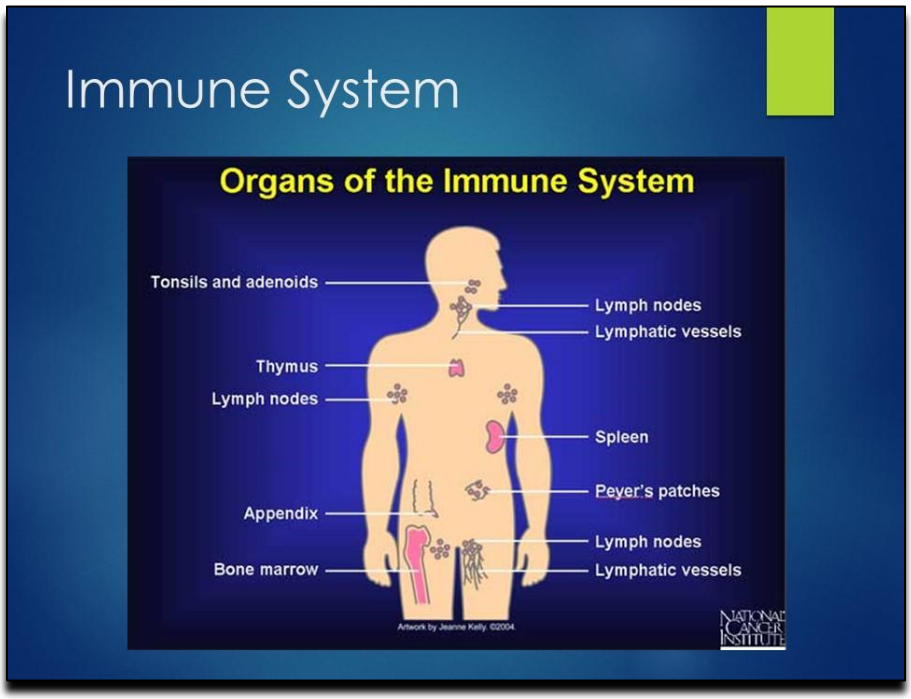


Lymphocytes

So, a little bit of a science lesson here. In the upper left-hand corner on your screen, you'll see that this is a bone—a picture of a bone. And in the middle of your bones is your bone marrow. And this is where all your blood cells are made.

The blood cells start out as a very immature cell with a lot of potential. And through different signalings, can end up going down different pathways. One pathway can take it down the myeloid progenitor cell pathway, where it will become a red cell or a platelet or a neutrophil or a monocyte.

And in other signalings, other signals will take it down the lymphoid pathway, where it will become a lymphoid cell, either a T cell, B cell, or natural killer cell. So, there's a lot of intricate development of the blood cells. But they all do start, for the most part, in the bone marrow.

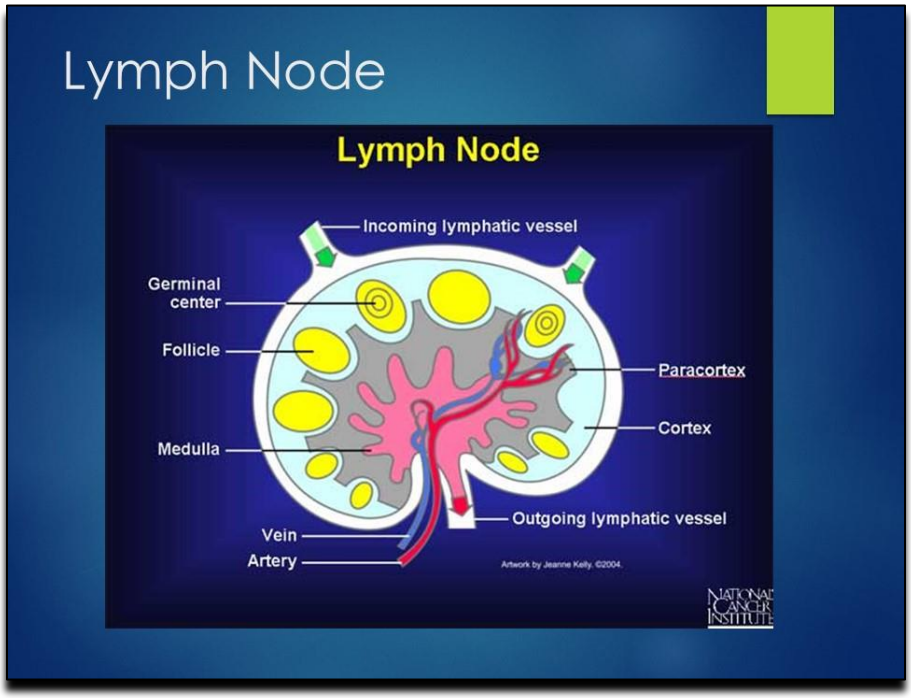


Immune System

The organs of your immune system are your lymph nodes, as most people on this webinar will attest to. But you also have your tonsils and adenoids. They're part of the lymphatic system. You have your thymus gland, which is where a lot of the T cells develop in your body. You have your spleen, which is kind of a huge filter, per se.

You have your Peyer's patches, which are areas of lymphocytes in the intestines and in your gut to help fight infections that might come through the intestinal or GI tract And then you have your lymphatic vessels, which connects your different lymph nodes.

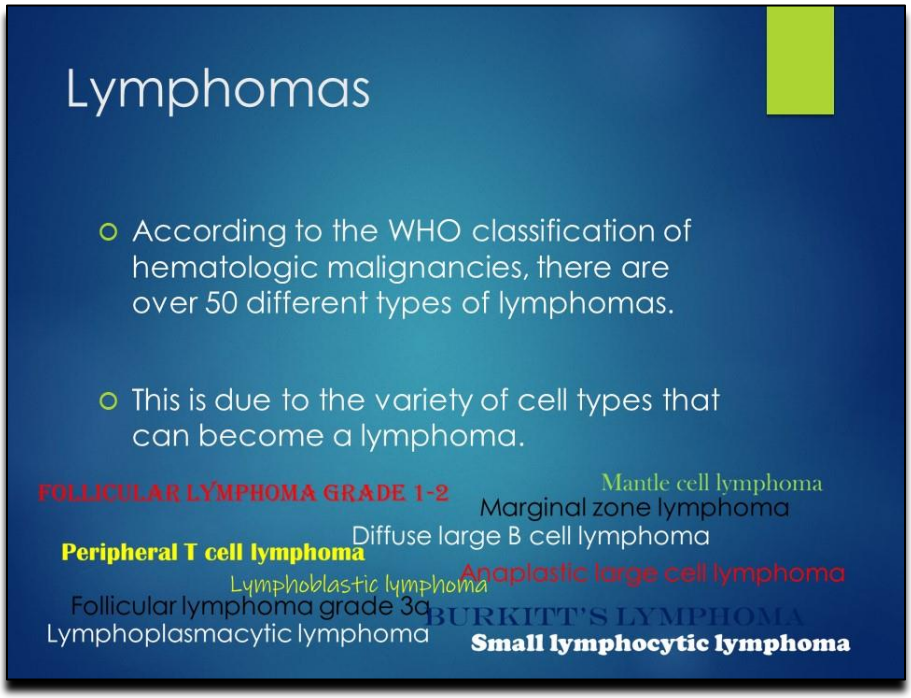
And again, this is just kind of a diagram of just different areas of the lymphatic or immune system. But you have lymph nodes all over your body—thousands of them. So, this is by no means all-inclusive of where your lymph nodes are only located.



Lymph Node

So, the lymph node. The lymph node is really the key to what we're talking about here. The lymph node serves a few purposes. The main purpose is that it is kind of a filter for your lymphatic system, and your lymphatic cells will sit there and wait to come across a pathogen or antigen where they'll attack and kill it.

But also, these areas in the lymph nodes called germinal centers in the follicles are where your B cells, most of your B cells will mature and develop in those areas. So, the lymph node is important for fighting infection, but also for the development of your lymphocytes.



Lymphomas

So, lymphoma. So now, we'll get to the meat here. So, according to the World Health Organization—the WHO—the classification of hematologic malignancies states that there are over 50 different types of lymphomas.

So, that's a lot of different types. So, just saying "lymphoma" is not very helpful because there are so many different types. And really, the reason there are so many types is because there's a variety of different cells that are called lymphocytes. We already said there's B cells, T cells, natural killer cells.

Then you have the different stages of development of the cells. And wherever the lymphoma occurs during that development process will lend itself to a different type of lymphoma. So with that, you have multiple types of lymphomas. Over 50, really, over 60 for the new classification, the most recent WHO classing.

So, this kind of—I was just showing here a slide where these are just all the different names of different types of lymphomas you might hear about: follicular lymphomas grade 1/2, anaplastic large cell, diffuse large B cell, mantle cell. And this is just really to name a few.

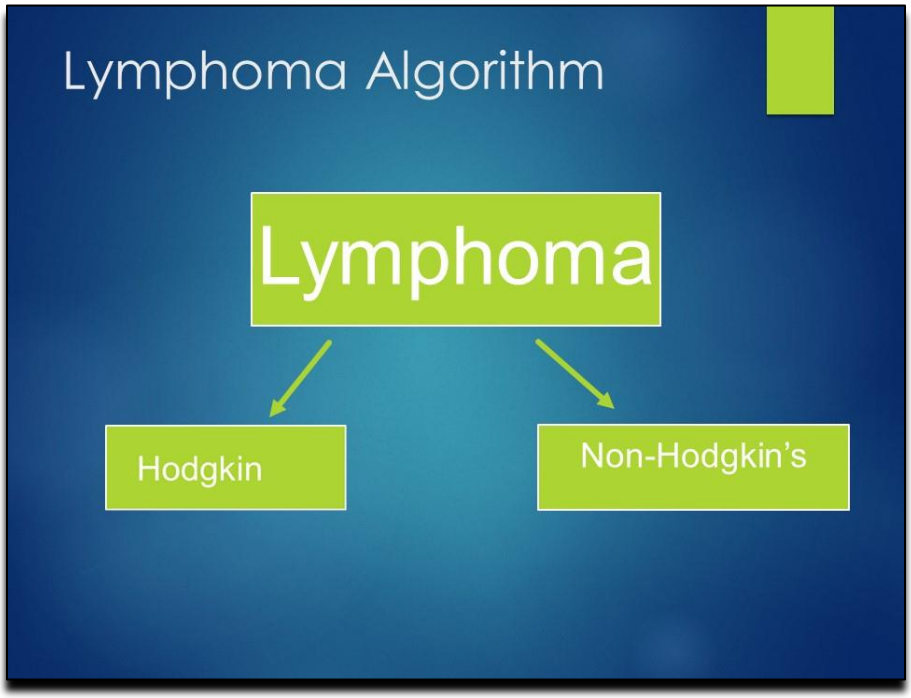
Image

So, this slide I usually like to start with when I give this talk to, like, the residents, too. I think it's kind of a neat slide because there are a ton of different types of lymphomas. But the types of people affected by lymphoma are also as varied as the different types.

So, this slide here, these are all people that have had a type of lymphoma. So, in the upper left-hand corner: Jon Lester, who used to pitch for the Cubs, he had a type of anaplastic large cell lymphoma and got chemotherapy for it and is essentially cured. He's been in remission for quite a long time.

Below him is Jacqueline Kennedy. She had, I believe, a type of anaplastic large cell also, although there's not really much about her medical history that I could find. And then in the bottom right corner is Paul Allen, one of the Microsoft guys. And he had a type of diffuse large B-cell lymphoma.

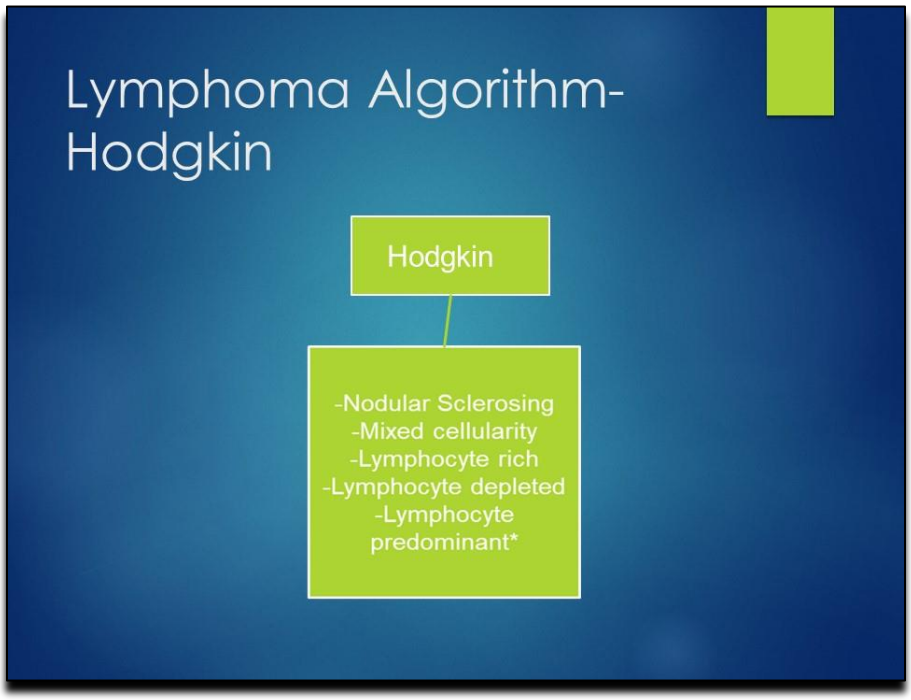
And in the upper right corner is Mr. T, who actually had a type of T-cell lymphoma, which is a little ironic. But all of these people—very different people—with varying different lymphomas.



Lymphoma Algorithm

So, because there are so many different lymphomas, we kind of put them into categories. So, the algorithm that's basically used is you have your suspected lymphoma. You'll run tests on it. And based on the way the cells look and the markers on the cells, they will be categorized into Hodgkin's and non-Hodgkin's lymphomas.

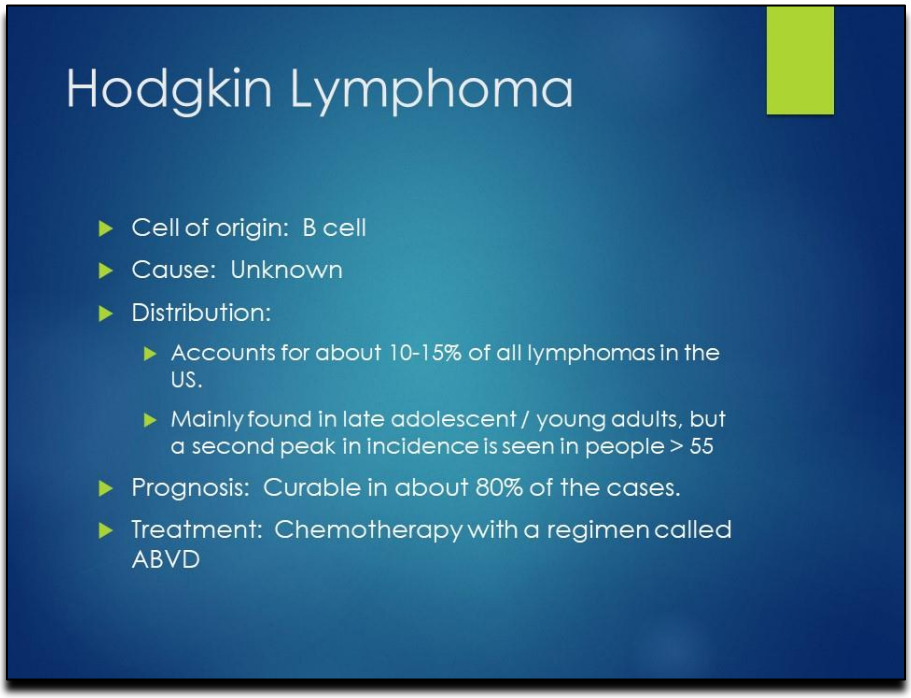
One is not better than the other. They all have their pluses and minuses. But this is just a categorical classification system just to make things a little simpler.



Lymphoma Algorithm- Hodgkin

So, within Hodgkin's. Hodgkin's plays a small piece of the pie of lymphomas. It's a small percentage. The majority of lymphomas in the United States and in adults are non-Hodgkin's lymphomas. But I thought I'd briefly touch on Hodgkin's. Hodgkin's—there's five types. The first four types: nodular sclerosing, mixed cellularity, lymphocyte rich, and lymphocyte depleted. Those are considered the classical Hodgkin's lymphomas.

The lymphocyte predominant, which I put an asterisk by, that's kind of the nonclassical one. So, when people are usually talking about Hodgkin's lymphomas, they're talking about classical Hodgkin's, which are the first four. And the first four types, they're all treated pretty much the same.

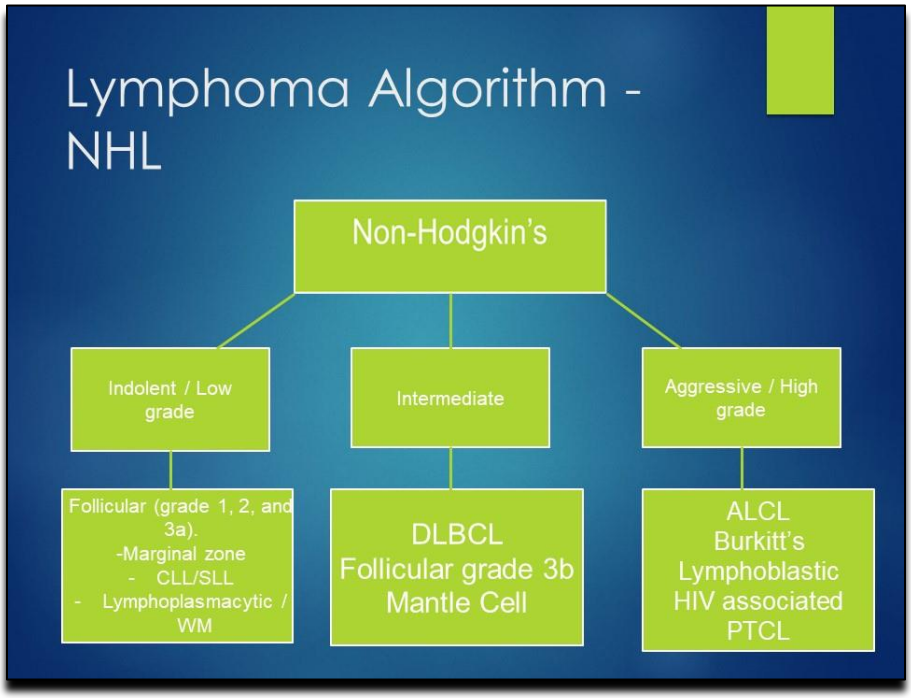


Hodgkin Lymphoma

Hodgkin's is, initially, it arises from a B cell, with a B-cell origin. The cause of a lymphoma, because people ask this all the time, is unknown. And you'll see a common theme here. All of the causes are pretty much unknown, unfortunately, for most lymphomas. It only accounts for a small pie of the lymphomas: 10% to 15% of all lymphomas in the United States. And it's mainly found in younger people, like adolescent and young adults.

But then, there's a second peak in incidence of the disease in people over the age of 55. So, kind of a unique cancer. Whereas most cancers, you'll see the incidence will go up with age. This one kind of peaks in young people then goes back down, then peaks again in people over 55.

The prognosis is very good in most cases. It's curable in about 80% of all comers with Hodgkin's. But unfortunately, chemotherapy is the main way to treat it and really the only way to treat it for most people. And the basic regimen is the regimen called ABVD, which has been the background or the backbone of treatment for a couple decades now.



Lymphoma Algorithm - NHL

So, that was Hodgkin's in a very quick nutshell. So now, we'll move over to non-Hodgkin's, which is a little more complicated. And this is where the majority of the other subtypes or types of lymphomas lie in. And so, because there's so many types of non-Hodgkin's, we further break them down based on their level of aggressiveness. So, we break them down into indolent or low-grade, which are slow-growing types of lymphomas. And that's your follicular lymphoma, which I put grade 1, 2, and 3A. Because for those of you that are familiar with follicular lymphoma, you'll notice that most of them are divided based on a histologic grading, either 1, 2, 3A, or 3B.

Marginal zone lymphomas fall into the indolent low-grade category. CLL/SLL, which is chronic lymphocytic leukemia/small lymphocytic lymphoma, they're considered low-grade non-Hodgkin's lymphomas. And then lymphoplasmacytic lymphomas, or Waldenstrom's macroglobulinemia, abbreviated WM, is a low-grade indolent type also.

In the middle you then have your intermediate types of lymphomas, the most common being diffuse large B-cell lymphoma, which is abbreviated DLBCL. That one is the one that probably the majority of people that you come across with non-Hodgkin's lymphoma will be diagnosed with. But then you also have your follicular grade 3Bs, your higher-grade follicular lymphomas. And then mantle cell lymphoma is in this category. Although I will say mantle cell is a bit of a kind of an unusual type of lymphoma and that sometimes it can behave very slow-growing and indolent-like, too. So, but if I just put that one in the intermediate because I think that's more appropriate.

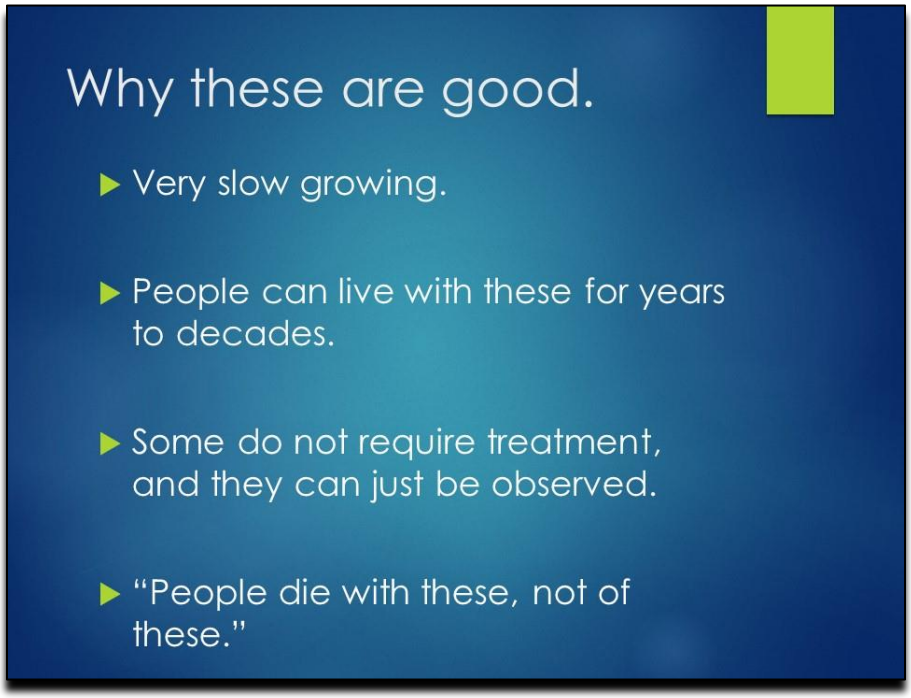
And then you have your aggressive high-grade lymphomas: your anaplastic large cell lymphomas, which is abbreviated ALCL, your Burkitt's lymphomas, your lymphoblastic lymphomas, your HIV-associated lymphomas. All go into the aggressive category. And then PTCL, which stands for peripheral T-cell lymphomas. So, those usually are in the aggressive or high-grade category.

The Good, The Bad, & The Ugly

So, this is kind of the scientific algorithm. But I also like to have like a less scientific algorithm. I like to refer to it as the good, the bad, and the ugly. And so, even though I say—I call one category the bad and the other category the ugly, I will say that, as a whole, most lymphomas have a pretty good prognosis compared to other cancers. But I kind of just break it down this way just to make it kind of easier to remember.

The Good

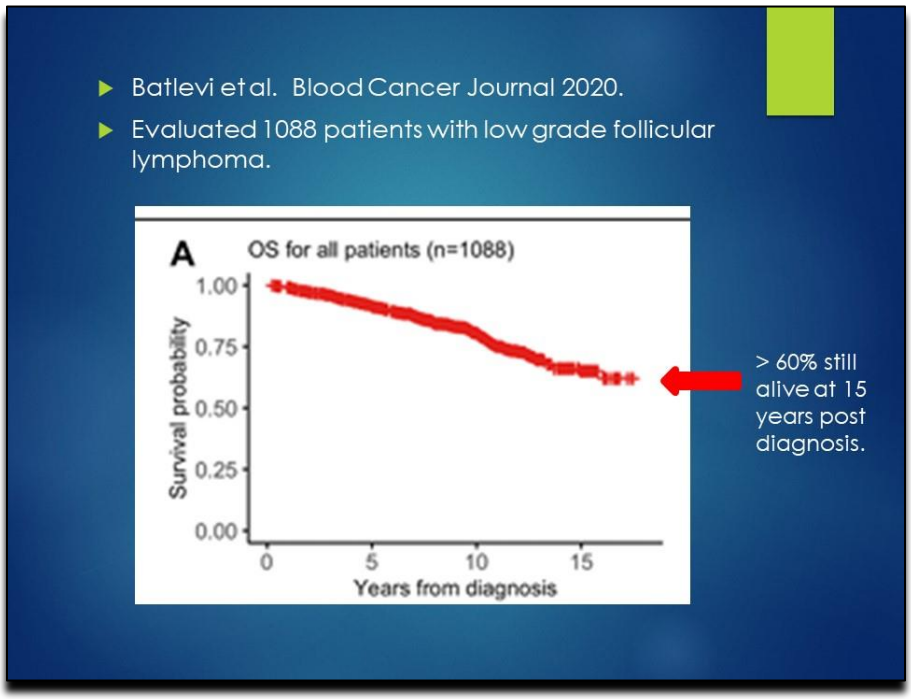
So, the first category, the good. So, this good would be your low-grade category: your follicular lymphomas; grade 1, 2, and 3A; your marginal zone lymphomas; your small lymphocytic lymphoma, chronic lymphocytic leukemia; your lymphoplasmacytic lymphoma and Waldenstrom's.



Why these are good

And why are these good? Well, these are good for a few reasons. The main reason is that the majority of these are very slow-growing, so people can live with these for years and even decades. And really even some don't even require treatment. They can just be observed over those decades.

And we usually, just to quote one of my prior teachers that said, "People usually die with these—not of these." And so, I think that's a good motto to throw out there, that it's more like a chronic illness, kind of will look like diabetes or high blood pressure where you kind of manage it. But it's something that will be with you forever. But forever can be quite a long time in these low-grade lymphomas.

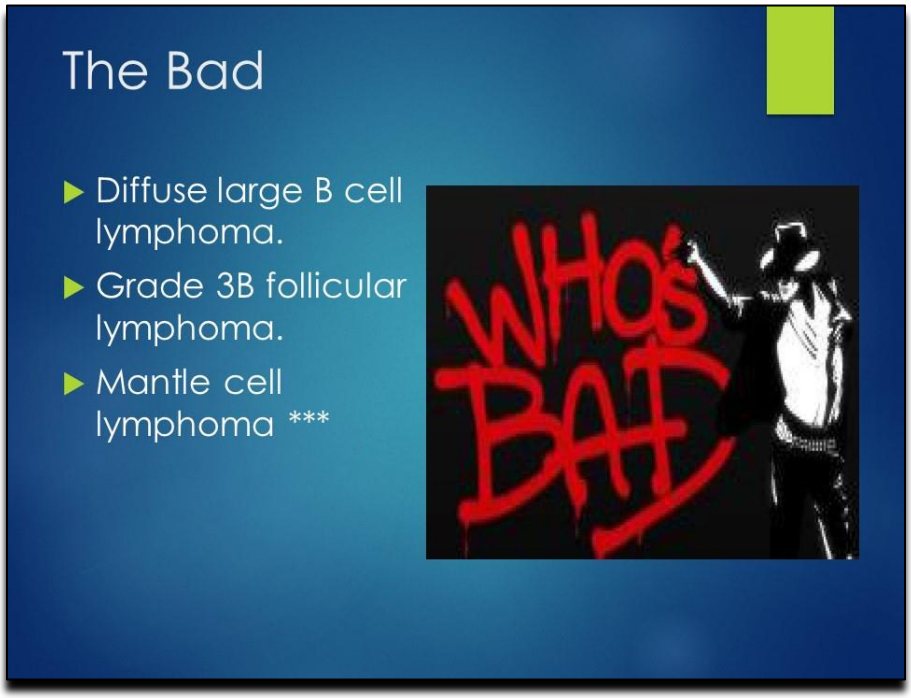


Image

And so, just to quote here, just to give you an example of the good prognosis that we see in this group. This was a study by Dr. Batlevi that was published last year. And it looked at a little bit over 1,000 patients with a low-grade follicular lymphoma. And it took all low-grade follicular lymphomas, people that got treated, people who didn't, and it showed their overall survival over like a 15-year period. And so, you can see that, per this graph, you could see where the arrow is pointing here that over 60% of the people with low-grade follicular lymphomas were still alive at 15 years post-diagnosis.

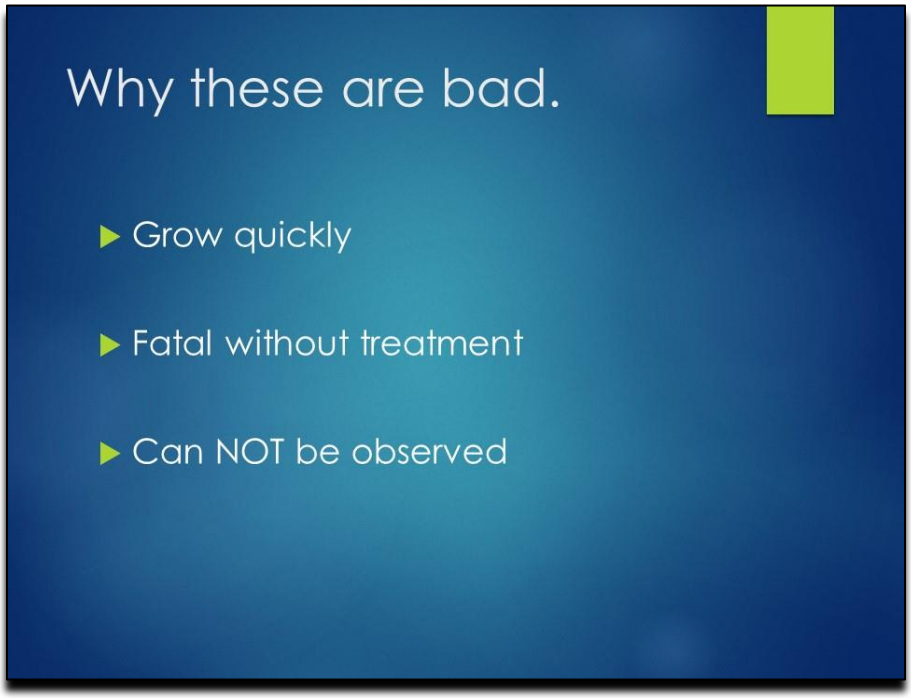
Now, this did not take into account what treatments they got or treatments. This just lumped them all together: all the low-grade folliculars.

But I think this graph shows you scientifically that there is evidence that these lymphomas behave quite indolently, and a lot of people live a very long time with these types of lymphomas.



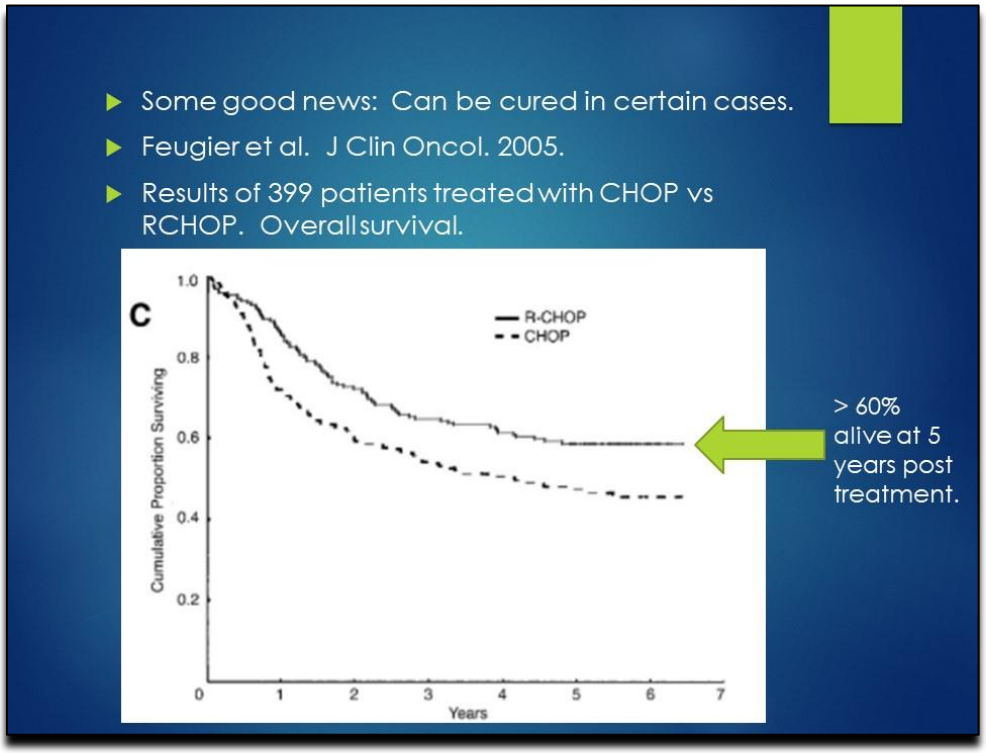
The Bad

So, who are the bad? The bad players are your diffuse large B-cell lymphomas, your grade 3B follicular lymphoma and then mantle cell lymphoma. And again, I put an asterisk by mantle cell lymphoma, because sometimes it actually behaves in the good category. But I had to put it somewhere.



Why these are bad

So, why are these bad? Well, the reason these are bad is because, unlike the low-grade indolent ones, these tend to grow kind of quickly. And they're usually fatal without treatment. So, they cannot be observed. They have to be treated. So, that's why they kind of get in the bad category.



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But I will say that there is good news. That some of these cases—a good number of them—can actually be cured with treatment. So, even though I call it the bad category, I just say it's bad because it needs treatment. But a lot of these are curable. And this graph here—this chart here that I'm showing—this was a study published in 2005. It's a little bit older study. But I thought it was a good example of, like, how long people live and that also people are cured in some of these cases, after receiving a chemotherapy/immunotherapy regimen called R-CHOP.

And so, what the green arrow is pointing at—that black line—are people with diffuse large B-cell lymphoma that got treated with R-CHOP. And you can see that the bottom axis there is the years posttreatment. And what it's showing is that you could see right around past 5 years posttreatment. The line kind of becomes flat. And there's no dip in the line. It just becomes a straight, flat line. And usually, when we see that in survival analysis, it usually means there's no more events after that time. That kind of equates to is that, if after 5 years these people have not recurred, recurrence does not happen. And so, basically, the lay term would be these people are cured.

So again, I think this is kind of a good example of people getting treated with diffuse large cell lymphoma and actually seeing cures in over 60% of them, post-5 years of treatment.

The Ugly

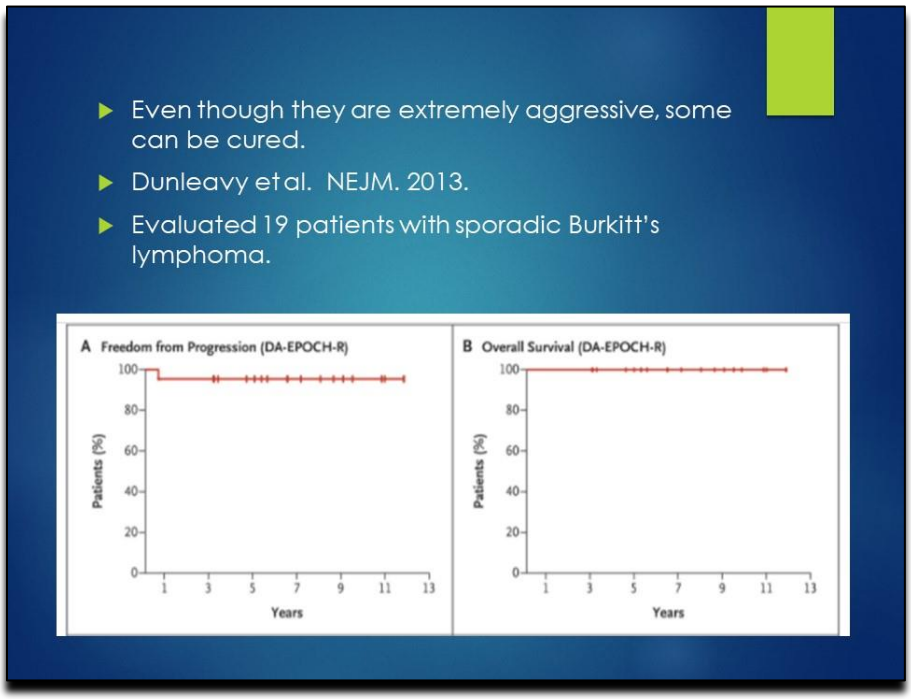
And then we get to the ugly category. So, the ugly. The ugly is your lymphoblastic lymphomas, your Burkitt's lymphomas, most peripheral T-cell lymphomas, anaplastic large cell lymphomas without a certain mutation called ALK, HIV-associated lymphomas, and your primary central nervous system lymphomas. These are all pretty ugly.

Why these are ugly

And the reason these are ugly is that they grow extremely quick. I mean, some will even double in size within a matter of days. And they can be rapidly fatal, without treatment. The picture here in the bottom right is showing you here is the image on the left. These are PET scan images, and these are gray-

scale PET scan images. And what it's showing you is this person is facing us. And so, in their left—the big black circle thing at the top is their brain. So, that's not a tumor. But on the left kind of neck/shoulder area, you'll see a bunch of little black dots. And in the left kind of under their arm, there's a lot of black dots here. And those are all areas of lymphoma.

Lower down, you'll see the kidneys. That's not lymphomas. The contrast is excreted into the urine, so it always lights the kidneys up, and the bladder is really at the bottom of the screen. That always lights up too, because the contrast gets excreted in the urine. But this person looks like they have disease in the left neck and upper chest area. And the picture on the right is showing this person, 8 weeks later, without treatment. And you can see the extensive progression of their lymphoma, which is quite quick for any kind of cancer to grow this fast. But you can see it's like tripled—at least, tripled in size. And I think this is a good picture of how rapid some of these lymphomas can grow in the ugly, ugly category.



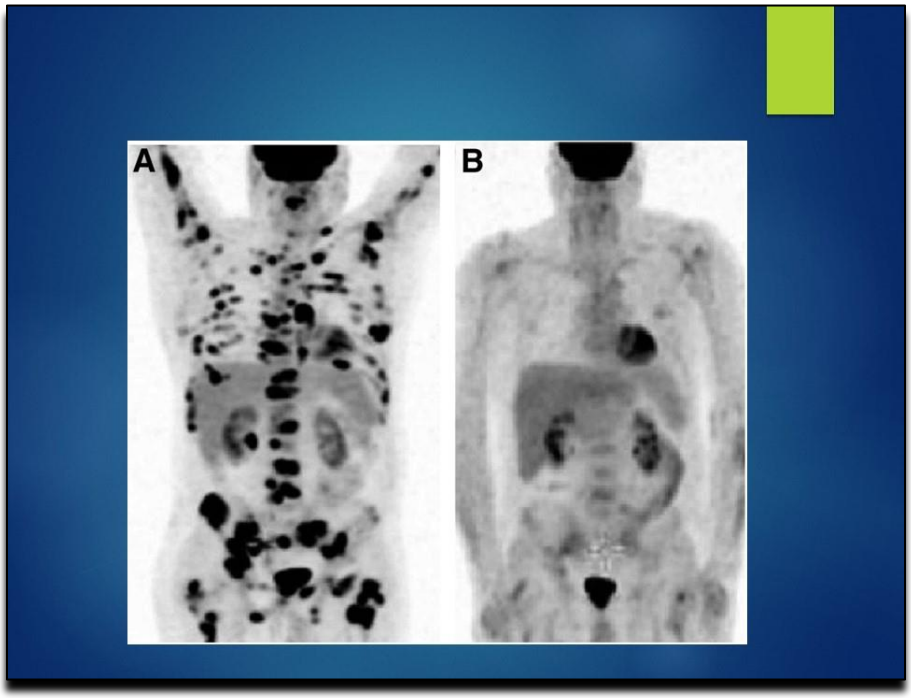
Image

But again, we still like to have some good news here. And that, even though these are ugly because they're so aggressive, they can be cured. And actually, a lot of them can be cured. Your Burkitt's lymphoma is highly curable and in a quite short period of time.

And so, this chart here is just showing survival in people with Burkitt's lymphoma who got treated with a regimen called dose-adjusted EPOCH and Rituxan® (rituximab), or DA-EPOCH-R. The graph on the left is showing their freedom from progression after treatment, which means the amount of time they went without the lymphoma coming back. The right is their overall survival, which means how many people were still alive after treatment.

And you can see that even 9, 10, 11 years out, 100% of the people on this small study were still alive posttreatment of their Burkitt's lymphoma. And the majority of these people were also without their lymphoma.

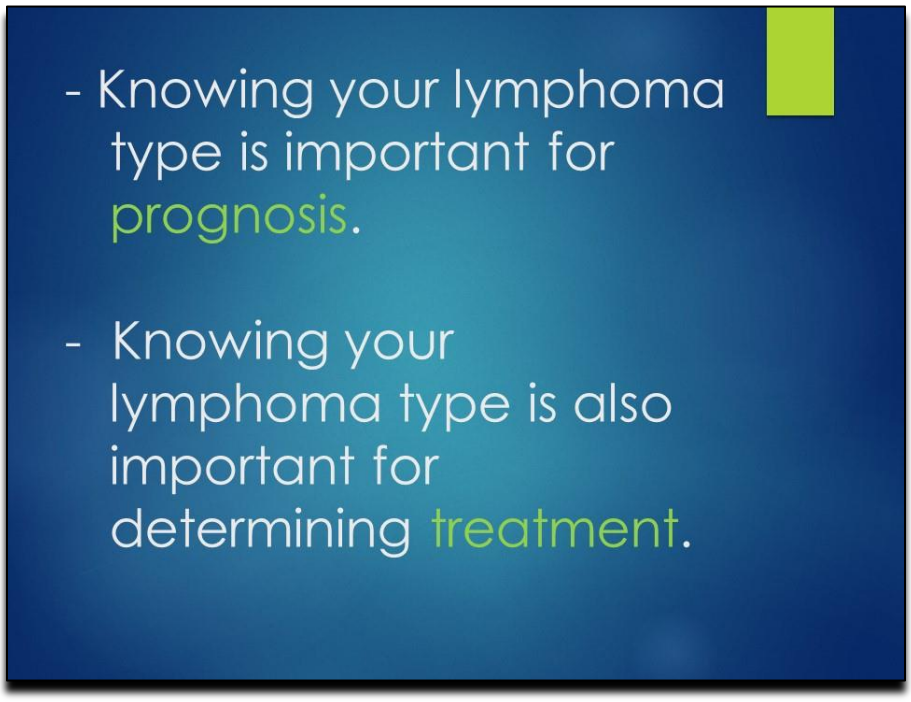
So again, I think this is kind of a nice graph showing you that, yes, we have ugly lymphomas. But even the ugly can be cured in some cases.



Image

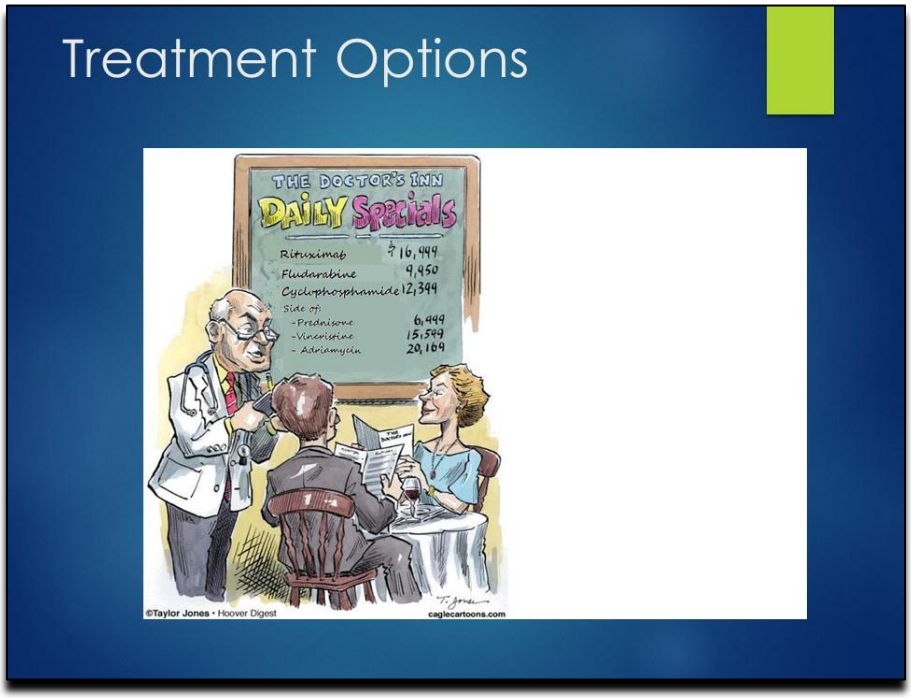
And here—this graph here, this chart here—I'm just showing you a before and after photo. So, A is somebody that, all those black spots are lymphomas, except for the brain and the bladder and kidney areas. But after treatment, the one in B is a complete remission.

So, those black areas, like I mentioned previously, those are physiologic uptake areas, that those are normal tissue areas. So, you can see this person got a complete remission where previously they were full of lymphoma.



Know your lymphoma type is important for prognosis

So, to summarize, knowing your lymphoma is really important for prognosis. But it's also knowing your lymphoma type is also important for determining treatment. So, we just went over kind of the prognosis part. But now, let's go over more of the treatment part.



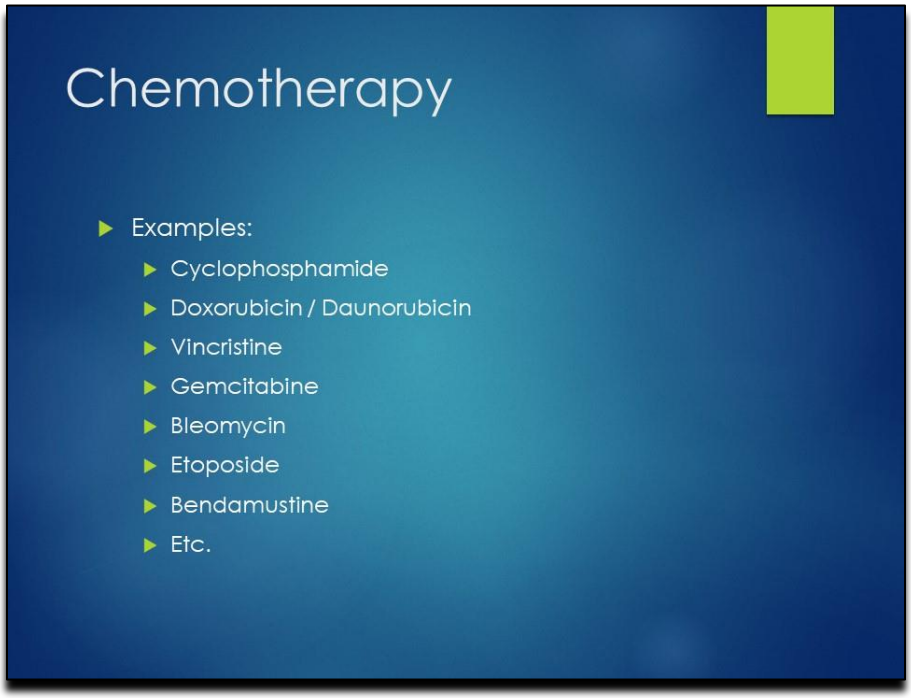
Treatment Options

And the reason that it's so important for the treatment is that we have so many treatment options.

There's like a virtual—I like to refer to it like a menu of options here. And that's a good thing because it's better to have more options. But also, it can make things a little more difficult when you have options, because now it requires a little more thought on determining which is the right treatment and which would work best in each individual situation.

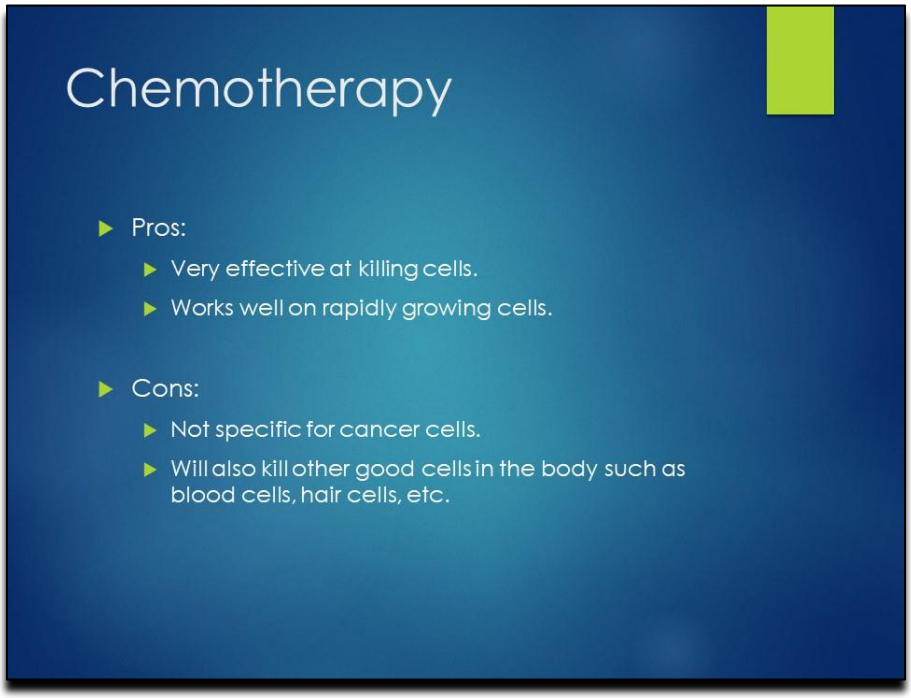
Chemotherapy

So, our first option of treatments would be the group of treatments called chemotherapy. So, chemotherapy, basically, it's just a word to describe chemicals that kill fast-growing cells. They mainly work by attacking some part of the cell process that's necessary for replication and division, such as the copying and splitting of the DNA strands in the cells. And so, it's not specific for any one cell type, but it will kill pretty much any cell that is rapidly dividing.



Chemotherapy

Examples of chemotherapy that a lot of you are probably familiar with would be cyclophosphamide, doxorubicin, vincristine, gemcitabine, bleomycin, etoposide, bendamustine, etc. And so, these are all commonly used chemotherapy drugs in the lymphoma world.



Chemotherapy

So, the pros of chemotherapy is they work extremely well on rapidly growing cells.

So, your more aggressive lymphomas will respond very well to, a lot of times, chemotherapy. But the downside or the cons is that, again, like I mentioned previously, the chemotherapy drugs are not specific for any particular cancer cells. It'll also kill other good cells in your body that are growing fast, such as your blood cells, your hair cells, etc.

And that's why it causes the side effects. So again, very good at killing but not very specific. You'll see that—back on that list that I mentioned there—some of those medicines we use, not just for lymphoma but for breast cancer, for colon cancer. So, it works on rapidly dividing cells but doesn't care what the cell type is.

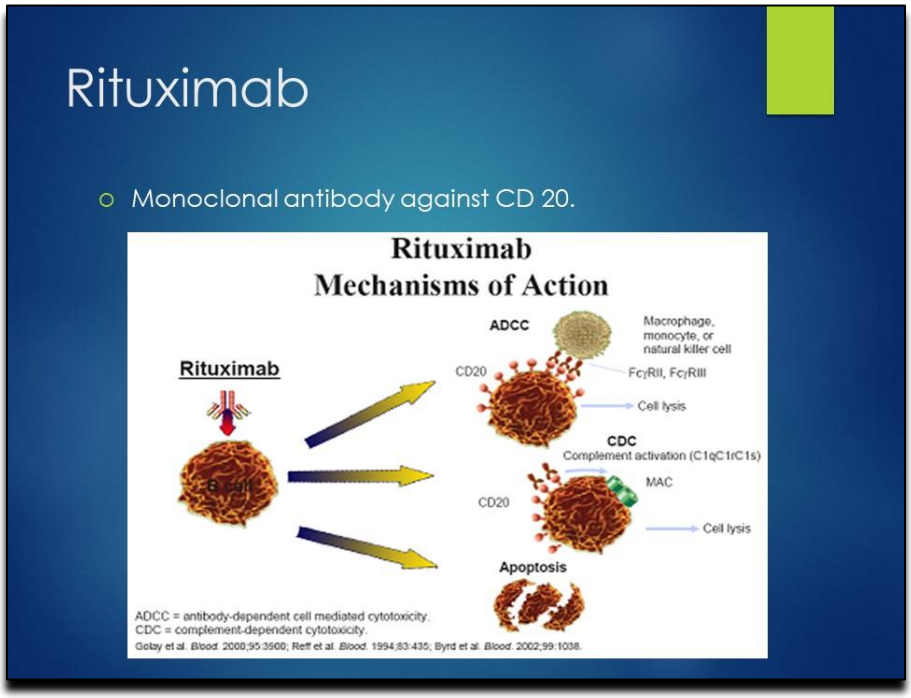
Targeted Therapies

So, because of the side effects, they're really the limiting part of the ability for chemotherapy to be delivered. The past couple of decades, more people have been working on targeted therapies: therapies that would specifically kill a certain cancer without causing multiple side effects or with reduced side effects.

And so, some examples of targeted therapies are your monoclonal antibodies; your antibody-drug conjugates; your small molecule inhibitors, which include Bruton's tyrosine kinase inhibitors, or BTK inhibitors; your phosphatidylinositol 3-kinase inhibitors, or PI3K inhibitors; and your BCL2 inhibitors.

Chemotherapy vs Targeted therapy

So, the way I like to compare chemo versus targeted therapy is that conventional chemotherapy is like a shotgun at a target. You'll hit the target, but you'll also have a lot of collateral damage. Targeted therapy is like hitting a bullseye with an arrow just pinpoints one area and—boom!—gets it.



Rituximab

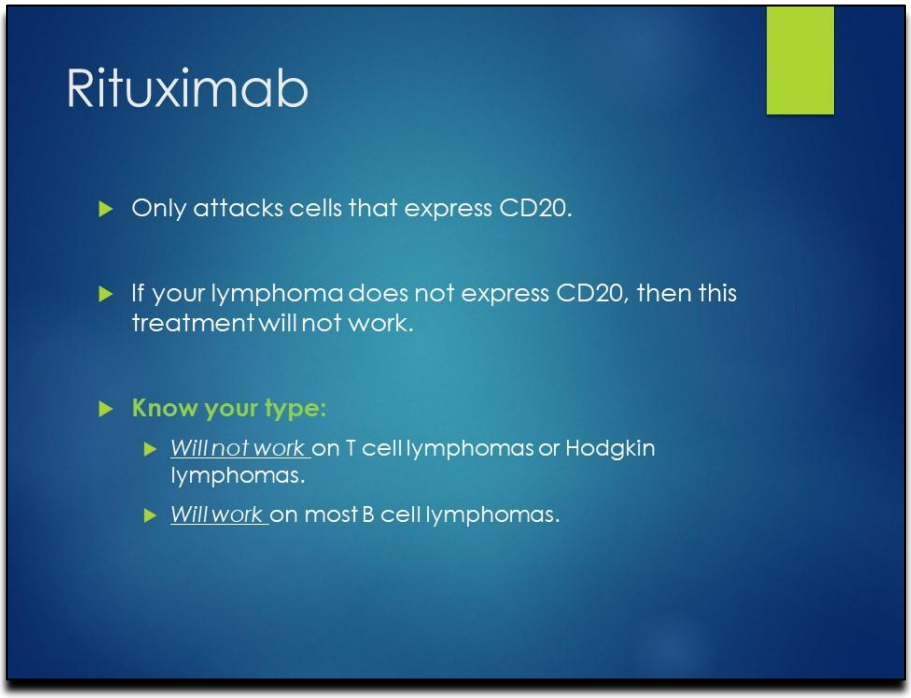
So, the first one I wanted to talk about, first targeted therapy, is one called rituximab. A lot of you with B-cell lymphomas are probably very familiar with this medicine because it is the component or main component of most B-cell lymphoma treatments.

Rituximab is a monoclonal antibody against CD20. And what this means is that it's an immune therapy–type treatment, and it's an antibody that binds to a protein called CD20. And what this graph or diagram here is showing you is, on the left, you have your little Y-shaped Rituxan® (rituximab) antibody, and it's come in contact with a tumor cell. When it comes in contact with a tumor cell, it will bind to a protein called CD20 on the surface of these cells. And then it will kill it through three different mechanisms.

The top arrow is showing you what's called antibody-dependent cell-mediated cytotoxicity. What that is, is that when the Rituxan® (rituximab) binds to the little CD20 protein, it will kind of flag over your other cells of the immune system and say, "Come over, attack this cell." So, in that way it will cause the cells to die under the influence of your own immune system.

The middle arrow is showing a second mechanism called complement-dependent cytotoxicity, where binding of the Rituxan® (rituximab) to the CD20 will activate another part of your immune system called the complement system. The complement system is usually a bunch of enzymes that will, when triggered, poke holes in the cell and eventually cause the cell to die.

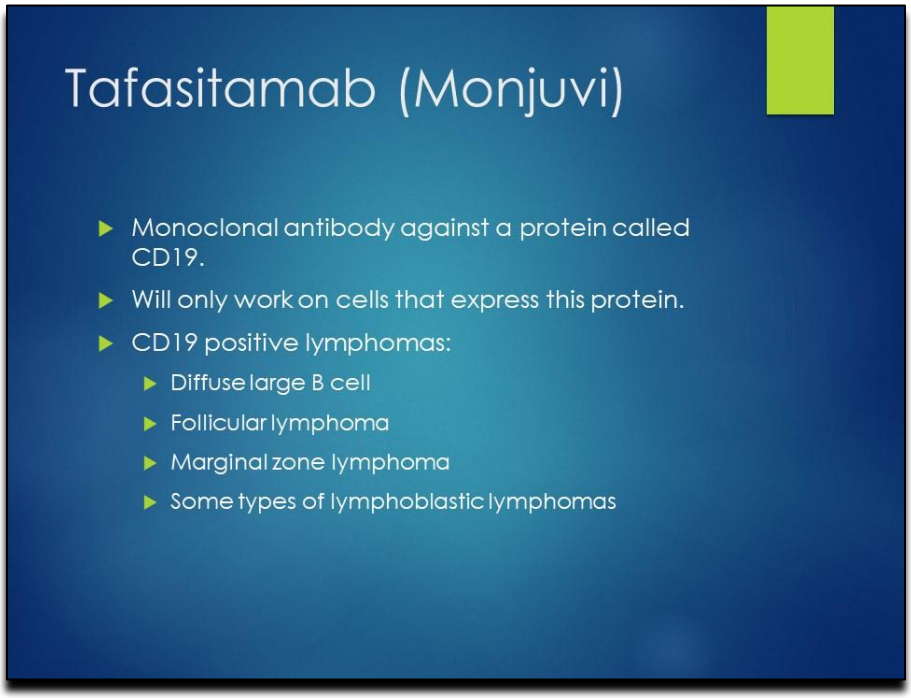
And then the bottom arrow is showing apoptosis, or direct cell killing, where the binding of the Rituxan® (rituximab) to CD20 triggers the cell to undergo suicide, basically. And so, this is how Rituxan® (rituximab) works against B-cell lymphomas or lymphomas that are CD20 positive.



Rituximab

However, this is where knowing your type is important because rituximab will only attack cells that express CD20. If your lymphoma does not express CD20, then this treatment will not work and it's pretty useless. So again, know your type. It will not work on T-cell lymphomas or Hodgkin's lymphomas because they don't have CD20. It will work on most B-cell lymphomas.

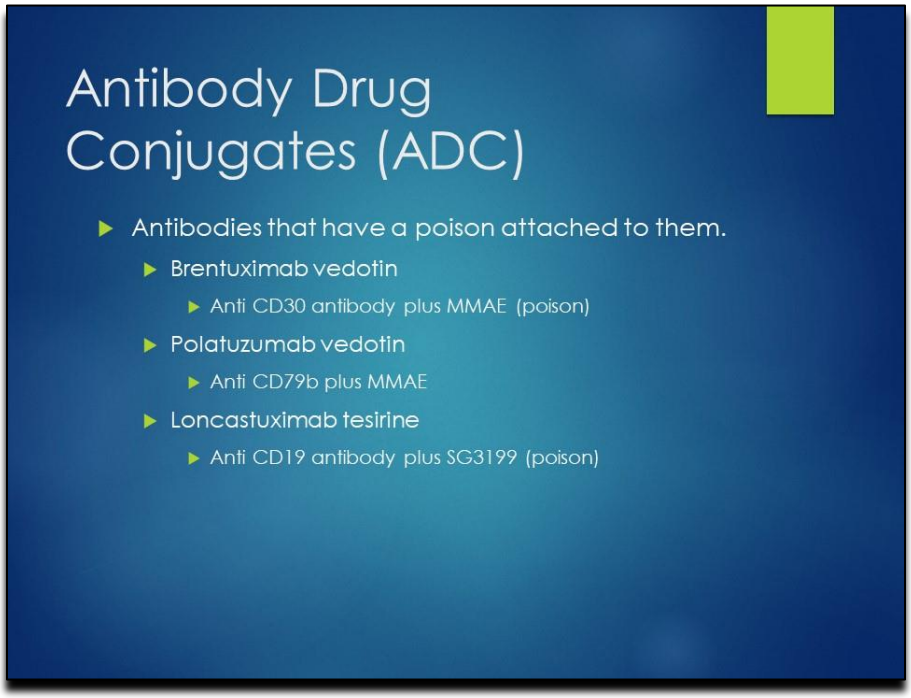
So, this is the key part. And this is the key theme that I'm going to mention with each of the treatments I'm going over here, is that you really need to know your type because not all of these treatments work on all types of lymphomas.



Tafasitamab (Monjuvi®)

So, another type of monoclonal antibody is a medicine called tafasitamab, or Monjuvi® is the brand name. And this is another monoclonal antibody. And it's against a different protein called CD19. It works the same way or similar to Rituxan® (rituximab). But instead of binding to a protein called CD20, it binds to a protein called CD19. Again, it will only work on cells that express this protein. So, you need to know your type of lymphoma because this won't work on diffuse large B cells. It will work on follicular lymphoma, marginal zone lymphomas, some types of lymphoblastic lymphomas.

But it won't work on Hodgkin's, and it won't work on most T-cell lymphomas. So again, important to know of your type because it will determine what treatments will be effective.



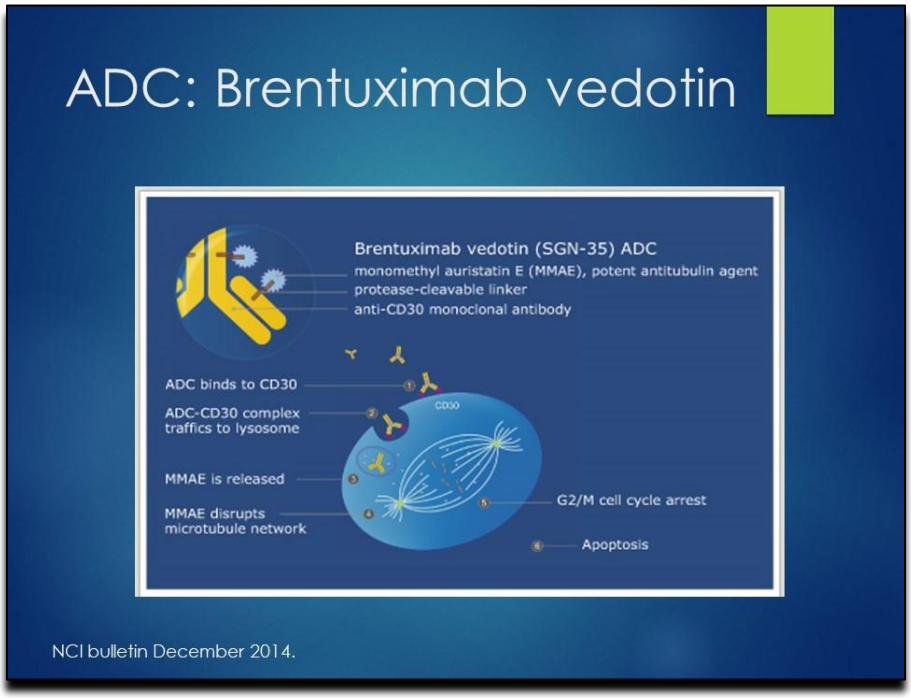
Antibody Drug Conjugates (ADC)

Then we move in another class of targeted therapies are your antibody-drug conjugates. We call them ADCs for short. And basically, these are antibodies also. But instead of just being an antibody by itself, or a naked antibody, it has a little poison attached to them. So, I like to kind of compare these to, like, a Trojan horse, where they come over and the cell lets them in. And when they come in, they have a poison that they release when inside the cell. So, these are kind of unique class of drugs.

So, the first one that's probably the most commonly used in lymphomas is one called brentuximab vedotin (Adcetris®). This is an anti-CD30 antibody, so it binds to a protein called CD30 and has a poison attached to it called MMAE. And this poison is what causes the lymphoma cells to die.

Another antibody-drug conjugate that's relatively new is one called polatuzumab vedotin (Polivy®). It binds to a protein called CD79B. And then there's a third one called loncastuximab tesirine (Zynlonta®). I don't know where they get these names from, but it binds to CD19 and it has another different toxin attached to it called SG3199.

So, the reason I'm bringing these up is that, again, these are three different drugs that work on three different proteins, which are expressed on different types of lymphomas. So again, it's important to know your type because your type may not have this marker. And so, thus, these treatments will not be effective if you don't have these markers.

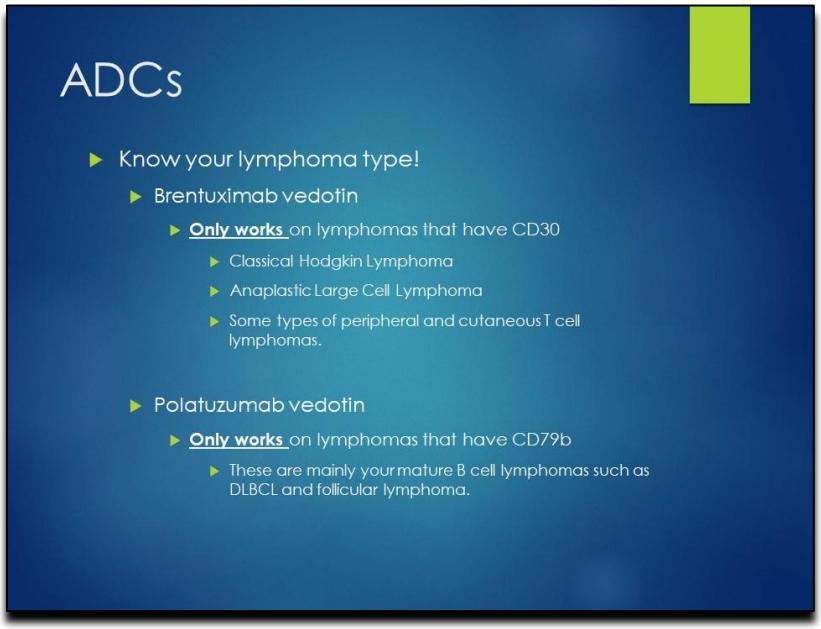


ADC: Brentuximab vedotin

So, kind of to go into depth a little bit more about the antibody-drug conjugates, or the ADCs. I want to just go over brentuximab a little bit more in detail because, again, this is the most commonly used one—I'd say—in the lymphoma realm. And so, what this diagram is showing you here—this little yellow kind of upside-down Y—is an antibody against CD30. And the little spurs attached to it are the poison, the MMAE toxin attached to it.

So, when they come over and they run across a cell that has CD30 on it, it will bind to that CD30. And then, the cell will kind of engulf it and it'll bring that antibody inside. And then once inside, that poison MMAE is released. And this poison specifically disrupts microtubule formation and stabilization, which is necessary for cells to divide.

So, when that happens they then undergo apoptosis, or cell death. And so, that's the way most antibody-drug conjugates work. The three that I mentioned previously work that way. They just bind to a different protein on the cell's surface.

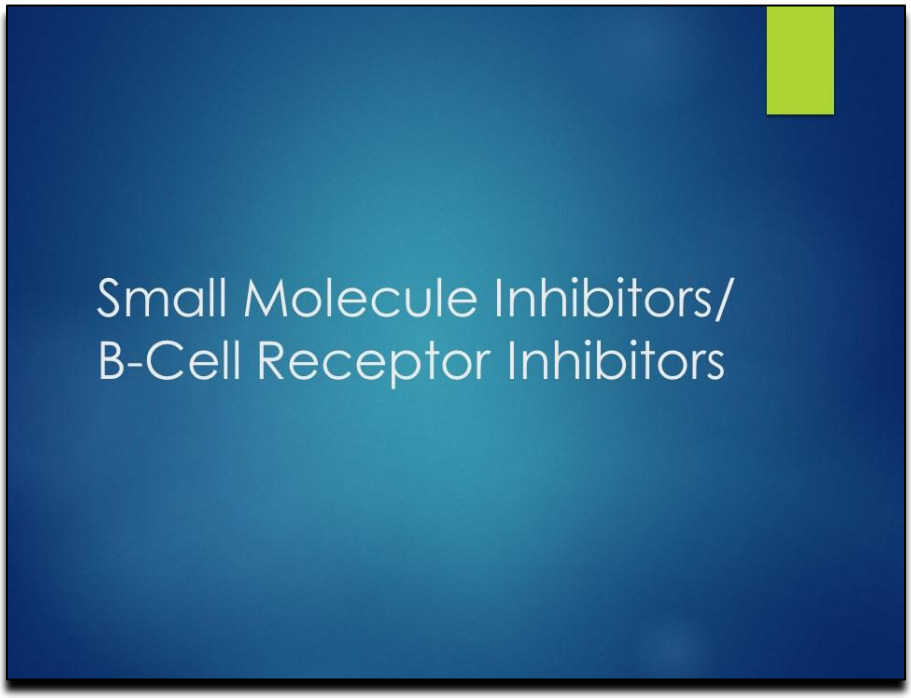


ADCs

So again, I know I'm, like, beating this in, but you need to know your type because, again, brentuximab vedotin only works on lymphomas that have CD30. Well, which lymphomas have CD30 on them? Your classical Hodgkin's lymphomas do. So, this drug works very well for classical Hodgkin's. Your anaplastic large cell lymphomas have this, so works very well in that group, too. And then some types of peripheral and cutaneous T-cell lymphomas also have this.

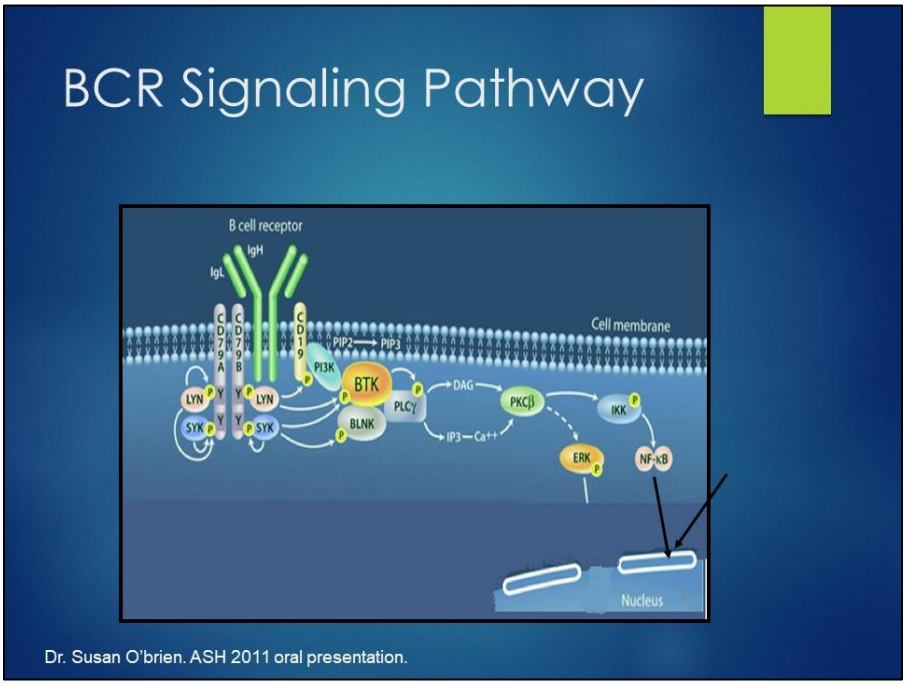
So, it does not really work that well on B-cell lymphomas, but there are some that it can work with. But these are the three main categories that it's used for.

And then, again, polatuzumab only works on lymphomas that have CD79B. So, these are mainly your mature B-cell lymphomas, just a few large B cell and follicular lymphoma. So again, another example. You really need to know your type, especially nowadays with these targeted therapies.



Small Molecule Inhibitors/B-Cell Receptor Inhibitors

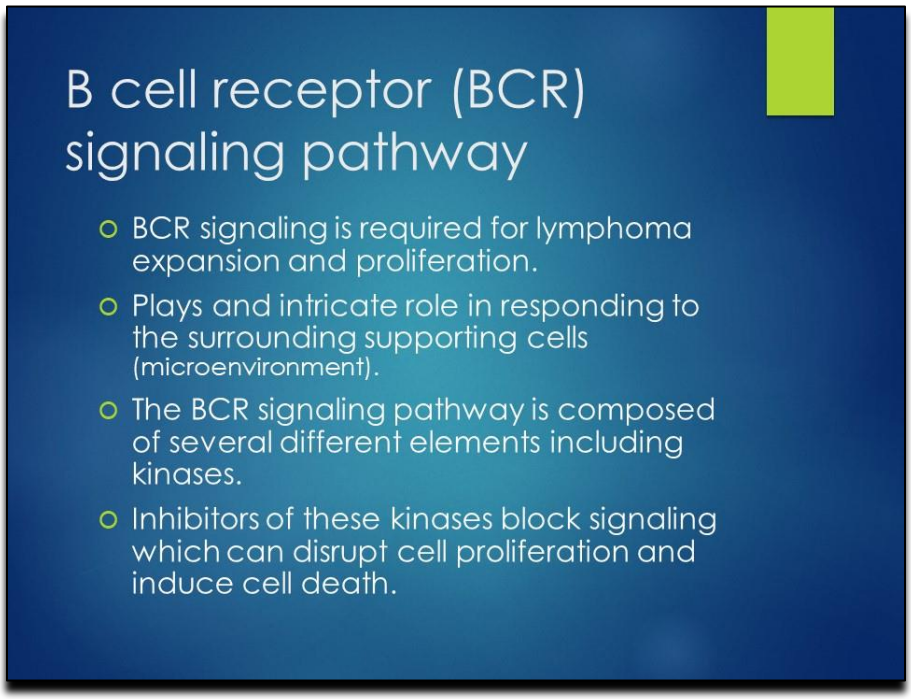
So now, we'll go into the small molecule inhibitors, or the B-cell receptor inhibitors.



BCR Signaling Pathway

Back to science class again. Basically, what this diagram is showing you here is the cell membrane of a B cell. And the little green Y is a B-cell receptor.

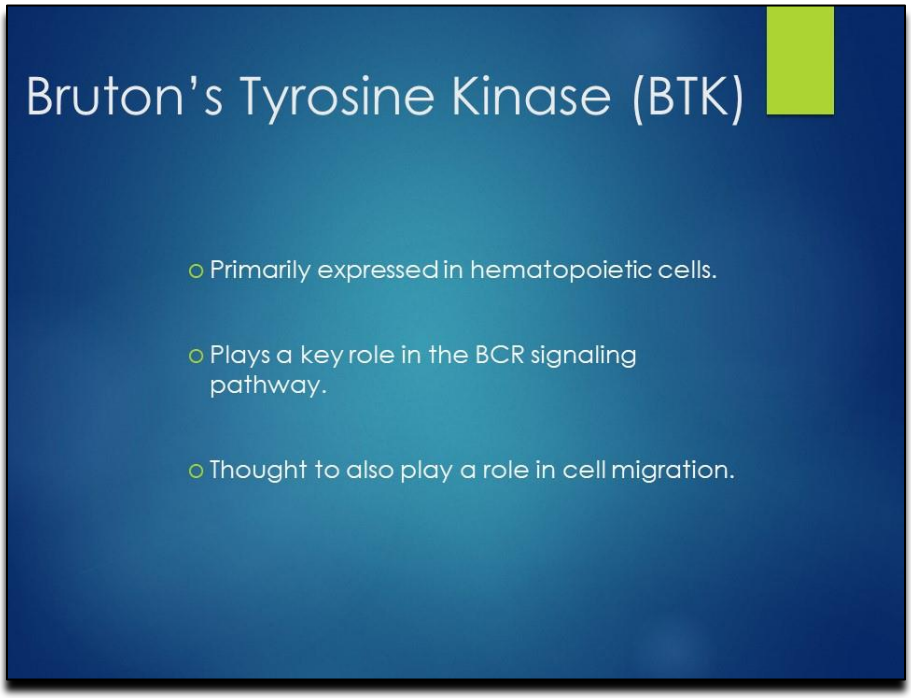
And when something attaches or bumps into that receptor and that receptor binds to it, it signals a whole cascade of enzymes that send a signal to the nucleus of the cell and triggers the cell to do some type of function: either replicate, move, several different functions. So, there's a lot of different enzymes involved in this pathway. This pathway is called the B-cell receptor signaling pathway.



B cell receptor (BCR) signaling pathway

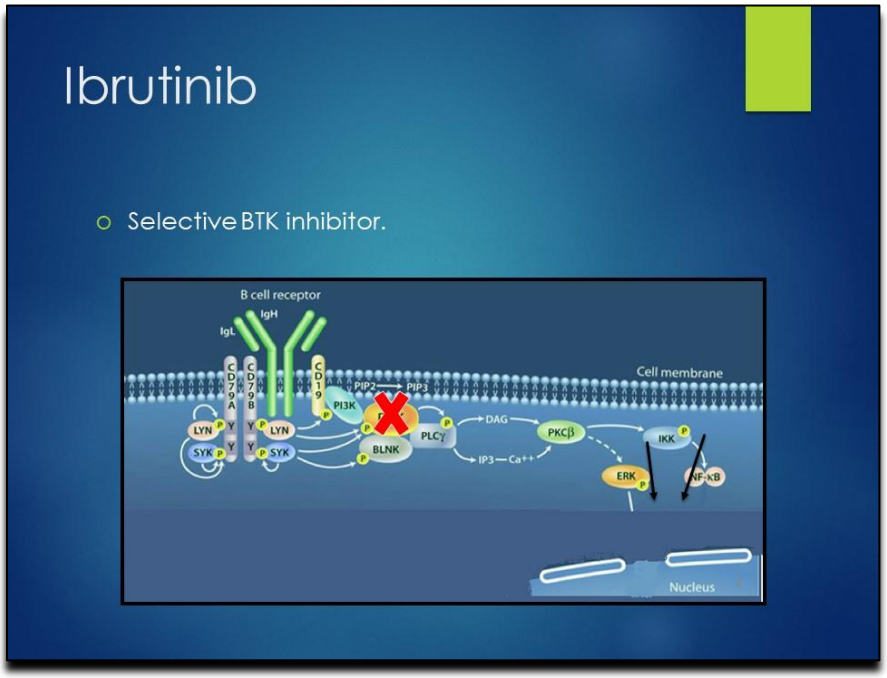
It's required. The really important step or really important pathway for expansion and proliferation of these lymphoma cells and regular B cells, too. It also plays a pretty intricate role in responding to the surrounding supporting cells, which we call the microenvironment, because these cells, they don't live in your body in a vacuum. They interact with the other cells in your body. And they interact with signals.

The B-cell receptor pathway is composed of a lot of different kinases, which are the enzymes that were in that slide above. Inhibitors of these kinases block signaling that disrupt cell migration.



Bruton's Tyrosine Kinase (BTK)

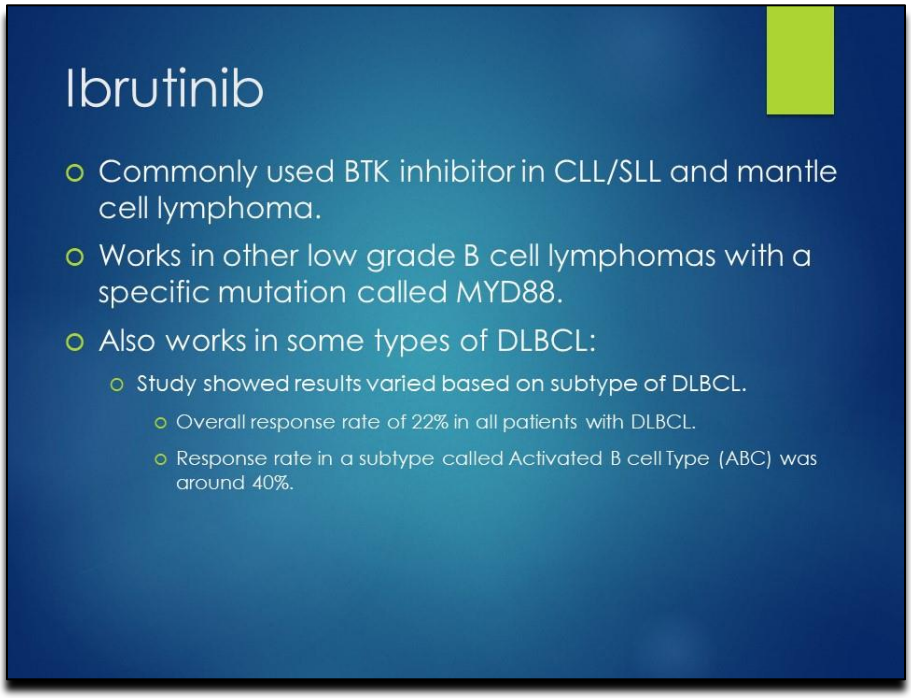
So, BTK is one of the enzymes that we can target with medications nowadays. And BTK is a B-cell receptor important enzyme and is primarily expressed in hematopoietic cells, which are kind of early blood cells. And again, it plays a key role in the B-cell receptor signaling pathway and in cell migration.



Ibrutinib

So, how do BTK inhibitors work? Well, basically, here's your B-cell receptor signaling pathway again. And the BTK drug will come in and block that enzyme, where the X just went on there. And once it blocks that enzyme, it stops this whole downstream cascade from happening and blocks signals to the nucleus, which are necessary for the cells to survive.

Now, as you can see, it only blocks the one area. And there's other—you may notice some others: LYN, SYK BLNK, PLC gamma (ɣ). There's other enzymes that are involved in signaling, too. So, the cells can get around this area, but it does a pretty good job at killing lymphoma cells but not curing it because there are secondary or alternative detours that the cell can use to survive.

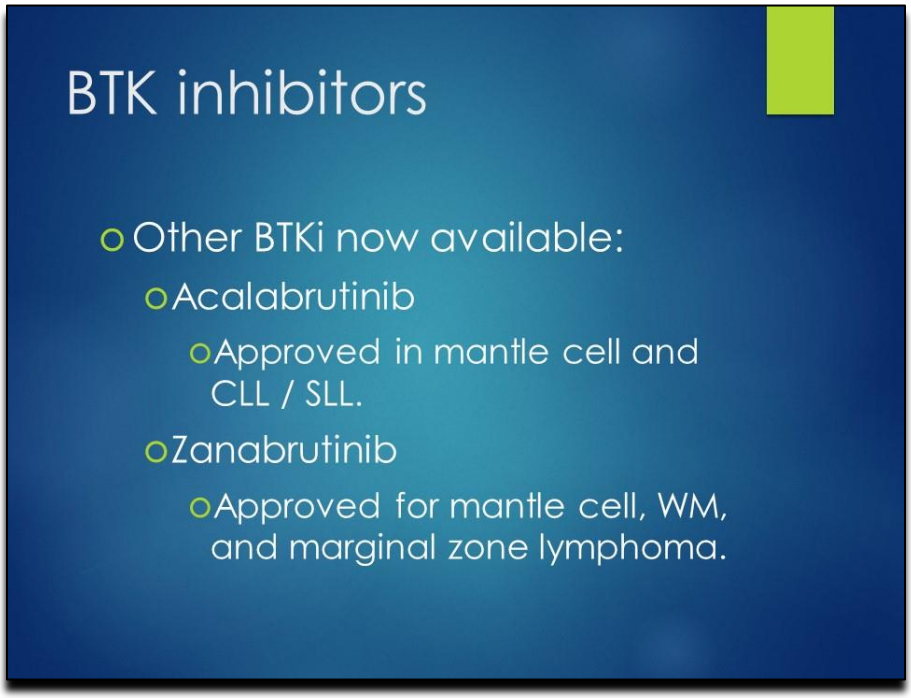


Ibrutinib

So, ibrutinib is probably the most common of the BTK inhibitors. It's the one that's been on the market the longest. It's mainly used in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) but also in mantle cell lymphoma, too. It also works in some other low-grade B-cell types of lymphomas with a specific mutation called MYD88 and in some types of diffuse large B-cell lymphoma.

So, just to kind of point out that it's not the greatest treatment for diffuse large B-cell lymphoma. In one such study, it only had a response rate of 22%. Only 22% of people treated with this drug with diffuse large cell lymphoma had some type of remission. But what they did notice in the study was it was a specific subtype called ABC or activated B cell–type that had a 40% response rate.

So again, I think this is kind of important in knowing your type because we have these tests now that can further stratify the lymphoma into types. And there are some treatments that work very well for very select cases.



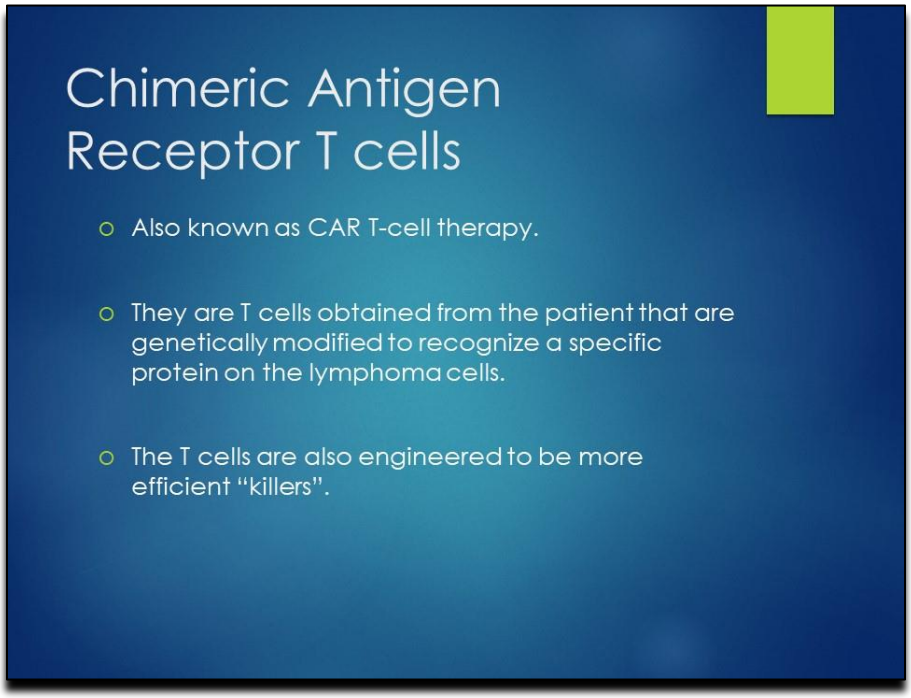
BTK inibitors

Other BTK inhibitors—which some of you may be familiar with, they're kind of the second-generation BTK inhibitors—are acalabrutinib ((Calquence®) , which is approved for mantle cell and CLL/SLL. And then there's zanubrutinib (Brukinsa®), which is approved for mantle cell, approved for Waldenstrom's. And it's also approved for marginal zone lymphoma.

So, newer BTK inhibitors that you may be hearing about, maybe even on treatment with, at this time, that are available. They've worked very well. They don't necessarily work better than ibrutinib, but they have less side effects. So, that's what makes them more appealing.

Immunotherapy Treatments

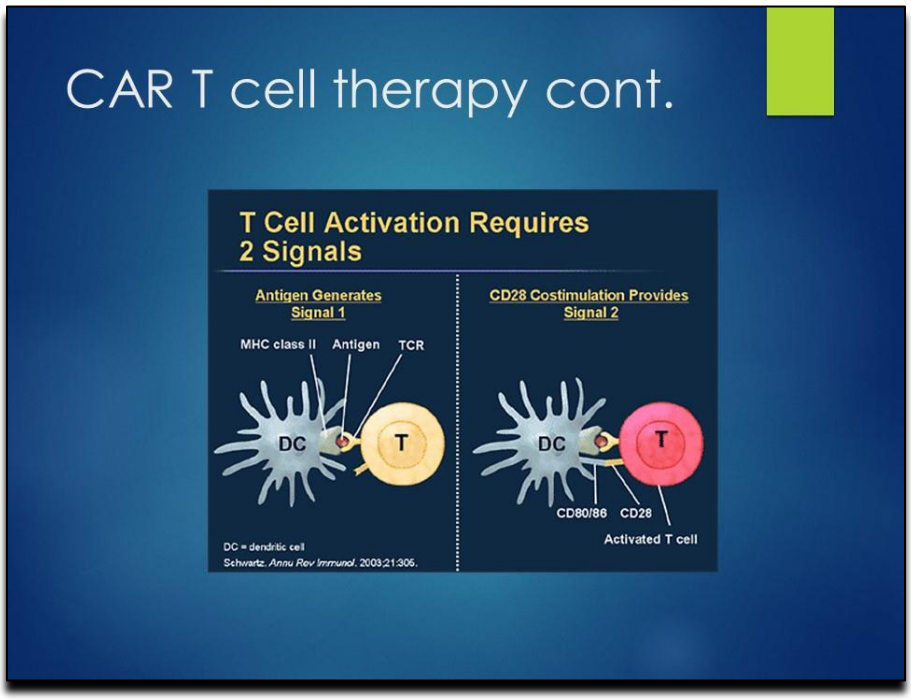
And then, we'll move to immunotherapy treatments. So, immunotherapy. There's kind of a lot of different types of immunotherapy treatments out there now.



Chimeric Antigen Receptor T cells

But the one I wanted to discuss is one that a lot of people have questions about, because it's fairly new, is the chimeric antigen receptor T-cell treatment, or CAR T-cell therapy.

So, this is a form of immunotherapy. And there are other immunotherapy treatments out there, but this one has been one that has been widely publicized. And so, the way this one works is that T cells are obtained from the patient, and they are genetically modified to recognize a specific protein on the lymphoma cells. And then they're also engineered to be kind of turned on or to be more efficient killers. And then they're placed back into the patient to attack the lymphoma.

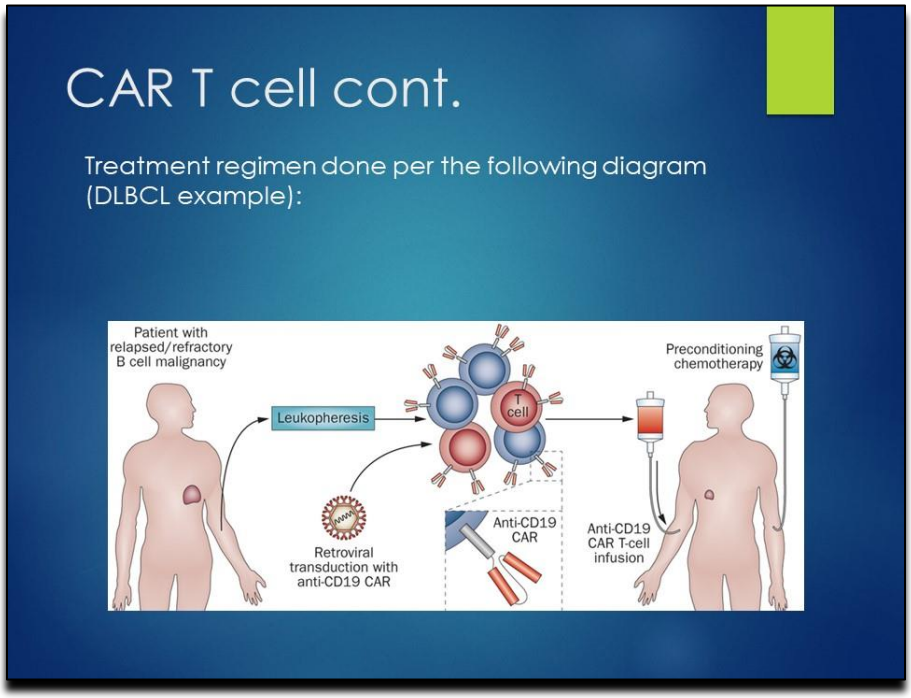


CAR T cell therapy cont.

So, what I mean by becoming more efficient killers or being engineered to be turned on is this diagram here is showing a normal T cell. So, this is not an engineered T cell. And what the little gold cell with the T on it is a T-cell recognizing an antigen or a pathogen and is binding to it on this dendritic cell, the one that says DC.

However, it's got a second little arm that you'll see, lower down, that needs to bind because just by binding to that antigen, it still can't kill that cell. But if the second signal occurs and everything checks out right and it can bind to it, then a switch is flipped on. And the T cell goes into action and kills that cell. And this is basically a safety mechanism in your body so your T cells don't go around attacking your normal good cells. It has to have a second, like a safety, basically, so two receptors have to be engaged for the T cell to work.

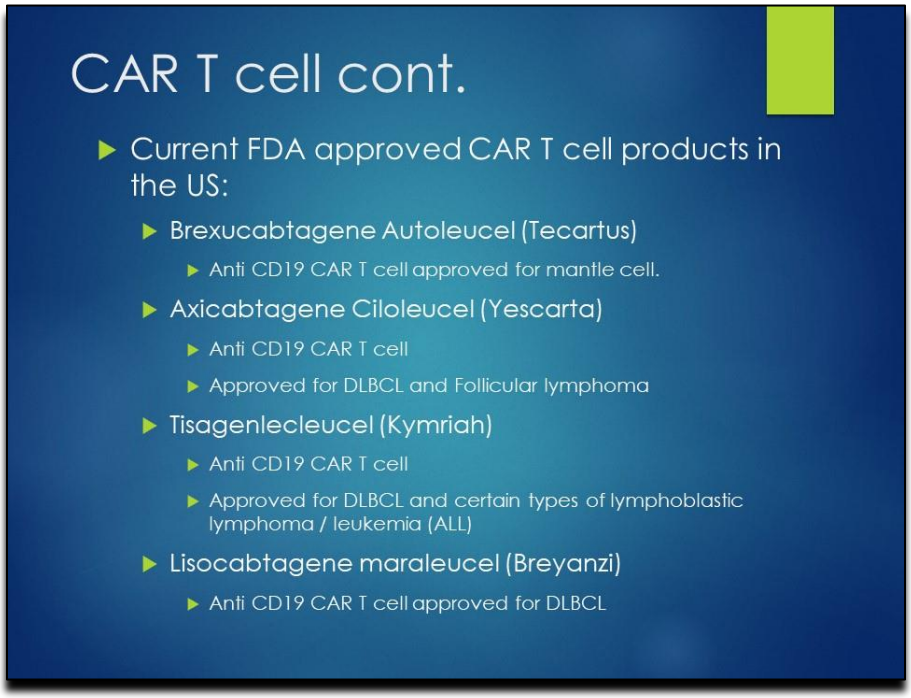
Well, these engineered T cells, that second receptor binding doesn't have to happen. That's already turned on. So, these T cells are ready to go when they're put into the patient's body.



CAR T cell therapy cont.

So, here's kind of a diagram of the steps that a person goes through to undergo the CAR T-cell treatment. This is an example of a CD19 CAR T therapy. Basically, the person on the left has refractory B-cell lymphoma, diffuse large B-cell lymphoma. They undergo leukapheresis, which is a process where their blood is collected in almost kind of like a dialysis machine where the white cells are filtered out—the lymphocytes are filtered out. And those lymphocytes are sent to a lab. And the T cells are engineered with a virus to recognize a certain receptor. And in this case, it's CD19. And then they're also turned on, too.

The cells are shipped back to the facility. And then the patient is admitted and given a small dose of a preconditioning chemotherapy. And then an infusion of their own T cells back through their veins, and then these cells start attacking the lymphoma. And so, that's how CAR T-cell therapy works. It's a form of a pretty aggressive immunotherapy.



Slide 51- CAR T cell therapy cont.

So currently, the FDA approved CAR T-cell products in the United States for lymphoma. I should have put that in here. There's a few of them.

So, the first one, Tecartus®, also brexucabtagene—I can't say these, I don't know where they come up with these names. But Tecartus® is the brand name, is one that's approved for mantle cell lymphoma. And it's an antibody against—I should say it's an anti-CAR T against CD19.

There's also Yescarta®, which is axicabtagene. And that one is also another anti-CD19 CAR T-cell therapy. But it's approved differently. It's approved for diffuse large cell lymphoma and for follicular lymphoma. And it's not that Tecartus® doesn't work in the other ones. These companies have to do the study in certain specific lymphomas to get their indication. If they don't test it in diffuse large cell or in mantle cell, then they don't get that FDA approval. So, that's why it's kind of specific.

There's also Kymriah® (tisagenlecleucel), which is another anti-CD19 CAR T-cell therapy. This one is approved for diffuse large B cell and also certain types of lymphoblastic lymphoma/leukemia, also known as acute lymphoblastic leukemia. And then, there's Breyanzi® (lisocabtagene maraleucel), which is another anti-CD19 CAR T cell approved for diffuse large B cell. So, a few products that are available for CAR T-cell therapy. But again, I think important to know your type because not all products are approved for all types of lymphomas. So, knowing your type is important in this situation also.

Summary

So, in summary I just want to say, to start out, communication is key. That's the thing. So, to know your subtype, you may have to ask some questions. Ask your physician if you're not clear. If you think you just have non-Hodgkin's lymphoma, but you don't know the exact type, ask them to further clarify.

Lymphoma is not just one type of cancer. There are over 50 different types, according to the World Health Organization.

Diffuse large B cell is the most common, but it's not the only one. And the type of lymphoma is really important for prognosis and for guiding your treatment. So, this is really the take-home message of this talk.

The Benefits of Discussing Quality of Life Concerns with Your Healthcare Team

And then lastly, with just a couple of slides. I just wanted to mention the benefits of discussing quality-of-life concerns with your healthcare team. We're switching gears a little bit here. But the previous one was more scientific, the previous talk. But just with these three slides I just want to say, yes, there are benefits to discussing quality-of-life concerns with your healthcare team. It's not all just doom and gloom.

No Two People Are the Same

The reason there's benefits is because no two people are the same. Our likes and dislikes are different. And you can't just assume what one person likes the other person will like, just by looking at them. So, expressing yourself is really important. I'm not saying to come in to your first visit and say, "Oh, gosh, I want to be comfortable." That's not what we're talking about here.

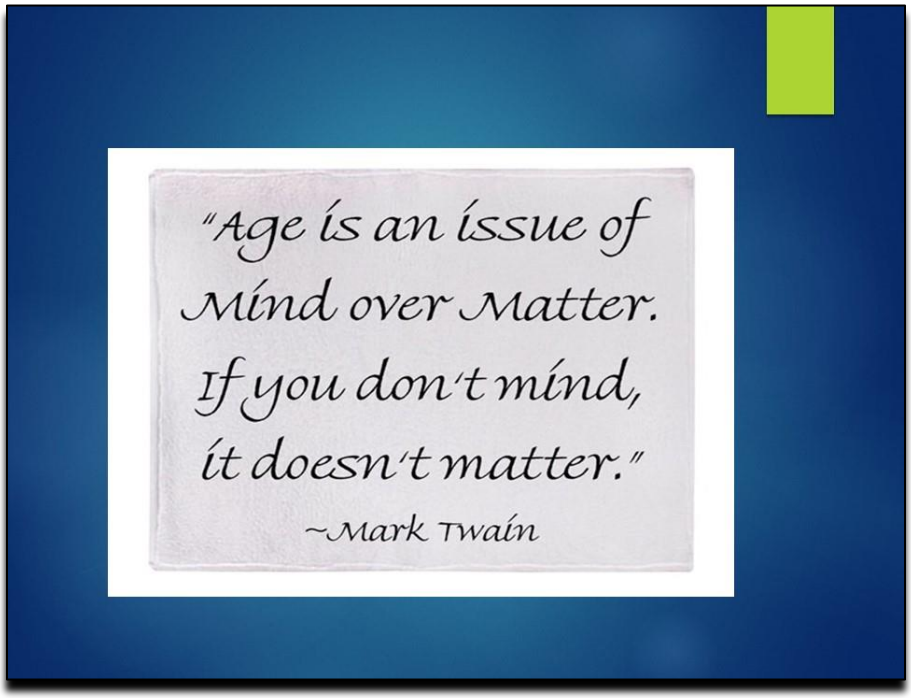
But letting your physician know or your healthcare team or even your spouse and family know is really important.

Quality of Life Concerns

And some of the key things that I just like people to focus on is that in aggressive diseases, aggressive lymphomas, quality of life is not as big of an issue because either the treatment works, or it doesn't. So, you're not going to have a good quality of life if you have this rip-roaring lymphoma that's just rapidly growing throughout your body. There's no quality of life. So, getting a treatment secured or not is really—really, there's not many other options for that.

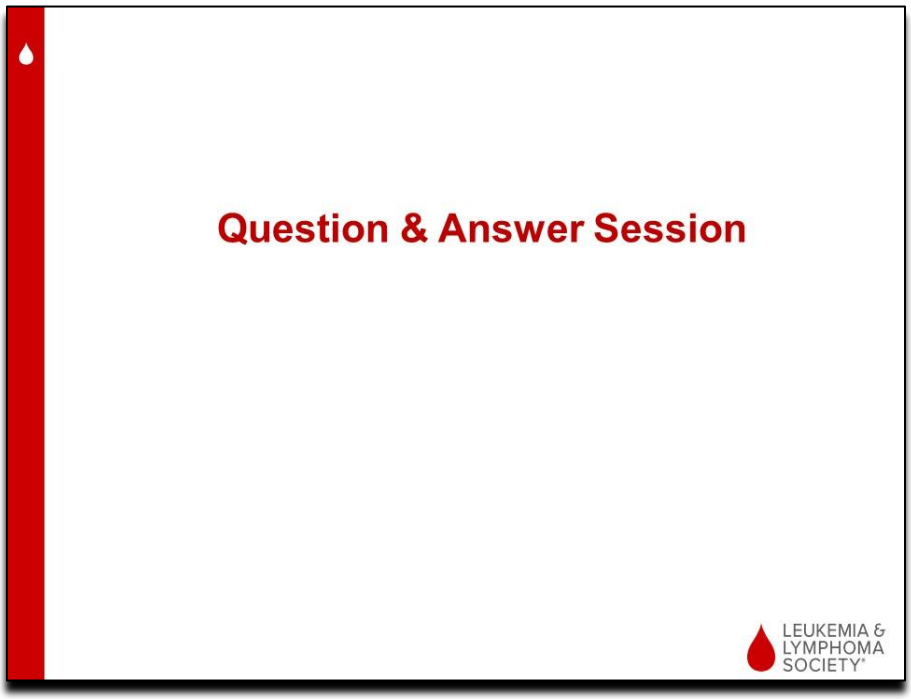
But the slow-growing diseases. This is where I feel like quality of life becomes more of an issue because there's so many treatment options out there. Duration of treatment comes into play. Do you want something that's a daily treatment? That's orally but it's every day, forever? Do you want something that's a finite treatment, but it's given intravenously? Does the location of the treatment matter to you? Do you have transportation issues?

And then, cost of the treatment can be pretty prohibitive, too. So, I think all of these are things to think about. And they all go into quality of life. I don't have the answers because we're all different. So, I don't know what is considered quality for one person may not be considered that for somebody else. But I think the key to this or the key point of this is talk to your provider and your family and it will be helpful in the end.



Quote

So, with that I am going to conclude my talk and hand it back over to Lizette.



Question & Answer Session

Lizette Figueroa-Rivera
Well, thank you so much, Dr. Bello, for your very informative presentation. It is now time for our question-and-answer portion of our program.

And for everyone's benefit: if you please keep your questions general in nature, without many personal details.

Lizette Figueroa-Rivera
Thank you. Now we'll take our first question from the web. Allison is asking, curable or remission? Which term should we use? So, I guess just to highlight that the indolent or the slow-growing types of NHL, are those generally the ones that we use the word remission?

Celeste Bello, MD, MSPH
Yeah, I'd say with all of the lymphomas, initially we would say remission because some lymphomas can recur several years later. So, we don't really say cure until a certain amount of time has gone by. So, when you're getting a treatment and you get a PET scan or a CT scan and it shows no evidence of lymphoma, we usually will refer to that as a remission. And then in the lymphomas that are curable, which are the more aggressive ones, we usually continue to call it a remission until they remain in remission for 5 years or more. And then, we kind of switch to the cure word.

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

Operator
Thank you. This question comes from Jennifer calling from California. Please go ahead.

Jennifer
Oh, hi. I'm not sure if my question is the same—maybe just worded differently. But with marginal zone B-cell lymphoma, which is a good category versus a bad category, which is considered cured after 5 years without a tumor or activity with marginal zone. Would that be the same if you haven't had tumors? Would that be considered cured or would it still be considered dormant? And when does it cross over? Because I've been told it can morph into a different type of lymphoma. When would that occur, or is that the same situation?

Celeste Bello, MD, MSPH
Yeah, no. That's a good question. So, marginal zone lymphomas are usually not curable. So, you'll usually have them for the rest of your life.

And so, when they go into remission we usually just call them remission. And people can be in remission for a long time: 5 years, 10 years. So, but it doesn't mean it's cured. It just means it's dormant. Now, they can mutate to a more aggressive kind of lymphoma. All of the low-grade indolent ones can do that. Fortunately, most of the time that does not happen. But about 10% that will happen in. And when that happens, then it kind of becomes more of a bad situation where you have to get a more aggressive chemotherapy. But most of the marginal zones stay as a slow-growing low-grade lymphoma.

Lizette Figueroa-Rivera
Thank you for the question. And our next question. Mary is asking, "Is it possible to have more than one subtype of lymphoma?"

Celeste Bello, MD, MSPH
Yeah, it is actually. Sometimes you can get these composite lymphomas. But sometimes we'll see people where they'll say they have a diffuse large B-cell lymphoma with a background of follicular lymphoma in the biopsy. It's not so much that you have two lymphomas. What it is, is these are kind of a spectrum. Sometimes you can start out as one and then you can have like a divergent clone that develops. So, I wouldn't say you have two different cancers. But you can definitely see two different kinds of pathologies or patterns on the biopsy.

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

Operator
Our next question comes from Stacy, calling from Florida. Please go ahead.

Stacy
Hi. Thank you so much. I am calling to ask, I have stage 3B follicular lymphoma and I have completed chemo in March. And my oncologist has always been keen to tell me that it comes back.

And being 44 years old, I don't know what that means for longevity of life, other than it would mean further chemo. But is this something that after you've been treated, you can 5 years out consider yourself cured? Or are we looking at something that is truly going to be monitored over the lifetime, as I'm told, and potentially need treatment again or transform into something more aggressive?

Celeste Bello, MD, MSPH
Yeah. So, stage and grade are different. So, stage is, like, how much of the disease you have or where in the body you have it. And if you're considered stage 3B, that means you have lymphoma above and below the diaphragm, which we use kind of as the borderline. And then, B means you have B symptoms, which means you either had fevers, night sweats, or weight loss.

So, if you're stage 3B follicular lymphoma, we still need to know are you a low-grade follicular or a high-grade follicular. So, the low-grade ones would be grade 1, 2, and 3A. Those are not cured. So, those can go into remission, but they're never cured. Now, if you're a high-grade. There is a grade 3B, which is different than stage 3B because grade 3B means the way the cells look under the microscope. Those are quite aggressive. And those can actually be cured in some cases with chemotherapy.

So, that's going to be the key thing. If you're a low-grade lymphoma—even no matter what your stage is—the majority are not cured. They always come back. But if you're a high-grade lymphoma, some of those can be cured. And at the 5-year mark, if they haven't come back, we usually say those are cured.

Lizette Figueroa-Rivera
Thank you. And I do have a question, also, referring to grade 3B. Rosemary is asking, where does she find her grade because she's asking about the different grades for follicular lymphoma.

Celeste Bello, MD, MSPH
It's on the pathology report. So, when you had your biopsy, whatever area you had biopsied, that report should give a grade.

Lizette Figueroa-Rivera
Great. And Rosemary, you can always ask your treatment team to let you know.

Celeste Bello, MD, MSPH
Definitely.

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

Operator
Our next question comes from Deborah, calling from Florida. Please go ahead with your question.

Deborah
Hi, I have Waldenstrom. And I'm on once-a-month Rituxan® (rituximab) infusions. And then I'm also on Imbruvica® (ibrutinib) at night. I take it once a night. And I was just wondering, can I drink wine while you're on this medication?

Celeste Bello, MD, MSPH
I would ask your primary care doctor that question or your primary oncologist. In general, we usually tell people no. But they will probably know more about your specific medical situation. And I would direct that more toward them.

Lizette Figueroa-Rivera
Thank you. And Julia is asking about treatment blocking any antibody response to the COVID vaccine. Could you please talk a little bit about the COVID vaccines for our lymphoma patients?

Celeste Bello, MD, MSPH
Yeah. So, the problem with it is that the COVID vaccine and, for instance, the monoclonal antibody treatment rituximab. The rituximab kills the cells that have CD20 on them. So, your B-cell lymphoma cells have that but so do some of your good B-cells.

So, when somebody is exposed to rituximab, not only does it kill their lymphoma cells, it will kill some of their good B cells. And it looks like the B cells are necessary for a vaccine to be effective because that's where your memory B cells will eventually come from.

So, rituximab lasts in your body for about 6 months. So, what we've been seeing is that when somebody gets rituximab and then they get a vaccine within, like, I'd say 5 to 6 months after their last dose of rituximab, the vaccine doesn't seem to take or work as well. So, we've kind of been recommending that people wait at least 3 months. But if possible, I've been telling my patients 6 months after their rituximab before getting the vaccine. It's not that anything bad would happen if you got the vaccine and you're on Rituxan® (rituximab) or recently received rituximab. It's just that it's less likely to work.

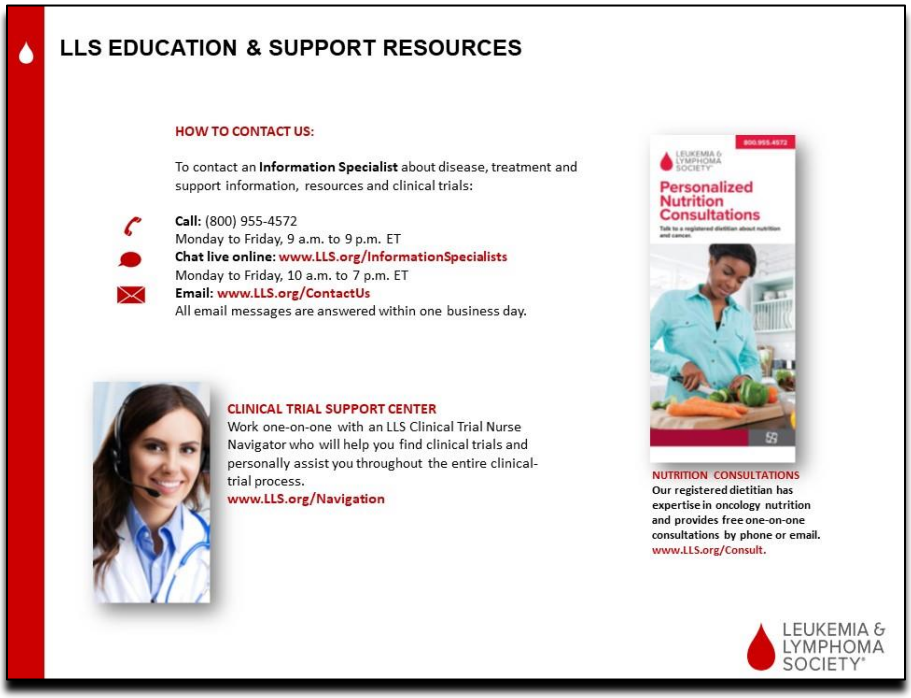
Lizette Figueroa-Rivera
Thank you so much. And our last question today is from Evy. Evy is asking to explain the difference between SLL and CLL, and why are they grouped together.

Celeste Bello, MD, MSPH
Yeah, no, that's a really good question because I always tell people that all through my medical residency, nobody would ever explain the difference to me. So, it wasn't until I went into fellowship that I really learned that they're the same.

Celeste Bello, MD, MSPH
So basically, what it is, is SLL stands for small lymphocytic lymphoma. CLL stands for chronic lymphocytic leukemia. If it's mainly in your blood and in your bone marrow, we call it the CLL. If it's mainly in your lymph nodes, we call it SLL.

So, the cells are identical. They have the exact same marker on them. They look the same under the microscope. It's just more of the pattern of distribution is how they get labeled SLL or CLL.

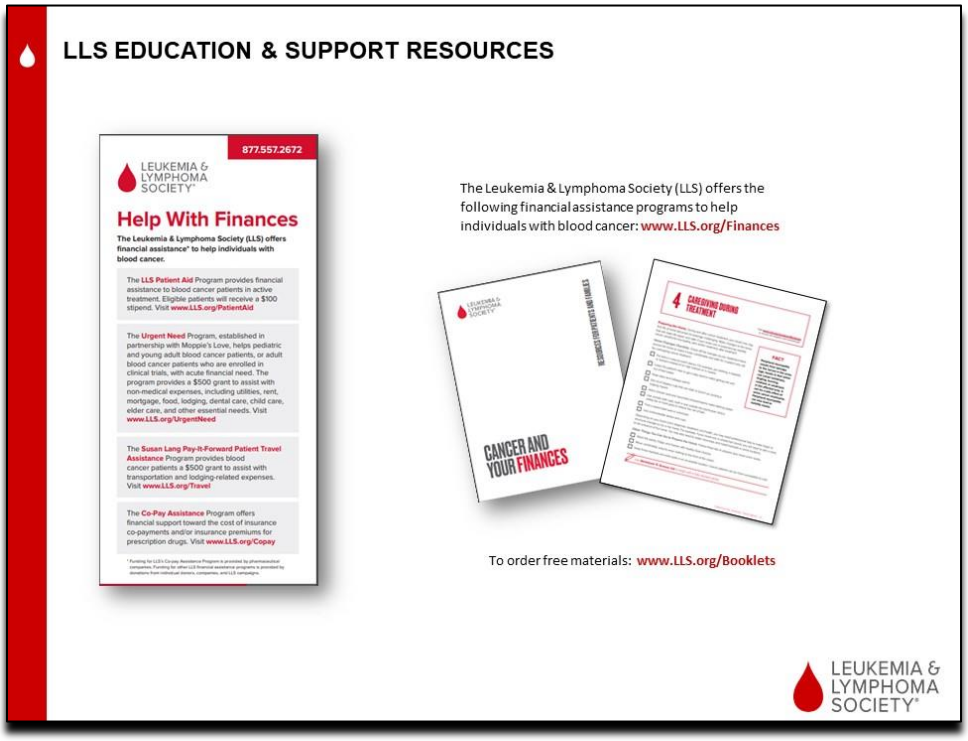
Lizette Figueroa-Rivera
Well, thank you so much, Evy, for that question, which was our last question today. And a special thanks to Dr. Bello for sharing her expertise with us and for her continued dedication to our blood cancer patients.



LLS Education & Support Resources

Lizette Figueroa-Rivera
If we weren't able to get to your question today—I see we have many questions still on the phone, as well as on the web—you can certainly contact one of our Information Specialists at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time. You can go to LLS.org/InformationSpecialist to chat online or email us LLS.org/ContactUs.

We have information about treatments, about diagnosis, clinical trials, as well as support services and financial assistance programs, where you can also go to LLS.org/Finances.



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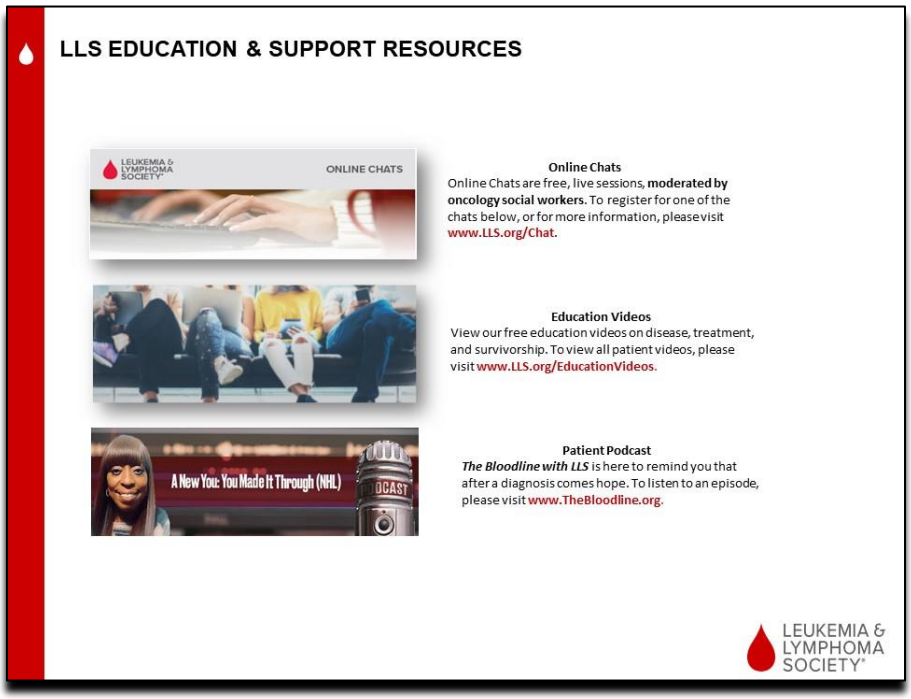
Again, we'd like to acknowledge and thank Bristol Myers Squibb, Genentech, Biogen and Pharmacyclics, an AbbVie Company, and Janssen Biotech for their support today.



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Dr. Bello, thank you again for volunteering your time with us.

Thank You

And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us on this program. Please let us know what you need from us during this time. And you take good care. Happy holidays.