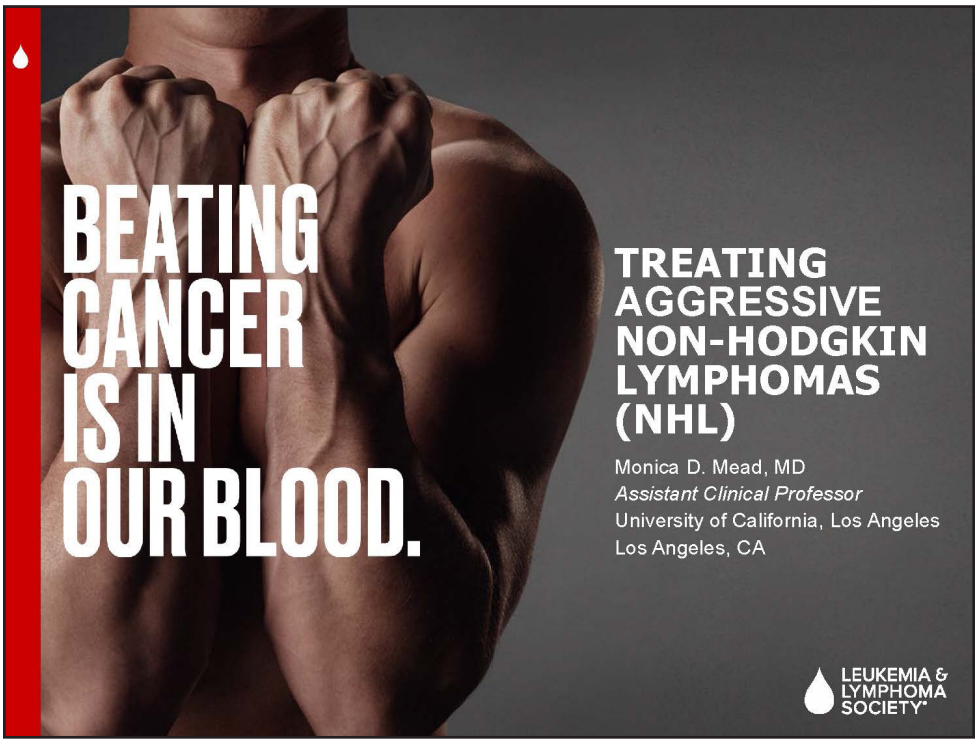


Slide 1: Treating Aggressive Non-Hodgkin Lymphomas (NHL)

Operator:

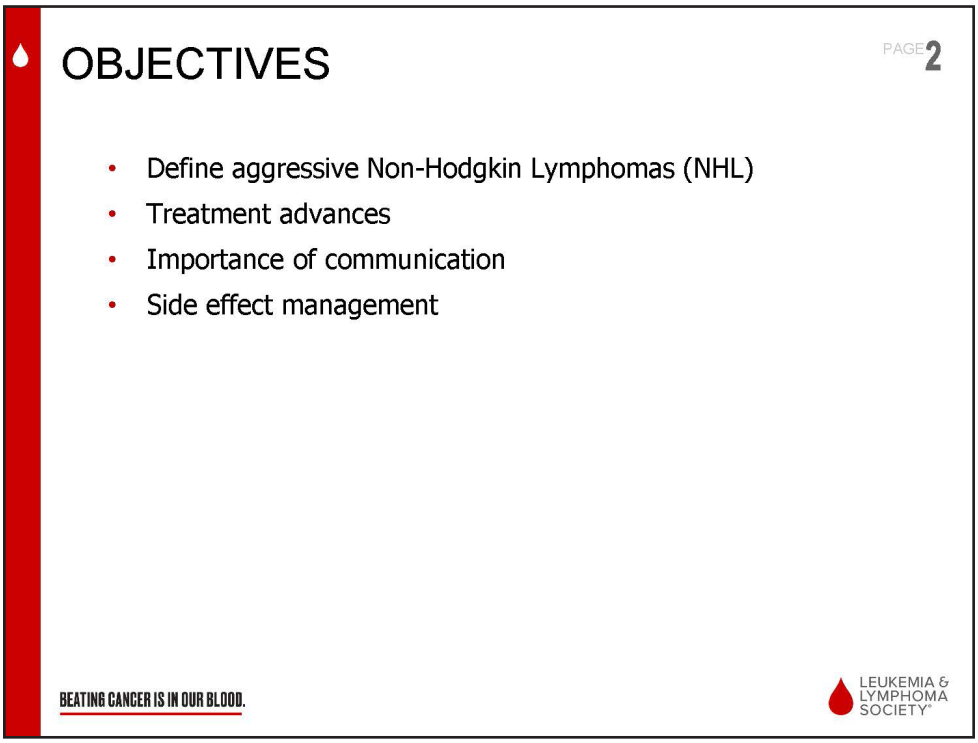
Hello, everyone, and welcome to *Treating Aggressive Non-Hodgkin Lymphomas*, a free telephone and web education program. It is my pleasure to introduce your moderator, Lizette Figueroa-Rivera.

Lizette Figueroa-Rivera:

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

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

I am now pleased to introduce Dr. Monica Mead from the University of California in Los Angeles, California. Dr. Mead, I am privileged to turn the program over to you.

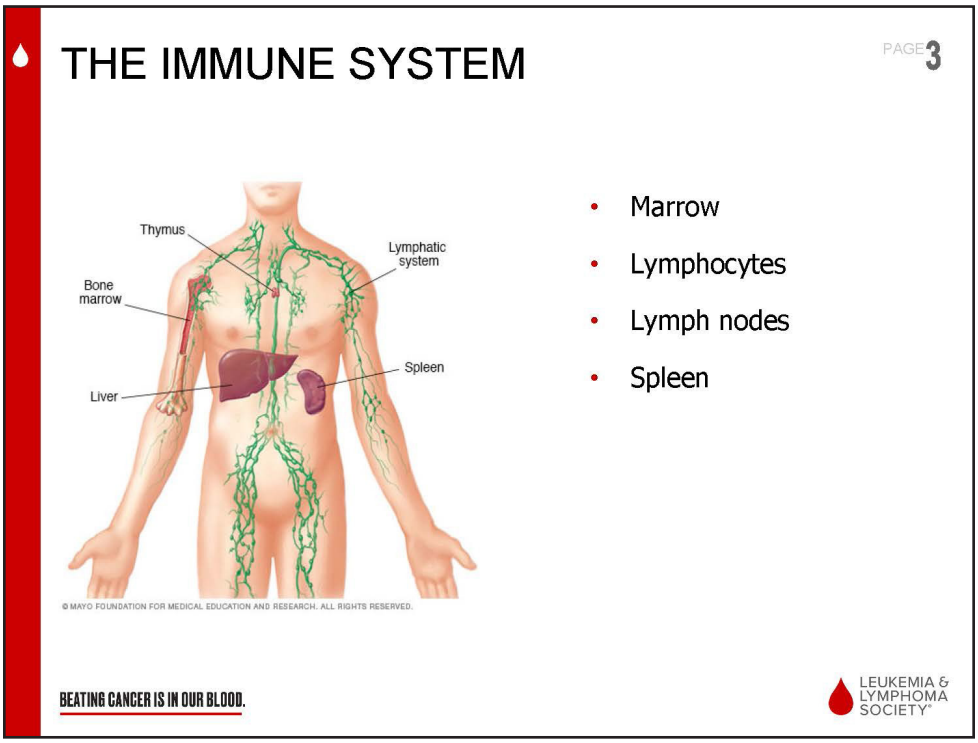


Slide 2: OBJECTIVES

Dr. Monica Mead:

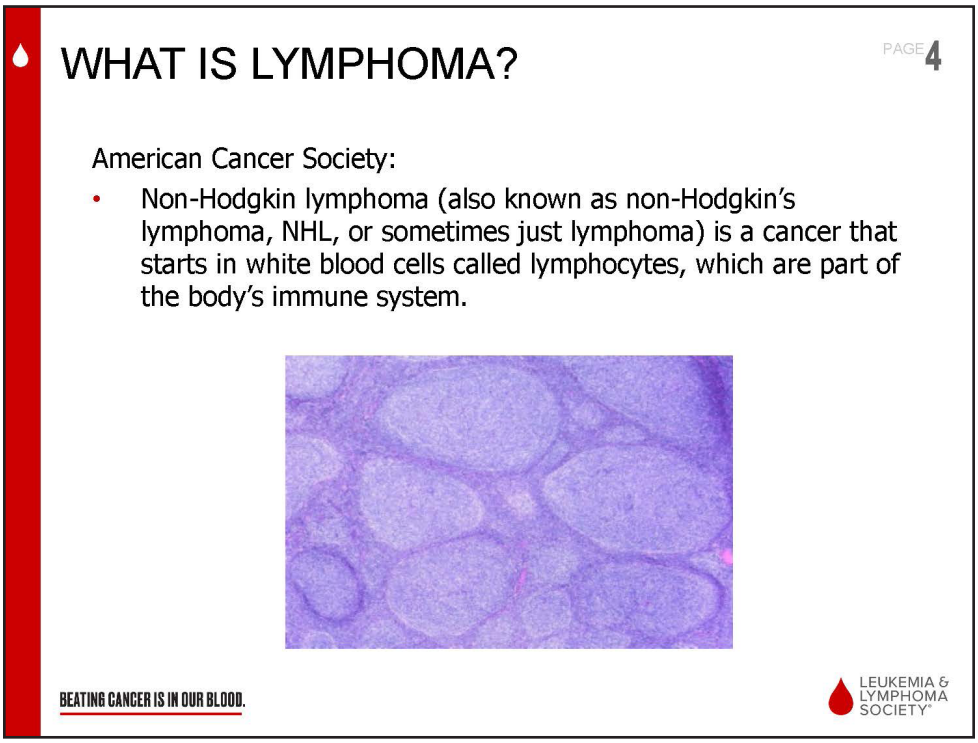
Good afternoon everyone and thank you for taking time out of your day to join me to discuss *Treating Aggressive Non-Hodgkin Lymphomas*. It is one of my favorite topics.

So, the objectives of my talk are to define aggressive non-Hodgkin lymphomas, discuss treatment advances, discuss the importance of communication between patients and their treatment care team, and also some recommendations for side effect management.



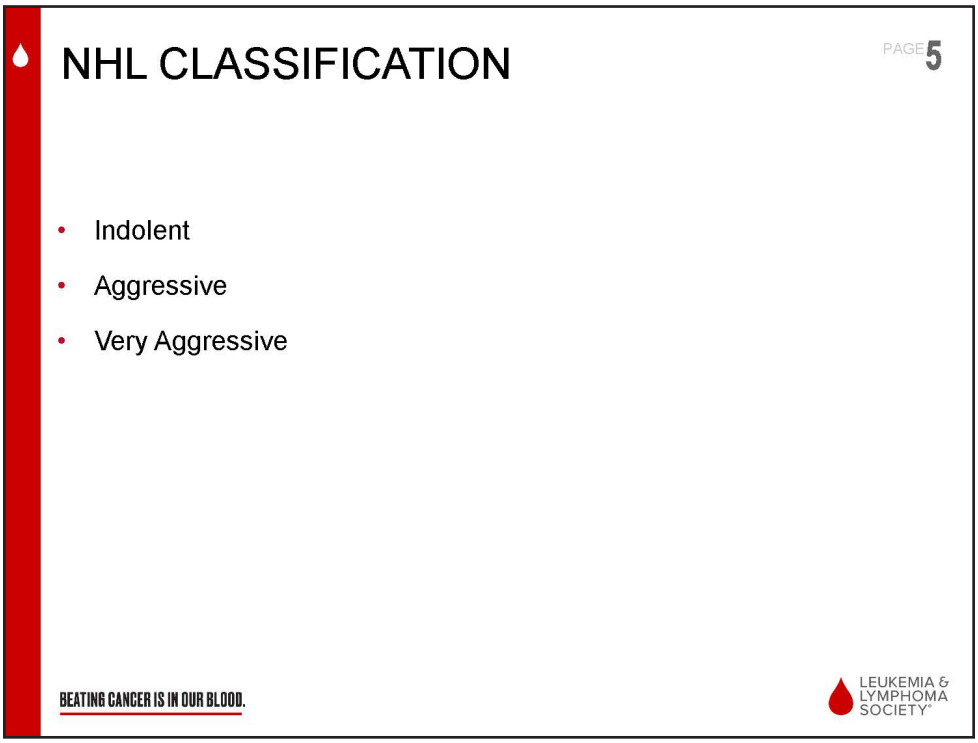
Slide 3: THE IMMUNE SYSTEM

I want to start off describing where lymphoma arises from. Lymphoma is a cancer of the lymphocytes, which is an immune system cell. And in the picture here, you can see the immune system drawn. The green areas are the lymphatic system, which function as the immune system highways. And, you can see they are intimately involved with the bone marrow and the spleen. So, when you are diagnosed with lymphoma, you may develop enlarged lymph nodes, an enlarged spleen, or you may have bone marrow involvement.



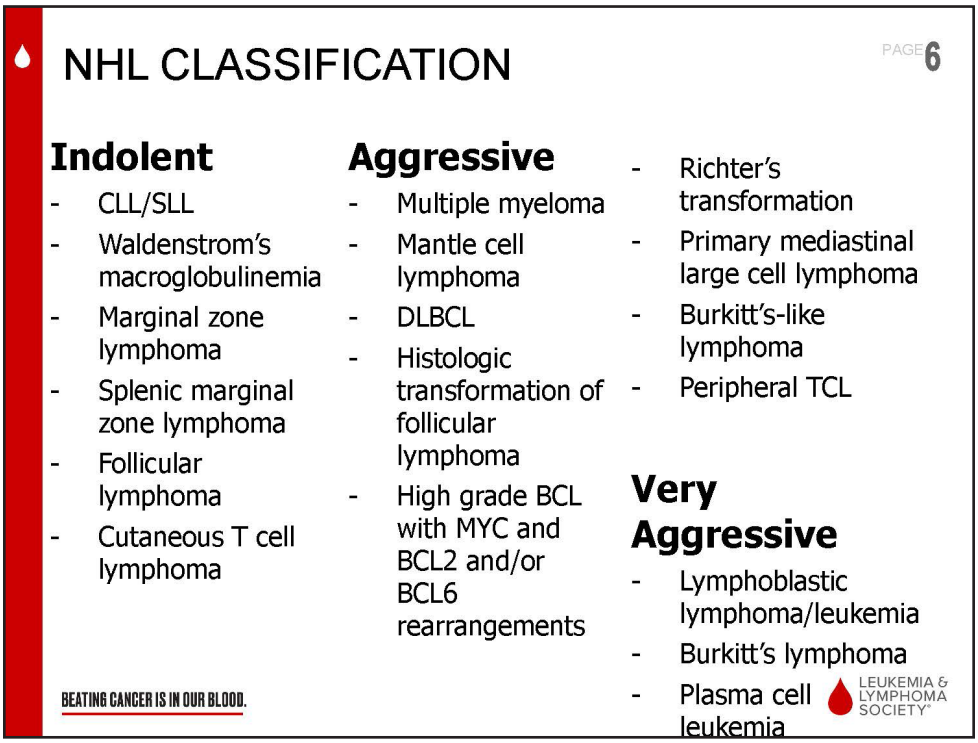
Slide 4: WHAT IS LYMPHOMA?

The American Cancer Society defines non-Hodgkin's lymphoma as a cancer that starts in white blood cells, called lymphocytes, which are part of the body's immune system. If you look at the picture on the bottom of the slide, that is what a portion of a lymphoma looks like underneath a microscope.



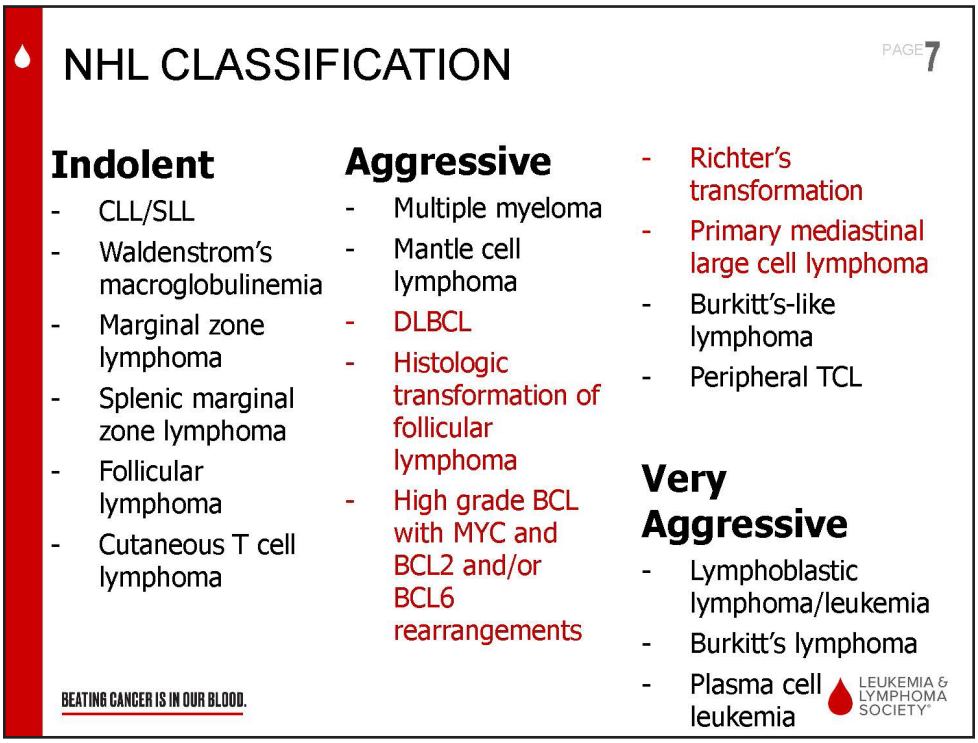
Slide 5: NHL CLASSIFICATION

Non-Hodgkin's lymphomas are mostly classified into 3 different categories: indolent, aggressive, and very aggressive. And, this categorization is based on how the lymphoma behaves clinically.



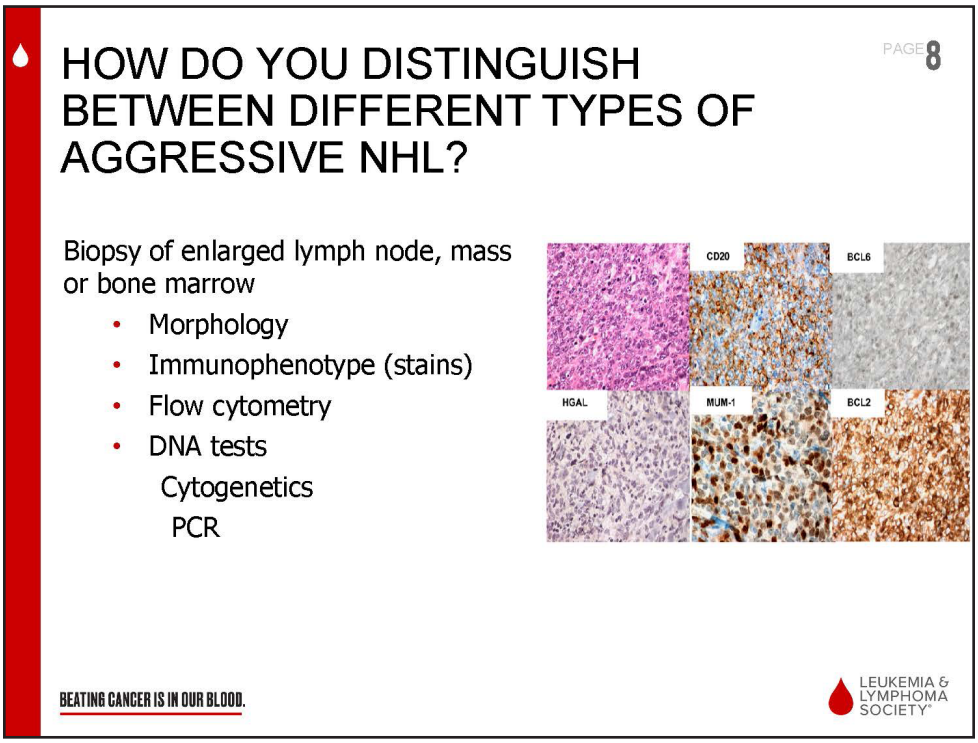
Slide 6: NHL CLASSIFICATION

Listed here are some of the more common variants within the 3 different categories.



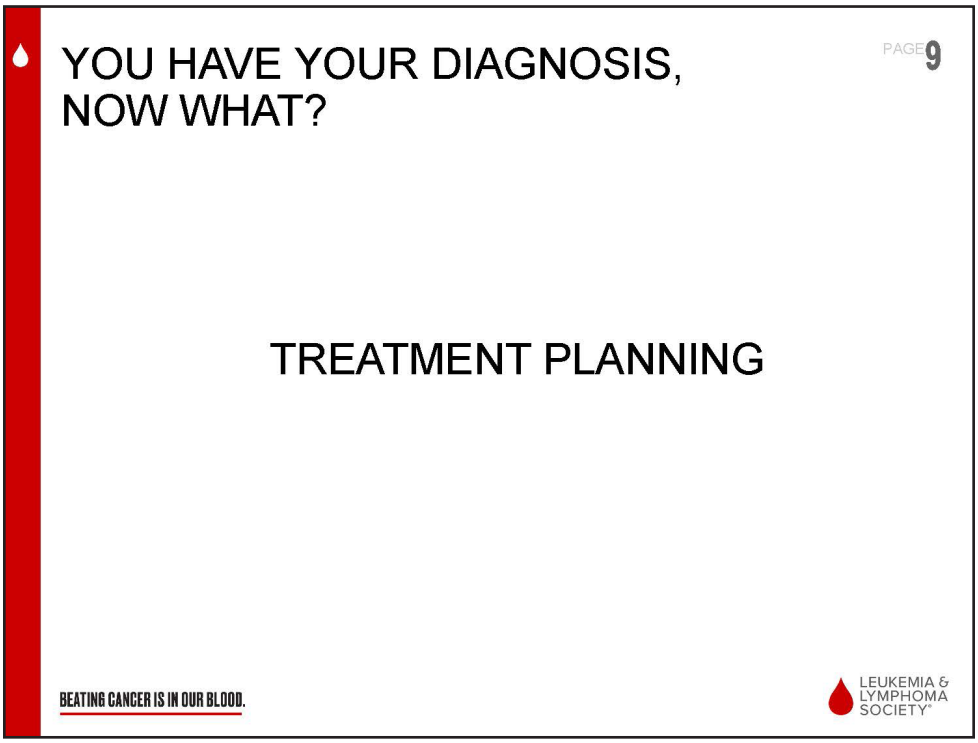
Slide 7: NHL CLASSIFICATION

For today's talk, we will be focusing on the lymphomas that are in red underneath the aggressive category: diffuse large B-cell lymphoma; histologic transformation of follicular lymphoma; high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement, this is more commonly referred to as a double-hit lymphoma; Richter's transformation, which is an aggressive lymphoma that arises from a preexisting CLL/SLL; and primary mediastinal large B-cell lymphoma.



Slide 8: HOW DO YOU DISTINGUISH BETWEEN DIFFERENT TYPES OF AGGRESSIVE NHL?

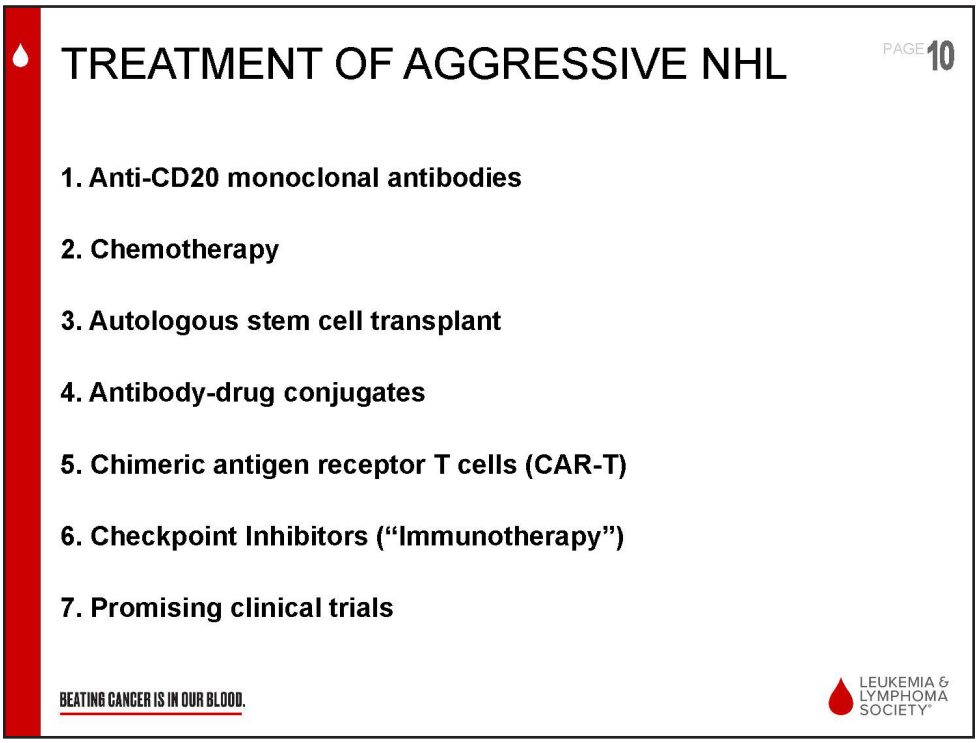
Just a quick word about how to distinguish between the different types of aggressive non-Hodgkin lymphomas. It is largely based on a tissue specimen that you obtain from a biopsy. So, patients may get a biopsy of an enlarged lymph node, an abnormal appearing mass, or the bone marrow. Once the pathologists have a sample of the lymphoma, the first thing they do is look at it underneath the microscope to see how the cells appear. This is called morphology. The next thing they do is apply various stains to the tissue sample. These stains bind to different proteins expressed on lymphoma cells, and certain subtypes of lymphomas are expected to have a particular protein expression pattern. This is called the immunophenotype. They also perform flow cytometry, which is a very sensitive test that helps define if there is a clonal population of lymphocytes present. Clonal cells generally indicate the presence of a lymphoma, as we expect our normal healthy lymphocytes to have a lot of variety. Lastly, they will perform DNA tests, looking at chromosome shape, which is the cytogenetics, and they will also look for the presence of certain mutations with a test called PCR.



Slide 9: YOU HAVE YOUR DIAGNOSIS, NOW WHAT?

So, you have your diagnosis of an aggressive non-Hodgkin's lymphoma, so what is next? That is when we move into the treatment planning phase.

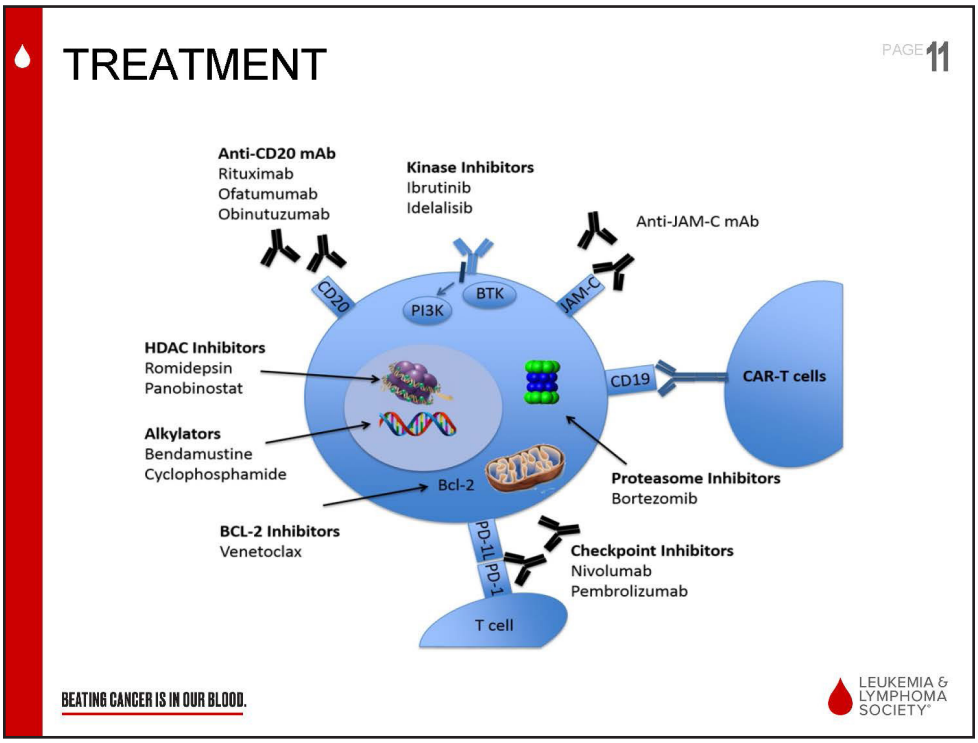
So, when I initially organized this talk, I was going to discuss each aggressive non-Hodgkin's lymphoma one at a time, starting off with diffuse large B-cell and moving on. But, the treatment for the various aggressive non-Hodgkin's lymphomas have a lot of overlap and so I thought it would be better to structure the talk based on the different treatments.



Slide 10: TREATMENT OF AGGRESSIVE NHL

So, when I think about how I am going to best treat a patient, I have the list in front of me, loosely in my head. So, potential treatment approaches for aggressive non-Hodgkin's lymphoma include, anti-CD20 monoclonal antibodies, chemotherapy, autologous stem cell transplant, more commonly referred to as a bone marrow transplant, antibody drug conjugates, chimeric antigen receptor T-cells, more commonly called CAR-T, checkpoint inhibitors, which is also known as immunotherapy or you may also have heard of something called PD-1 inhibitors, and promising clinical trials.

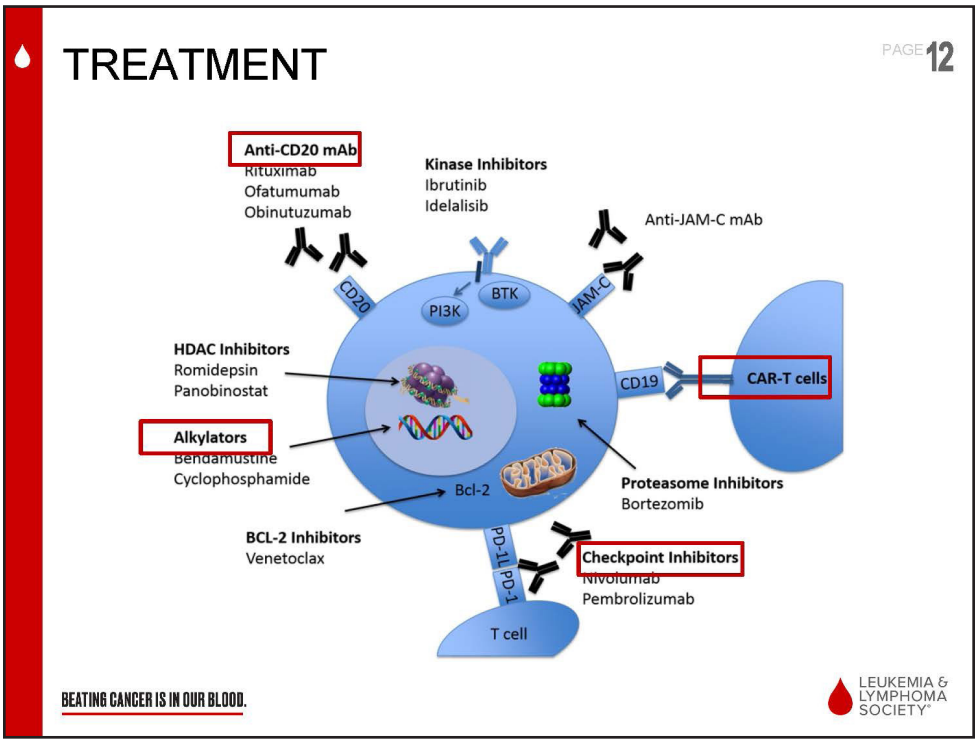
In retrospect, I wish I would have put clinical trials as the number one on this list because really this is the first thing, I think of any time I form a treatment plan for a patient. If there is a rationally well-designed clinical trial available, it is always something that I discuss with a patient.



Slide 11: TREATMENT

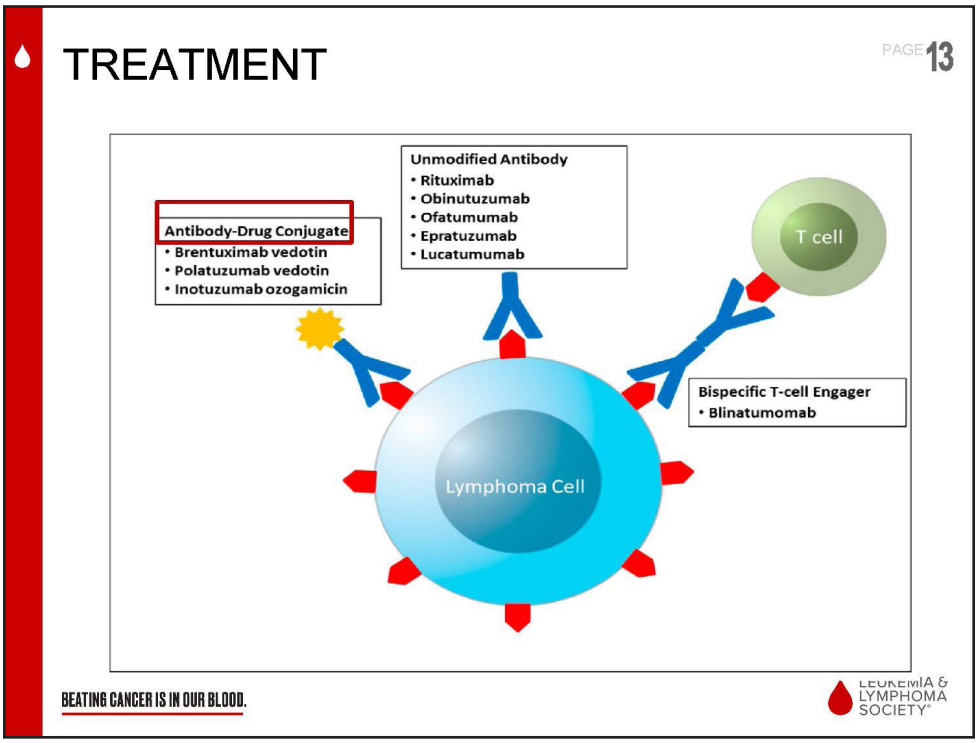
The treatment of lymphoma is increasingly complex, and we use a lot of very specific medical jargon, and I think that a picture can kind of help explain how these different treatments work. So, we are going to revisit this image multiple times throughout my talk, so I want to orient you to it quickly.

The cell in the center is a lymphoma cell. The little squares lining the lymphoma cell, these are proteins that are expressed on the cell surface and oftentimes we utilize these proteins to target our treatment to them. Inside the lymphoma cell is a light purple circle. That is the nucleus. And, you can think of that as the brain of the lymphoma cell. The cell down at the bottom is a healthy immune system T-cell. And, the cell over to the right is a CAR-T cell.



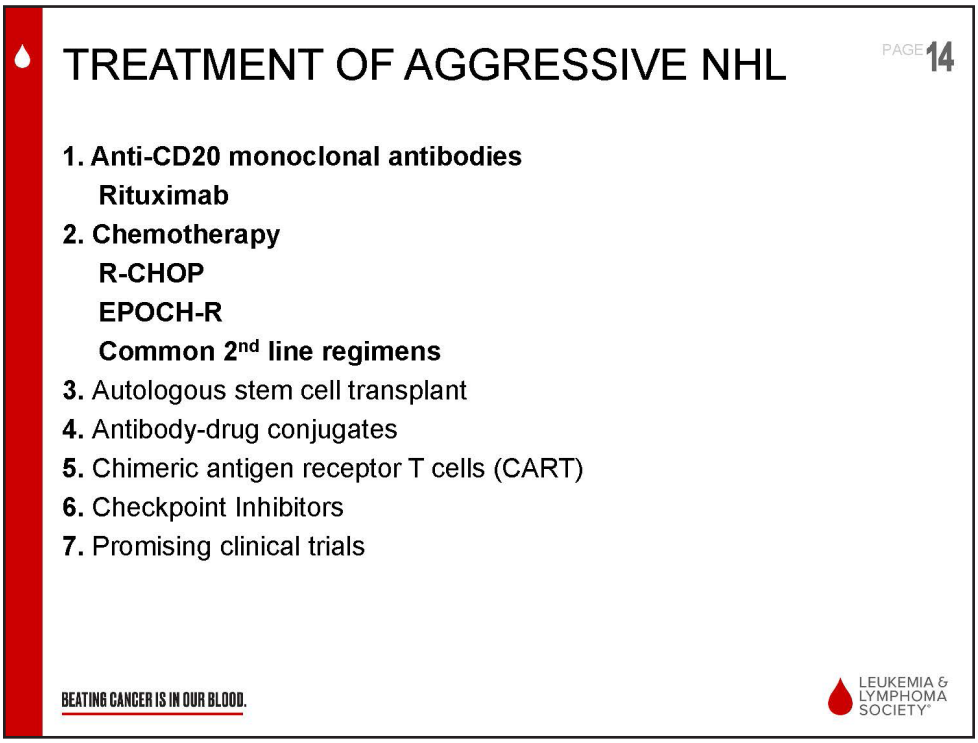
Slide 12: TREATMENT

So, some of the categories of treatment we will be discussing today are in the red squares. Anti-CD20 monoclonal antibodies, most commonly represented by a medication called rituximab. Alkylators is a form of chemotherapy. Some examples are listed below. Bendamustine and cyclophosphamide. These tend to act at the level of the nucleus. Checkpoint inhibitors. This is just another word for PD-1 inhibition or immunotherapy. They interact at the cross-talk between a lymphoma cell and a healthy T-cell. They are most commonly represented by medications called nivolumab and pembrolizumab. And, a CAR-T cell is an engineered T-cell that interacts at the CD19 protein that is expressed on a lymphoma cell.



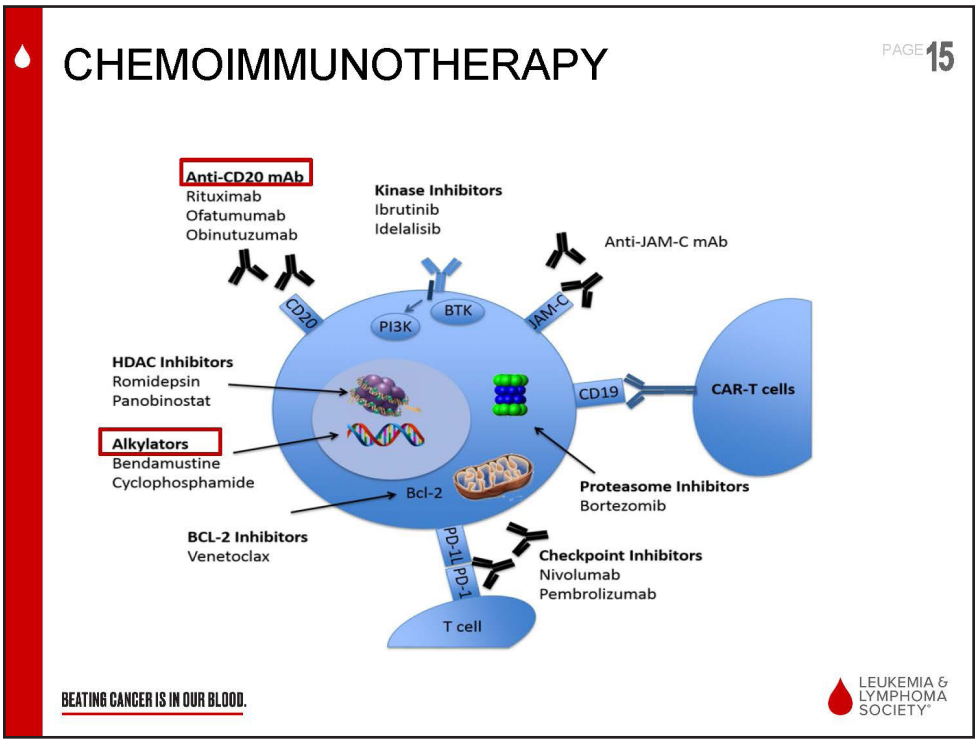
Slide 13: TREATMENT

We will also be discussing antibody drug conjugates. This particular type of therapy is a little bit newer. It uses similar technology to the CD20 monoclonal antibody Rituxan® that I mentioned, but it has an added benefit. It has a little molecule of chemotherapy attached to it that helps it be even more efficacious.



Slide 14: TREATMENT OF AGGRESSIVE NHL

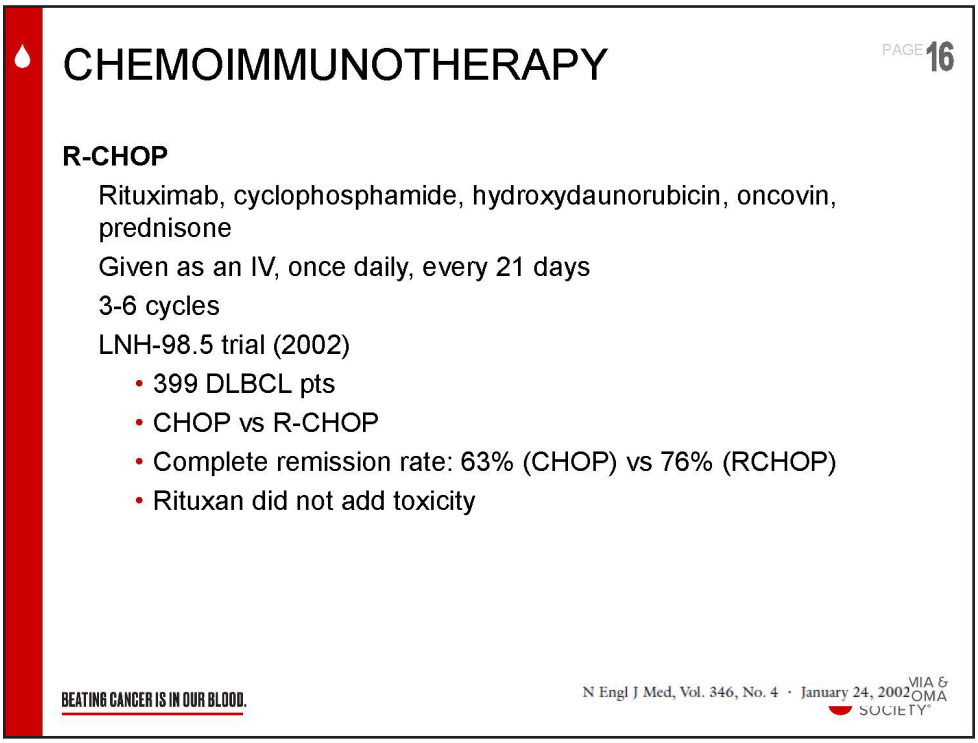
So, let us go through the treatments. We are going to start off discussing the 2 areas in bold, anti-CD20 monoclonal antibodies, as I said most commonly represented by Rituxan, and we will also discuss chemotherapy, including the 2 most common front-line regimens used for aggressive non-Hodgkin's lymphoma, which are R-CHOP, and to a lesser extent EPOCH-R, and we will briefly discuss common second-line chemotherapy regimens.



Slide 15: CHEMOIMMUNOTHERAPY

So again, revisiting our picture here, you can see the 2 areas that we will be discussing.

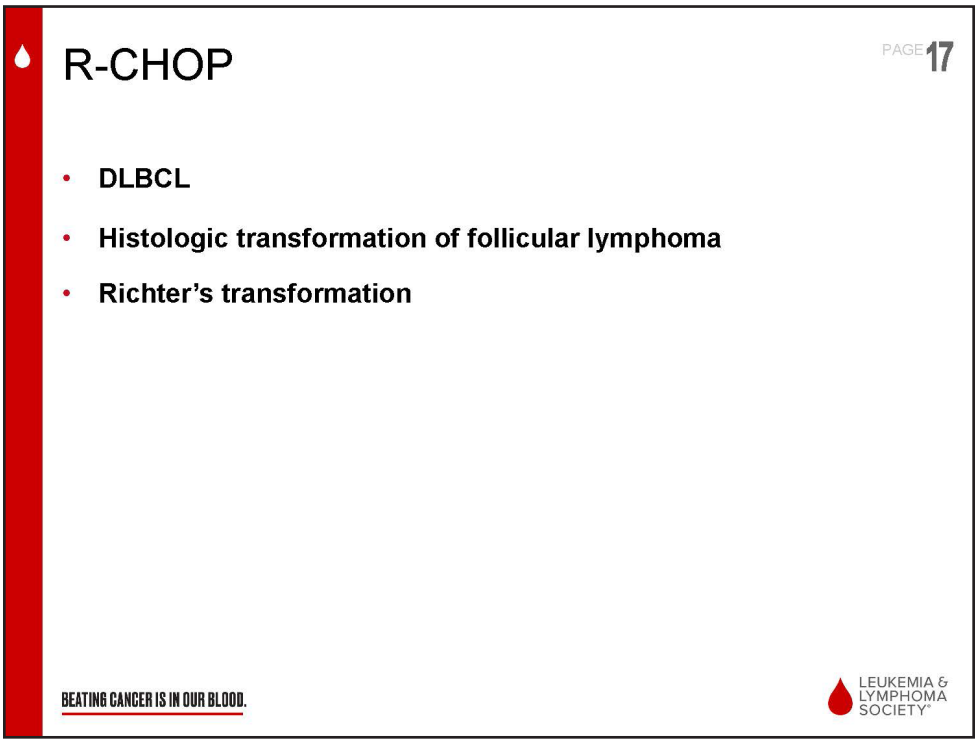
So, the CD20 monoclonal antibodies, the medication has a binding pocket that fits onto the CD20 protein expressed on the outer aspect of the majority of lymphoma cells. Once that binding occurs, it elicits a cascade of events that helps eradicate the lymphoma cell. And as I previously mentioned, many chemotherapies function inside the nucleus at the level of DNA. So, you can think of DNA as kind of the brain matter for the cell. And, if you disrupt that important portion of the cell, the lymphoma cell is not able to survive.



Slide 16: CHEMOIMMUNOTHERAPY

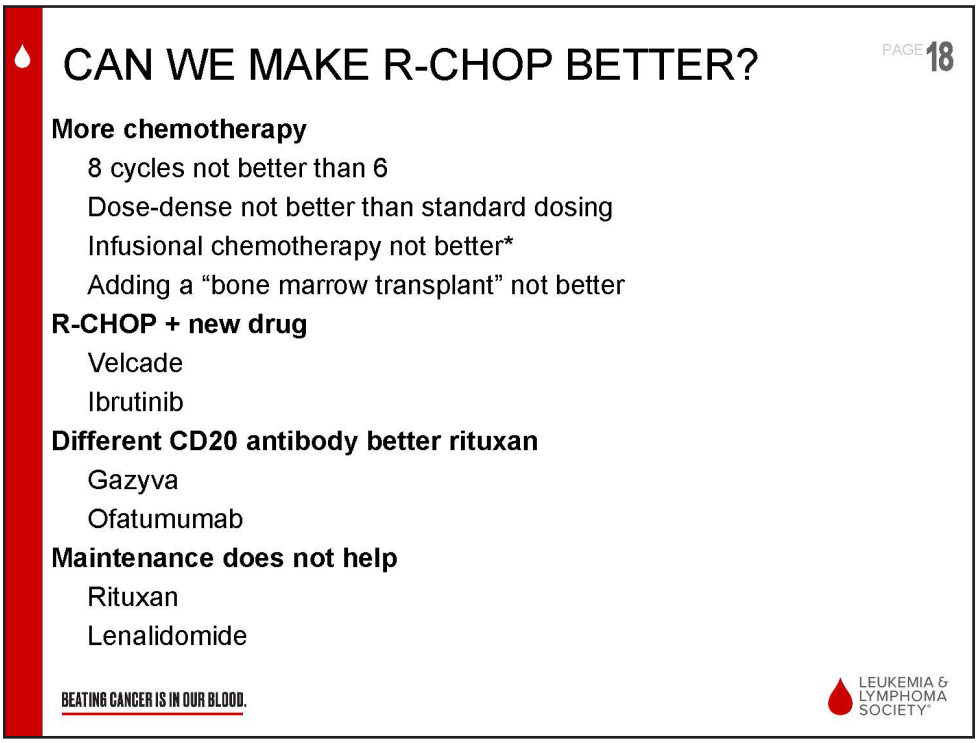
So, the most common front-line regimen for aggressive non-Hodgkin's lymphoma is called R-CHOP. It stands for rituximab and then 3 chemotherapies: cyclophosphamide, hydroxydaunorubicin, oncovin, and a steroid called prednisone. This regimen is given intravenously on one day and it is repeated every 21 days, generally for a total of 6 cycles. There are a subset of patients that may have very early stage disease that may be treated with fewer than 6 cycles.

R-CHOP came to the forefront as standard of care back in 2002, based on data, published from the LNH-98.5 trial. This trial enrolled 399 patients with diffuse large B-cell lymphoma. Approximately half of the patients received CHOP and the other half received CHOP with the addition of Rituxan. The complete remission rate for CHOP was 63%, while that for R-CHOP was 76%. Importantly, the addition of Rituxan to CHOP did not add any toxicity. So, based on these findings, R-CHOP became the standard of care.



Slide 17: R-CHOP

R-CHOP is considered the front-line regimen for diffuse large B-cell lymphoma, histologic transformation of follicular lymphoma, and Richter's transformation.

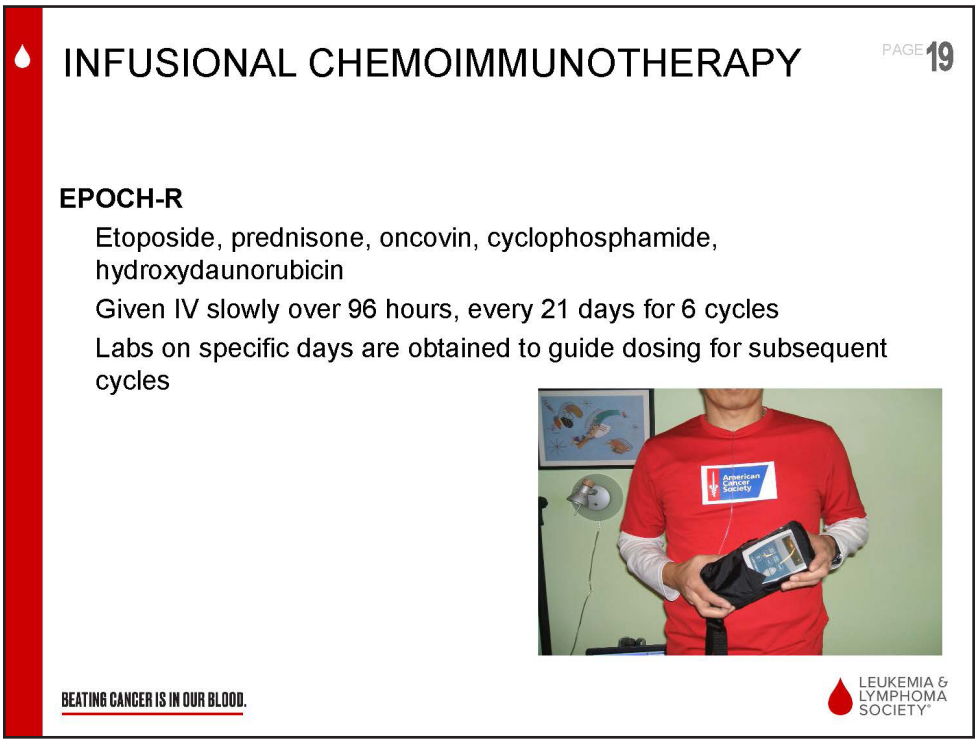


Slide 18: CAN WE MAKE R-CHOP BETTER?

You may ask yourself, if that has been the standard of care since 2002 and here we are in 2020, you guys are supposed to be doing a lot of research and why have we not come up with anything better? Well, it is certainly not for lack of trying. Multiple efforts have been made to see if we can build upon R-CHOP to make it a better regimen. So, we tried adding more chemotherapy. We found 8 cycles was no better than 6. We tried increasing the doses with dose-dense chemotherapy, but it was no better than standard dosing. We tried administering it in a different way, so-called infusional chemotherapy over a longer period of time, and that was largely found not to be better. There is an exception to this statement, which is why there is a little asterisk there, and we will discuss that exception a little bit later in the talk. We tried adding a bone marrow transplant to front-line treatment and that also was no better.

So, then we switched our efforts to adding a new type of non-chemotherapy drug to R-CHOP to see if that would help. We tried things called Velcade® and ibrutinib, but it was still no better than R-CHOP alone. We tried exchanging Rituxan for a different CD20 antibody, such as Gazyva® or ofatumumab, and again no improvement.

Then we asked ourselves, well, maybe if we placed patients on some type of maintenance therapy after they complete their 6 cycles of R-CHOP, this will help. And overall, these studies have not shown much benefit.



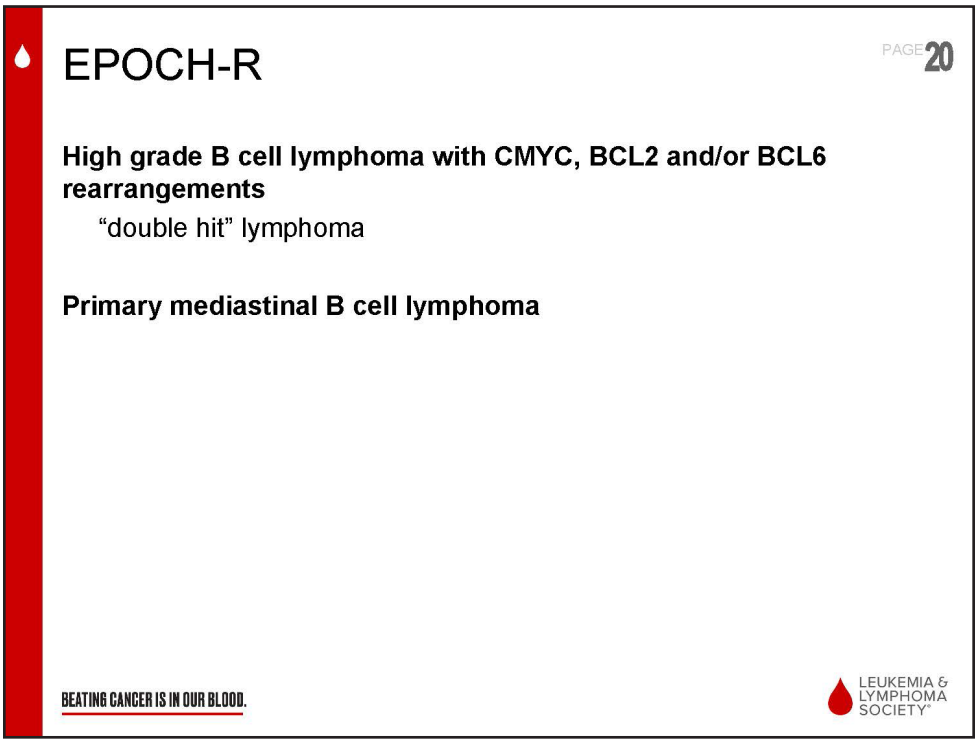
Slide 19: INFUSIONAL CHEMOIMMUNOTHERAPY

So, I want to take a moment to discuss infusional chemotherapy. This is best represented by a regimen called EPOCH-R. It stands for etoposide, which is a chemotherapy, prednisone, a steroid, and then 3 additional chemotherapies, oncovin, cyclophosphamide, and hydroxydaunorubicin.

So, as opposed to R-CHOP being administered all in 1 day, EPOCH-R is given intravenously, slowly, over 96 hours. This is repeated every 21 days for a total of 6 cycles.

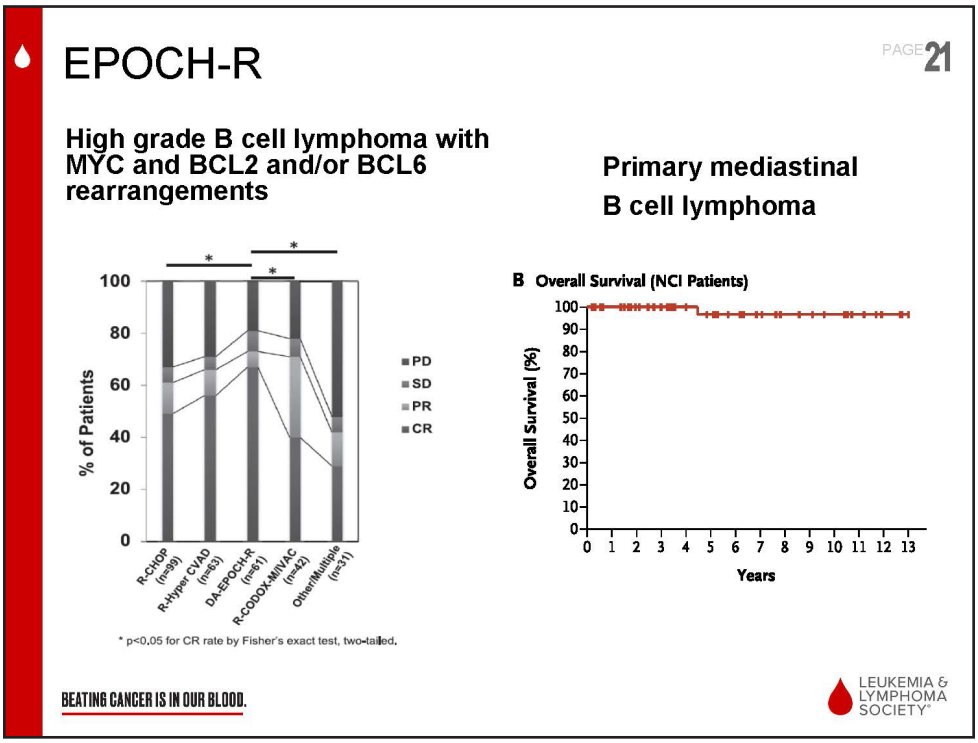
Now initially we had to give this regimen in the hospital, and patients would have to sit in the hospital for 4 nights. But, now that we have access to chemotherapy pumps, which are pictured in the photograph on the lower right-hand corner, we are actually able to give this in the clinic. So, the little pump that you see pictured there contains enough chemotherapy to infuse slowly into a line for 24 hours. So, a patient comes into the clinic, they get hooked up with their pump, and they get to go back to the comfort of their own home, and 24 hours later, they come back to the clinic, the empty pump is removed and a fresh pump with another 24 hours of medication is attached. This is repeated until all 96 hours of treatment have been completed.

Labs on specific days are obtained after each cycle to guide dosing for subsequent cycles. So, this is really a nice way to allow a physician to tailor the appropriate dosing for their patient.



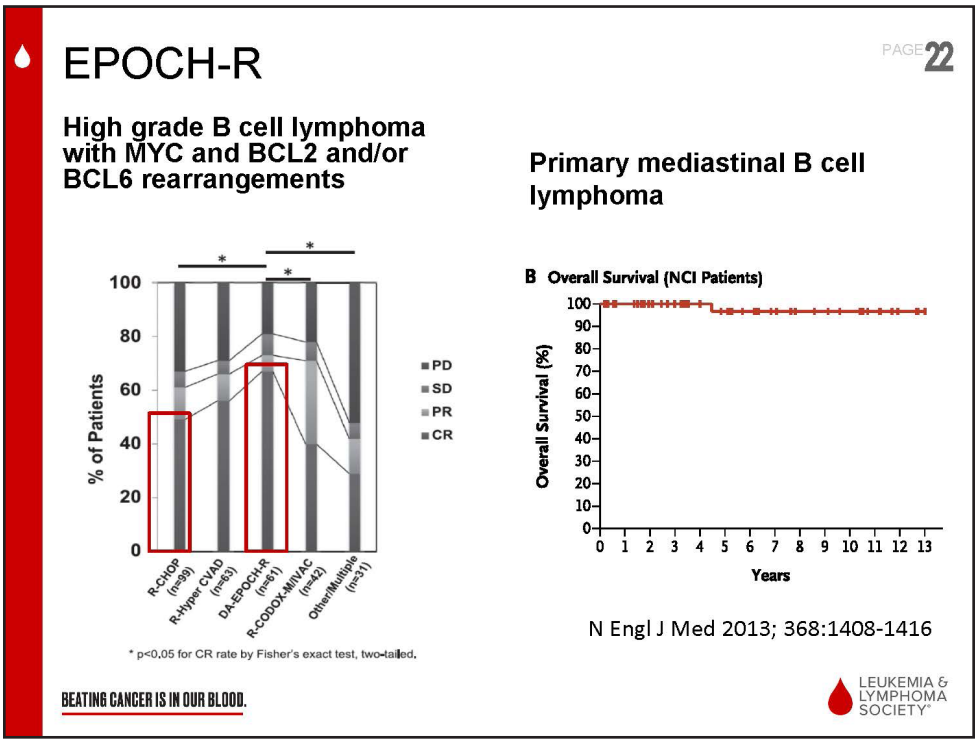
Slide 20: EPOCH-R

EPOCH-R is indicated for the front-line treatment of high grade B-cell lymphoma with CMYC, BCL2, and/or BCL6 rearrangement, the so-called double-hit lymphoma, or if you have all 3 abnormalities, it is called a triple-hit lymphoma. And, it is also indicated for the front-line treatment of primary mediastinal B-cell lymphoma.



Slide 21: EPOCH-R

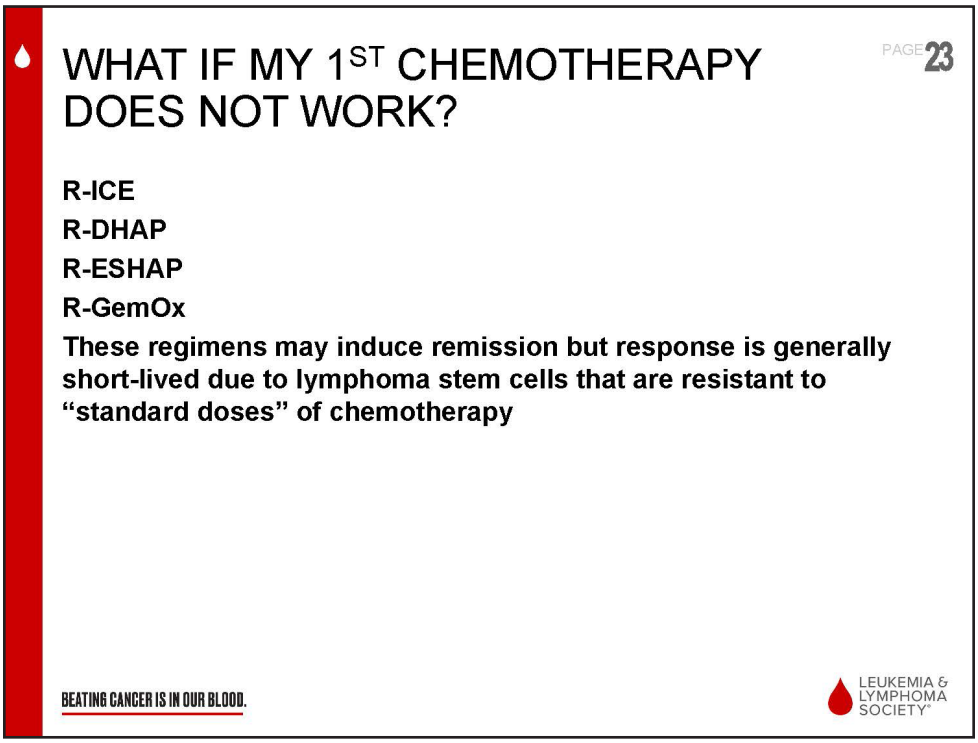
So, pictured here are 2 graphs to show the data supporting use of EPOCH-R in high grade B-cell lymphoma on the left, and in primary mediastinal B-cell lymphoma on the right.



Slide 22: EPOCH-R

I want to draw attention to the graph on the left. So, if you take a look at the X axis, it represents different chemotherapy regimens for the treatment of these high-grade B-cell lymphoma patients, and as you see R-CHOP and EPOCH-R are included. The Y axis is the percentage of patients having a certain response. The responses are color-coded, and you can see the legend over to the right. Now, the gray scale color-coding is difficult to decipher, so I have added some red boxes for clarity. So, the red box that you see above R-CHOP and dose-adjusted EPOCH-R represent the percentage of patients achieving a complete remission with their respective regimens. And as you can see, the bar for EPOCH-R is quite a bit higher than the bar for R-CHOP. So, this supports using EPOCH-R in patients with the high-grade B-cell lymphoma, these double-hit lymphomas.

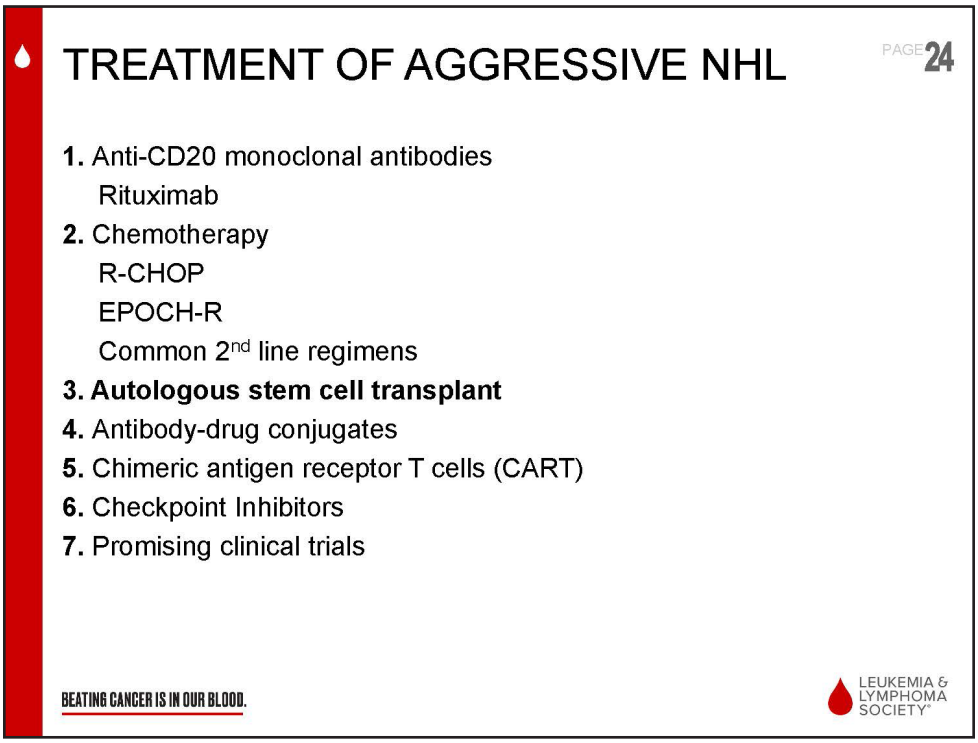
Now if you move your attention to the graph over on the right, this is explaining why we support EPOCH-R in primary mediastinal B-cell lymphoma. So, the X axis is in years. The Y axis is percentage of patients surviving. So, the red bar that you see is representing patients surviving over time. Now, as a lymphoma physician, the appearance of this curve, it really could not get any better. What this is representing is that the majority of patients are surviving, despite several years passing. And so, EPOCH-R is considered front-line for primary mediastinal B-cell lymphoma.



Slide 23: WHAT IF MY 1ST CHEMOTHERAPY DOES NOT WORK?

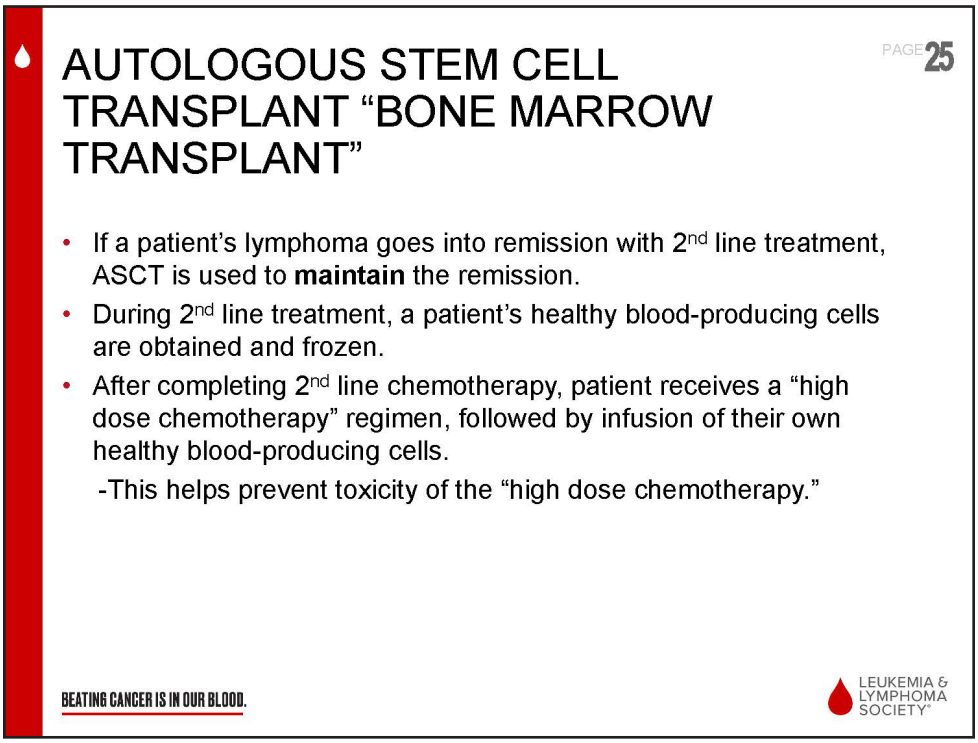
So, what many patients have asked me, so what if my first chemotherapy does not work? Well, again my first considerations are, is there a rationally designed clinical trial available for this patient? If there is not, or if a patient elects not to participate, or reasonably sick patients, we try a different type of chemotherapy. The most common second-line regimens are listed on the slide, R-ICE, R-DHAP, R-ESHAP, and R-Gem Ox. For the sake of time, we are not going to go through the individual components of these regimens. They are largely considered comparable and physicians choose it based on experience and toxicity profile.

So, these regimens may induce a remission, but unfortunately the response to second-line chemotherapy is short-lived. This is thought to be due to lymphoma stem cells that are resistant to the standard doses of the regimens listed above. So, these regimens generally eradicate the vast majority of the lymphoma, but a few resistant lymphoma stem cells likely remain.



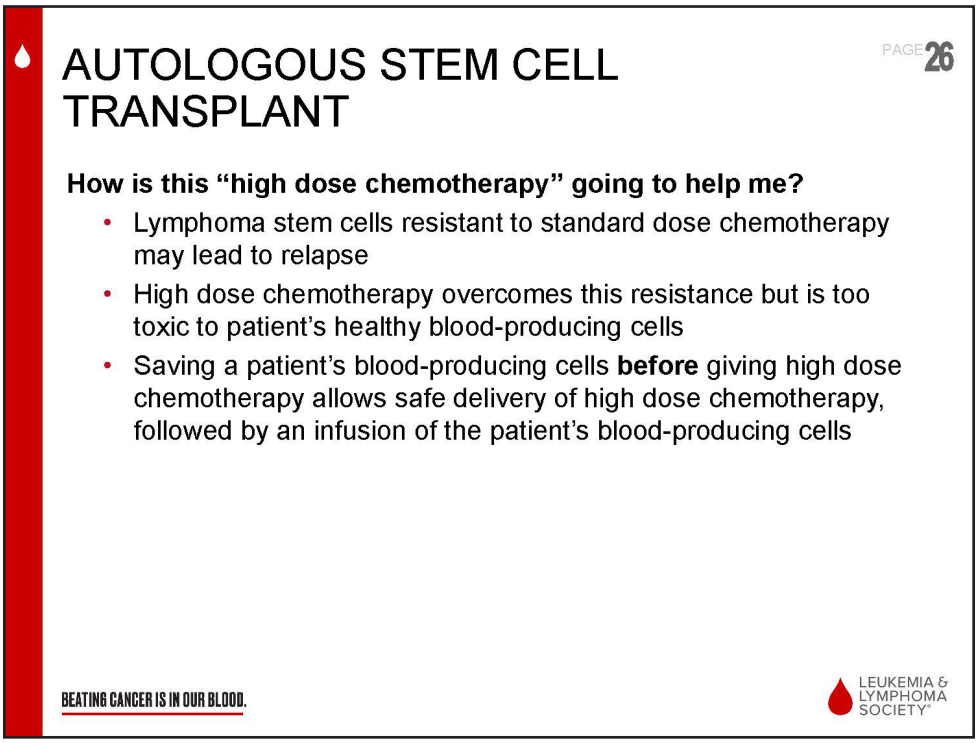
Slide 24: TREATMENT OF AGGRESSIVE NHL

So, addressing these resistant lymphoma stem cells is where an autologous stem cell transplant starts to come into play.



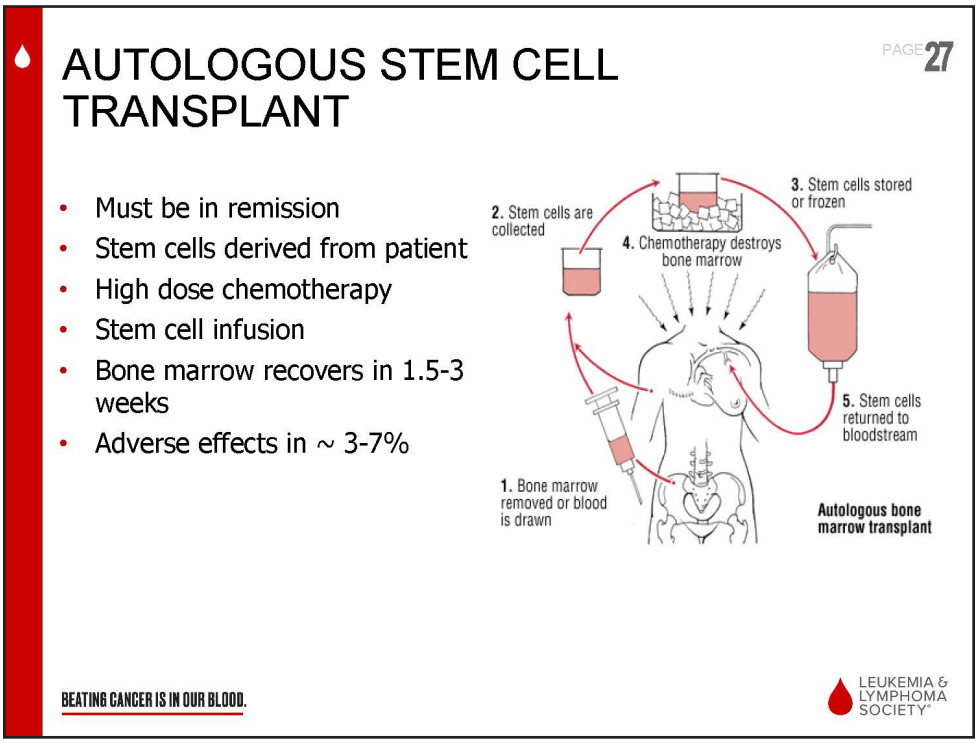
Slide 25: AUTOLOGOUS STEM CELL TRANSPLANT "BONE MARROW TRANSPLANT"

So, if a patient's lymphoma goes into remission with second-line treatment, transplant is used to maintain that remission. The way this is accomplished is, during second-line treatment a patient's healthy blood-producing, or in other words bone marrow cells, are obtained and frozen. Once a patient has completed their second-line chemotherapy and it is confirmed they are in a remission, they then move on to the bone marrow transplant step of their treatment. The bone marrow transplant step includes administration of high-dose chemotherapy, and this is followed by infusion of their own healthy blood-producing bone marrow cells. The infusion of their previously saved healthy bone marrow cells helps prevent toxicity of the high-dose chemotherapy.



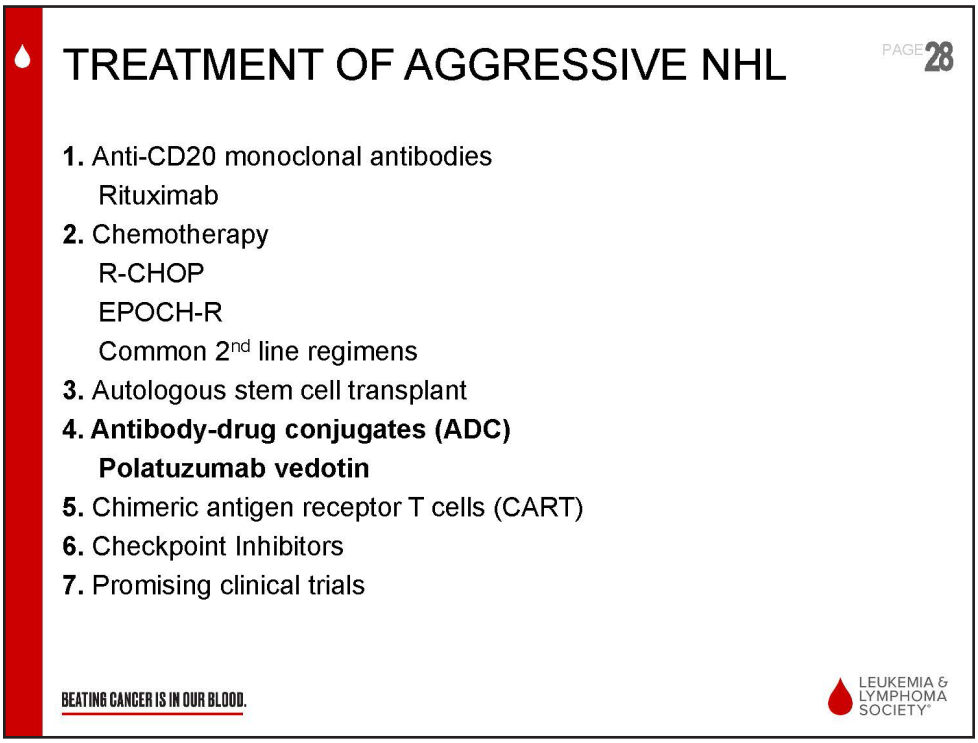
Slide 26: AUTOLOGOUS STEM CELL TRANSPLANT

So, how does high-dose chemotherapy help a patient? Well, I previously alluded to that studies in the lab show that there are lymphoma stem cells that are resistant to standard-dose chemotherapy that may lead to relapse of the lymphoma. So, the high-dose chemotherapy utilized in a bone marrow transplant overcomes this resistance, but unfortunately it is also very toxic to the patient's healthy blood-producing cells. So, this is why saving a patient's blood-producing cells, before giving the high dose chemotherapy, allows safe delivery of these high doses, followed by an infusion of the patient's blood-producing cells.



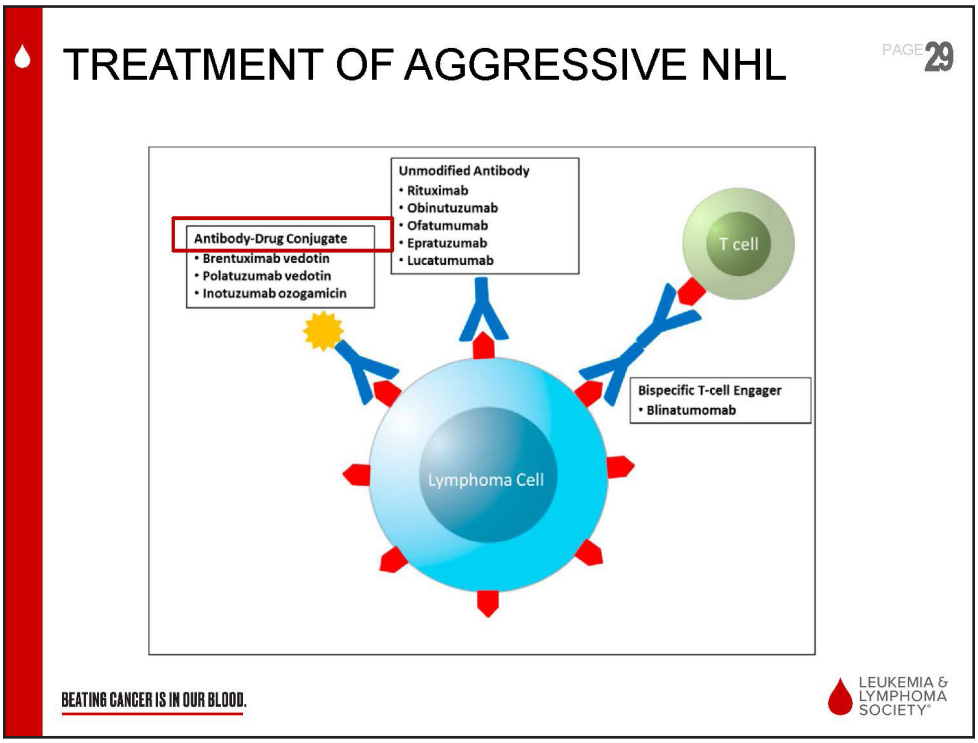
Slide 27: AUTOLOGOUS STEM CELL TRANSPLANT

So, I want to draw your attention to the picture over to the right. It is a schematic to show the steps of a bone marrow transplant. So, step number 1 is bone marrow, or more commonly we get the stem cells from a peripheral blood collection, are removed from the patient. The stem cells are collected. And then, moving on to step number 3, the stem cells are stored or frozen. Then, moving down to step number 4, the patient receives chemotherapy. This picture is a little bit dramatic, saying that the chemotherapy destroys the bone marrow, but it is targeted at eradicating those lymphoma stem cells that commonly reside in the bone marrow. And then, coming down to step number 5, the stem cells are returned to the healthy previously frozen stem cells are returned to the patient's bloodstream.



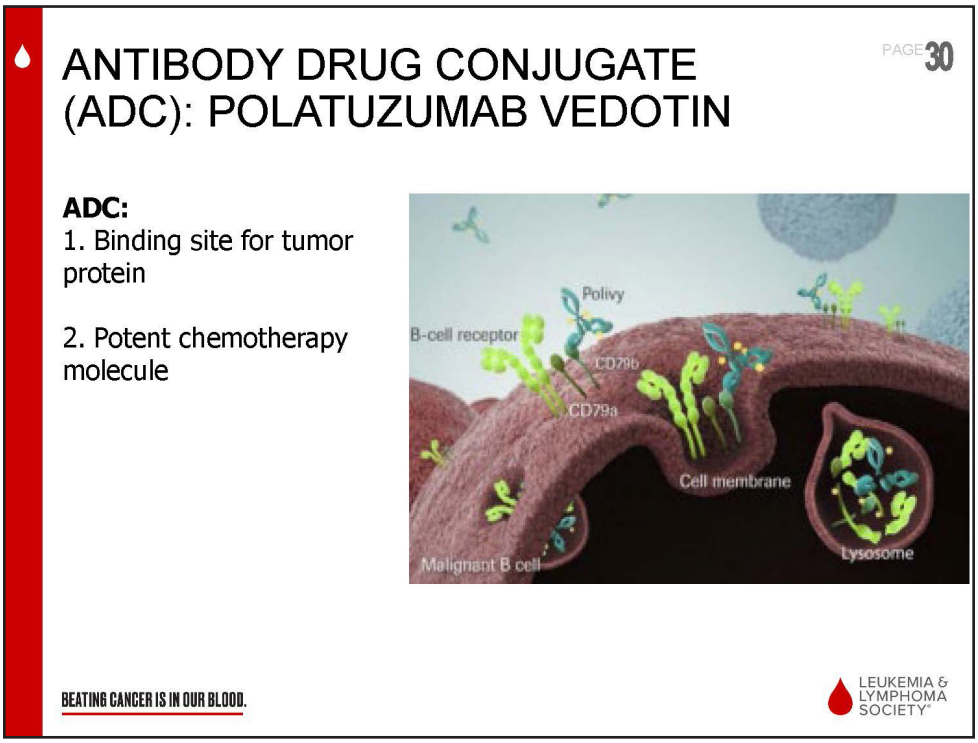
Slide 28: TREATMENT OF AGGRESSIVE NHL

So, now I want to switch gears and talk about antibody drug conjugates. In the lymphoma world, it is most commonly represented by a medication called polatuzumab vedotin.



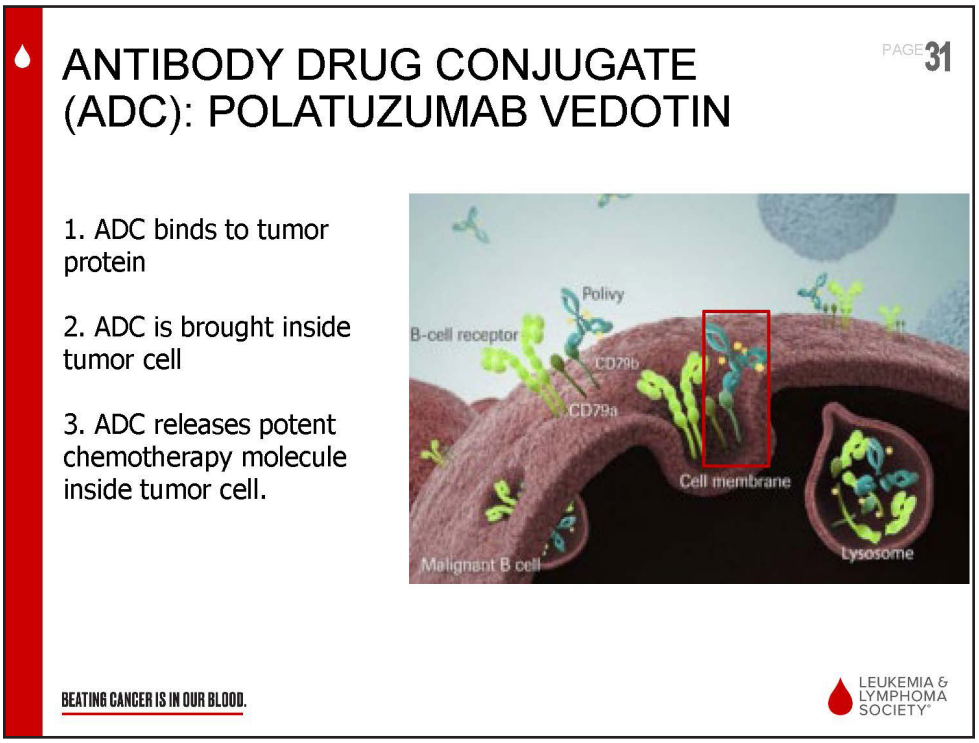
Slide 29: TREATMENT OF AGGRESSIVE NHL

So to reorient you to that introductory schematic, these are our antibody drug conjugates attaching to cell surface proteins on a lymphoma cell. I have said that polatuzumab was the most common in the lymphoma world and I should revise that. Polatuzumab is most commonly used in our aggressive non-Hodgkin's lymphoma, but brentuximab vedotin plays a very important role in our T-cell lymphoma patients and also our Hodgkin's lymphoma patients.



Slide 30: ANTIBODY DRUG CONJUGATE (ADC): POLATUZUMAB VEDOTIN

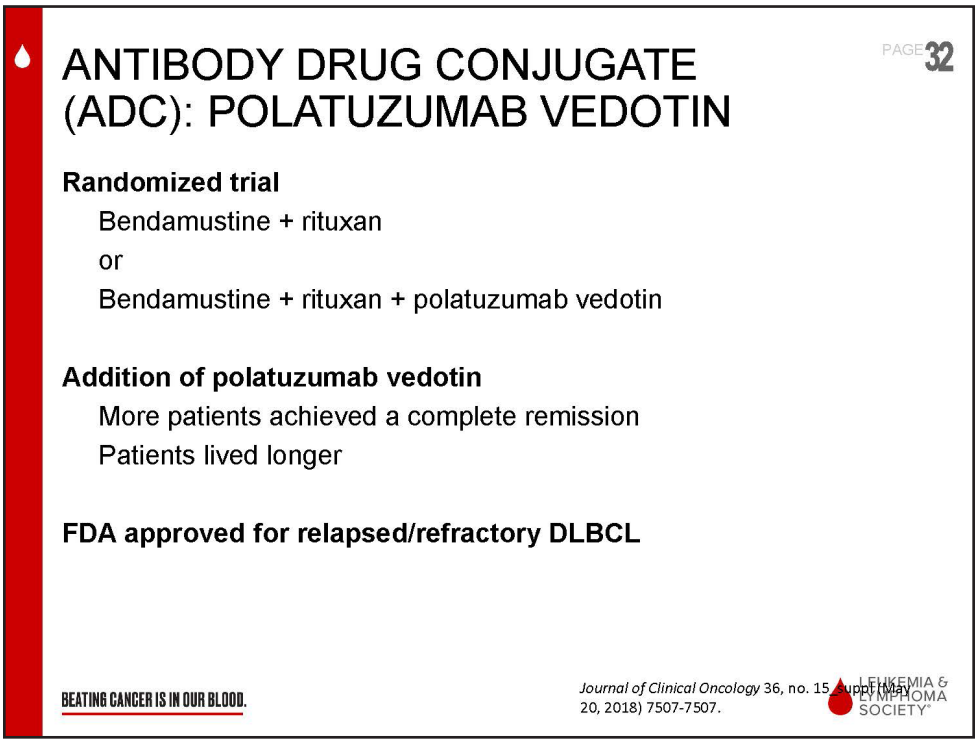
So, an antibody drug conjugate consists of 2 parts. So, the schematic on this slide, that reddish thing, is a lymphoma cell. And so, an antibody drug conjugate consists of, number 1, a binding site for a tumor protein, and then also, it has a potent chemotherapy molecule attached to it.



Slide 31: ANTIBODY DRUG CONJUGATE (ADC): POLATUZUMAB VEDOTIN

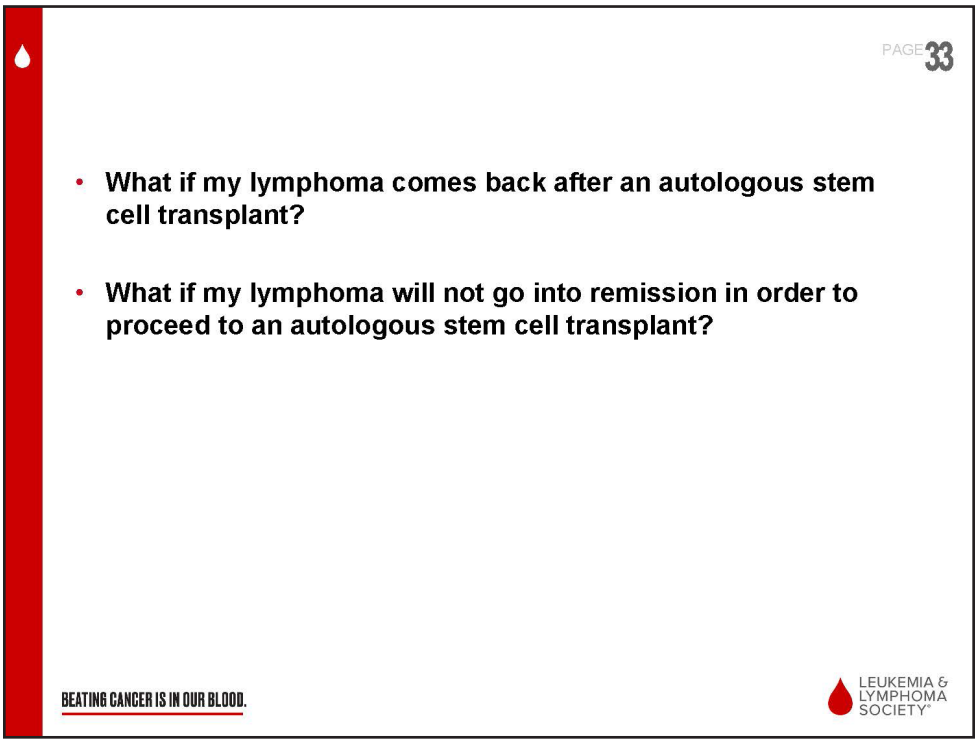
So, I will draw your attention to the antibody drug conjugate that is within the red box on this slide. So, if you look at the green portion at the bottom, that is the protein expressed on the surface of a lymphoma cell. The aqua green portion is the antibody drug conjugate that binds to that protein. And, those little yellow dots are the potent chemotherapy molecule that has bound to the antibody drug conjugate.

Once this binding occurs between the antibody drug conjugate and the lymphoma protein, the entire molecule is brought inside the cell. And you can see that represented on the right side. It is titled lysosome. Once that lysosome is brought inside the cell, the potent chemotherapy molecule is released, essentially like a little bomb inside the cell, eradicating the lymphoma cell, but sparing the patient a lot of toxicity that can be associated with more widespread use of chemotherapy.



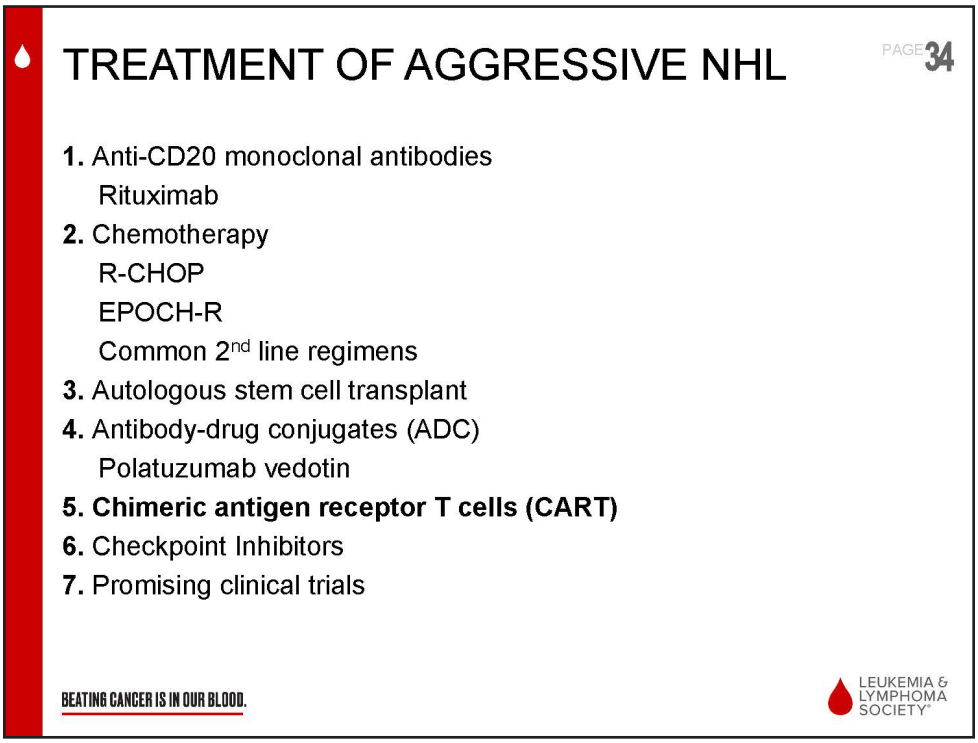
Slide 32: ANTIBODY DRUG CONJUGATE (ADC): POLATUZUMAB VEDOTIN

So, polatuzumab vedotin was recently FDA approved, based on a randomized trial that enrolled patients with diffuse large B-cell lymphoma and a smaller population of patients with follicular lymphoma. Approximately half of the patients received a chemotherapy called bendamustine combined with Rituxan. And, the other half received bendamustine combined with Rituxan with the addition of polatuzumab vedotin. So, the group that received polatuzumab, achieved a complete remission at a higher rate, and those patients also lived longer. So, based on this data, the FDA approved polatuzumab for relapsed/refractory diffuse large B-cell lymphoma.



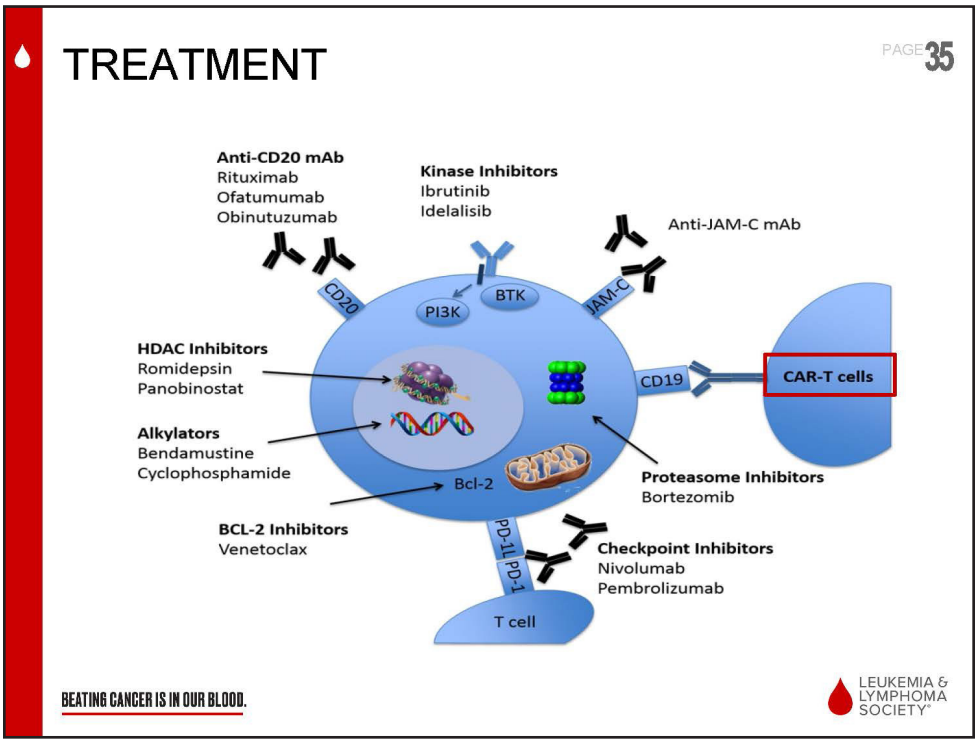
Slide 33: QUESTIONS

So, what if my lymphoma comes back after an autologous stem cell transplant or what if my lymphoma will not go into remission in order to even get to the step where you can proceed to an autologous stem cell transplant?



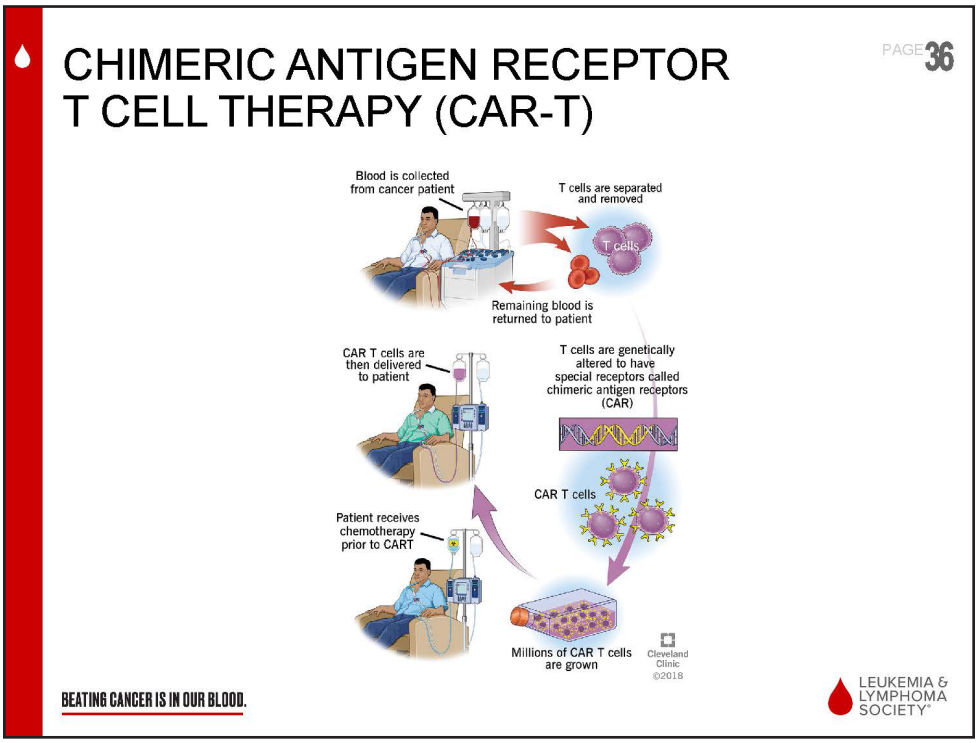
Slide 34: TREATMENT OF AGGRESSIVE NHL

With patients in this category we now have an exciting new therapy to offer them. It is called chimeric antigen receptor T-cells, more commonly called CAR-T cells.



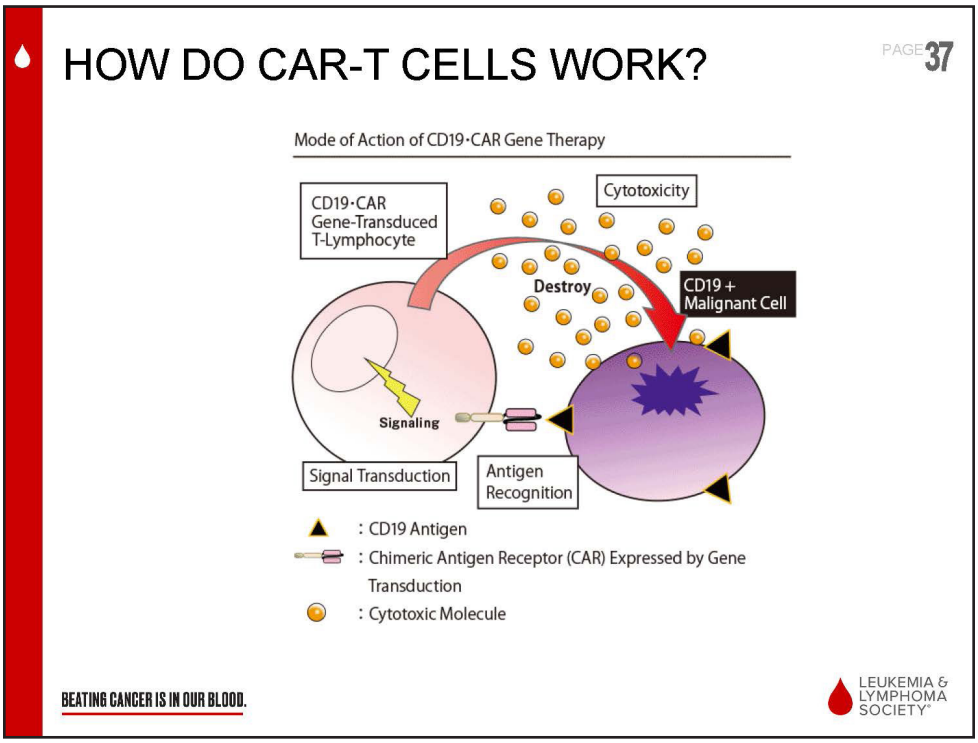
Slide 35: TREATMENT

So, bringing us back to our original picture of the lymphoma cell so you can see the lymphoma cell expressing a protein on its surface called CD19. This is the protein that the current first-generation CAR-T cells bind to.



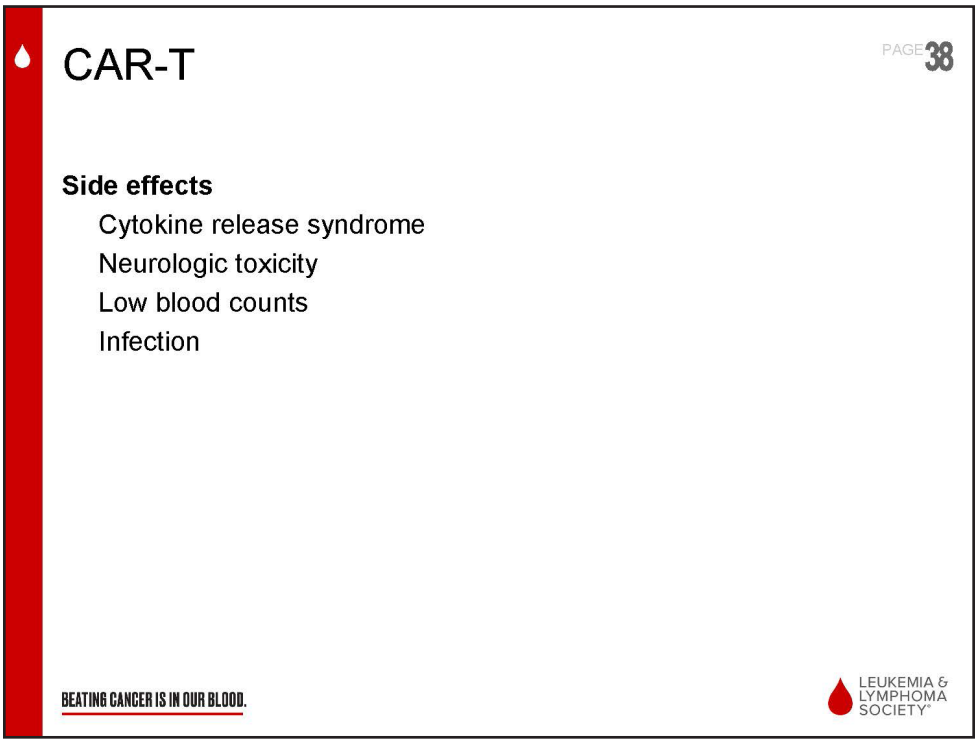
Slide 36: CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY (CAR-T)

So, this is a picture explaining the process of a CAR-T cell. So, starting in the upper left-hand corner, blood is collected from a patient and the T-cells are separated and removed. And, these are just healthy normal immune system T-cells. The remainder of the blood is returned to the patient. These T-cells are then taken to a laboratory where they are engineered or modified to express receptors on their surface that recognize lymphoma.



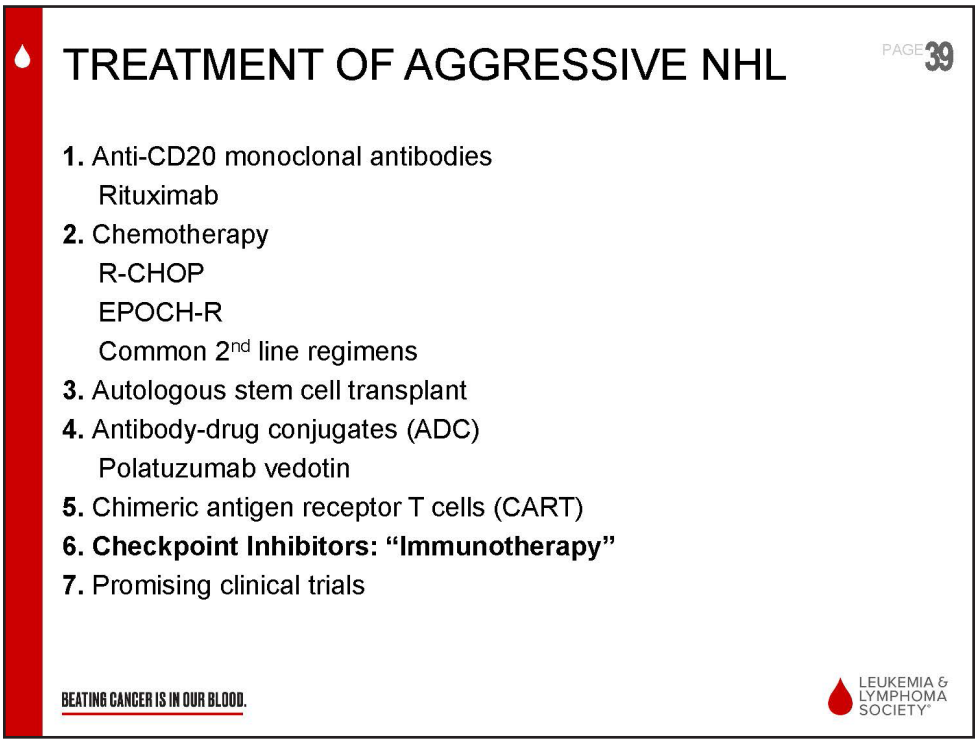
Slide 37: HOW DO CAR-T CELLS WORK?

The light pink cell on the left is a CAR-T cell and the purple cell on the right is a lymphoma cell. So, you can see the binding, the interaction between the CAR-T cell and the lymphoma cell down at the bottom. The receptor on the CAR-T cell is pink and it binds to that black triangle on the lymphoma cell. For our first-generation CAR-T cells, that black triangle is called CD19. Once this binding occurs, the CAR-T cell is activated, and it starts to secrete various molecules that help energize a patient's immune system to eradicate the lymphoma. Some of those molecules that it releases to energize the immune system are called cytokines. And, you can see them pictured as the orange round circles up towards the top.



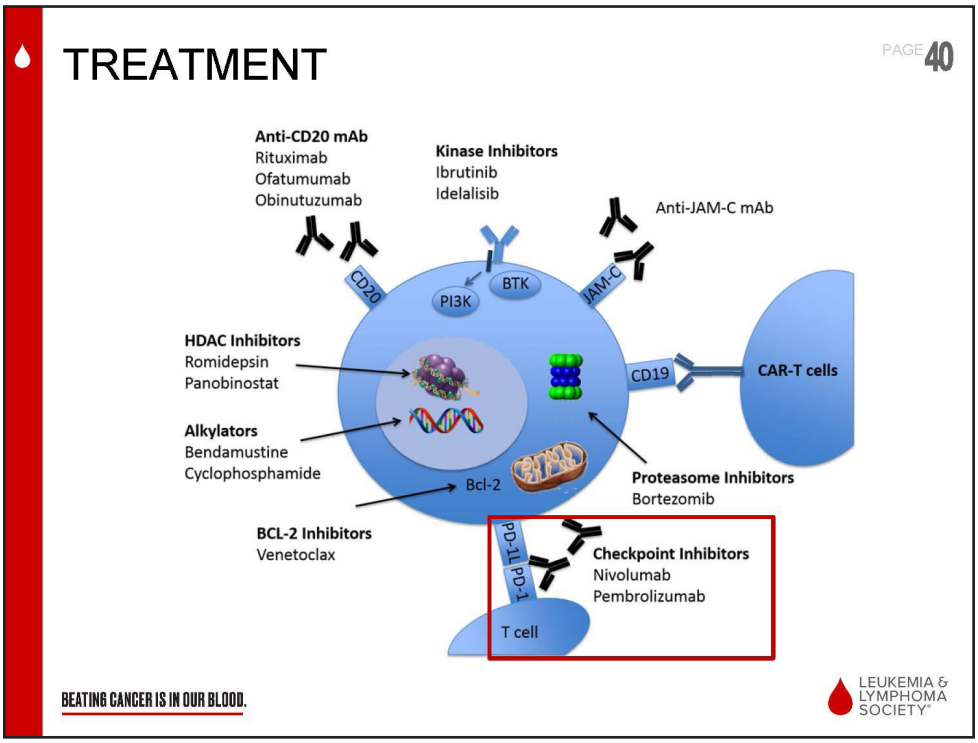
Slide 38: CAR-T

I want to say a special note about side effects that may be associated with administration of CAR-T cells. They include cytokine release syndrome that may manifest as fevers, chills, rash, fast heart rate and difficulty breathing, neurologic toxicity, which can manifest as confusion, sleepiness, and rarely if severe, a seizure, low blood counts, and infection. Due to this special potential side-effect profile, the majority of CAR-T cells, at least for now, are administered in the hospital and patients remain hospitalized for a certain period of time following CAR-T infusion for monitoring.



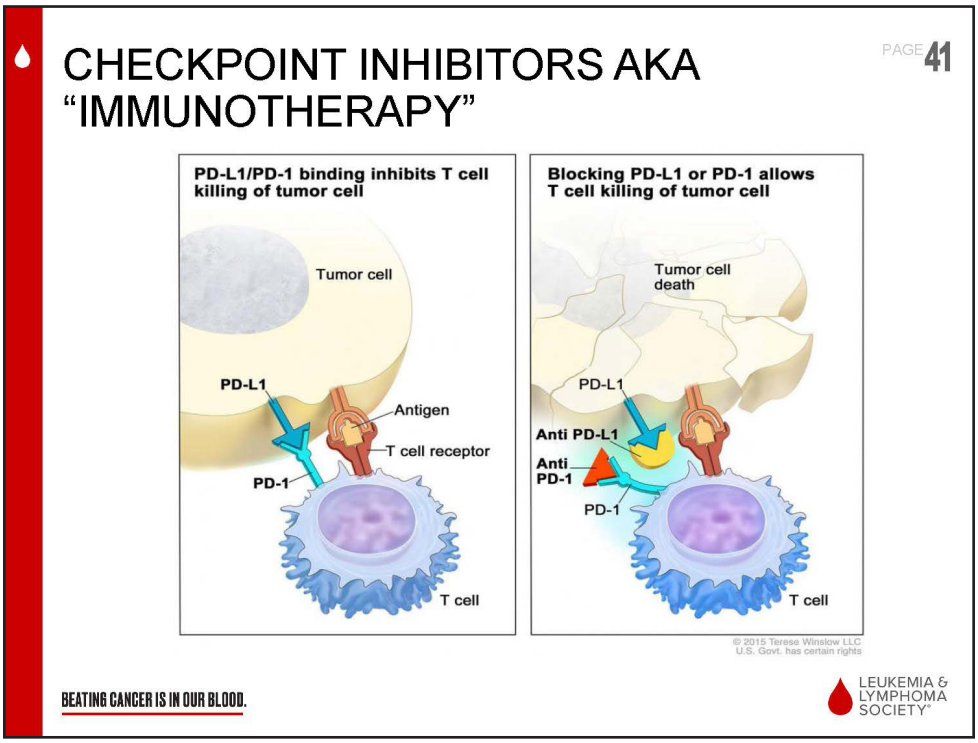
Slide 39: TREATMENT OF AGGRESSIVE NHL

Okay, switching gears to checkpoint inhibitors, more commonly called immunotherapy. I have to say this is probably the most common question I get when I am discussing treatment options with a patient. Very commonly someone will say, well, what about immunotherapy?



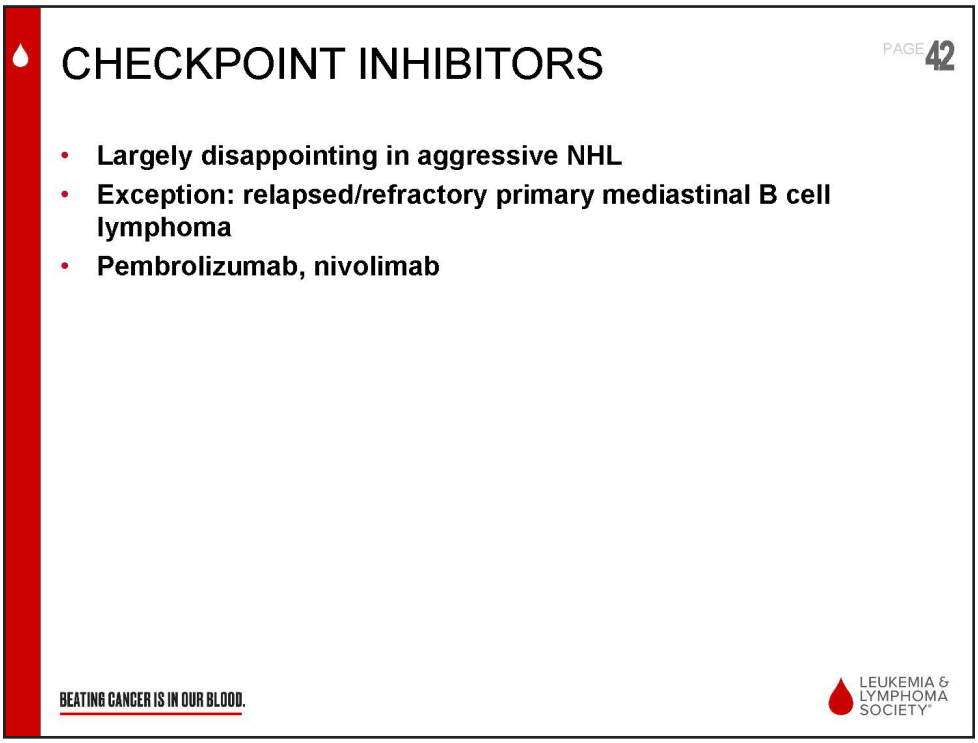
Slide 40: TREATMENT

To reorient you with where immunotherapy interacts, it is with the lymphoma cell and the healthy immune system T-cell.



Slide 41: CHECKPOINT INHIBITORS AKA "IMMUNOTHERAPY"

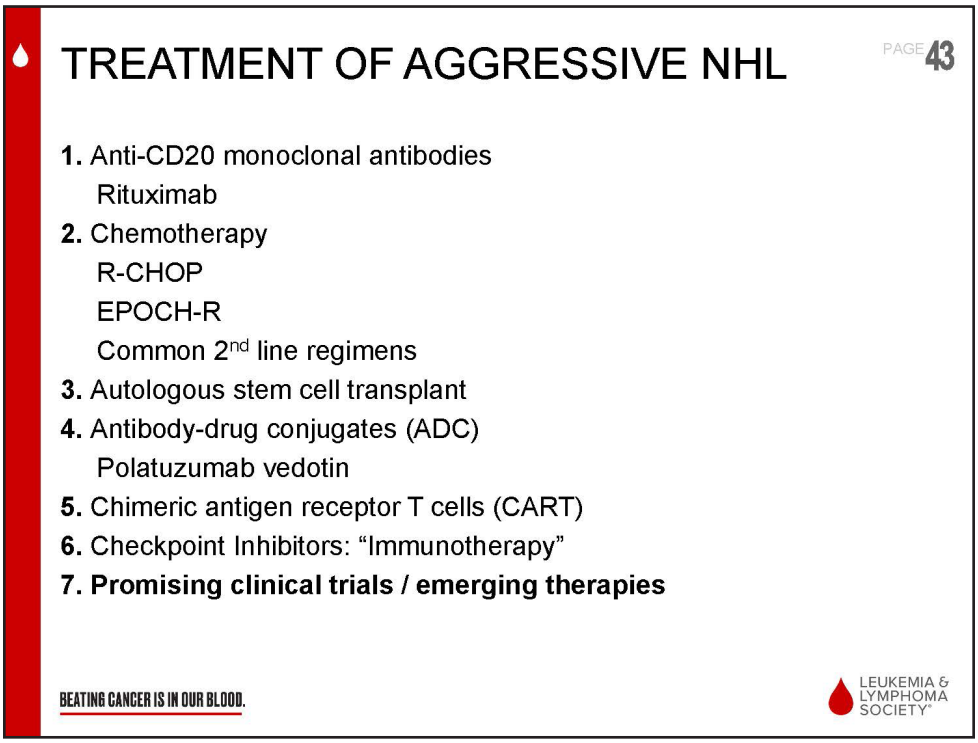
So, here is a more detailed graphic to explain how immunotherapy works. So, you can see the tumor cell in yellow and you can see the healthy T-cell in blue. So, if you draw your attention to the binding between PDL-1 and PD-1, this is a binding that has allowed the tumor cell to in effect hide from a patient's immune system. So, the PD-1 binding turns the healthy T-cell off and it is not able to do its job. However, if you look at the picture on the right, if you give a patient a checkpoint inhibitor, or also called an anti-PD-1 drug, it is represented as the red triangle, it disrupts that binding and the tumor is no longer allowed to hide from the patient's immune system. So, now the T-cell is able to be activated and to do its job in helping with tumor cell death.



Slide 42: CHECKPOINT INHIBITORS

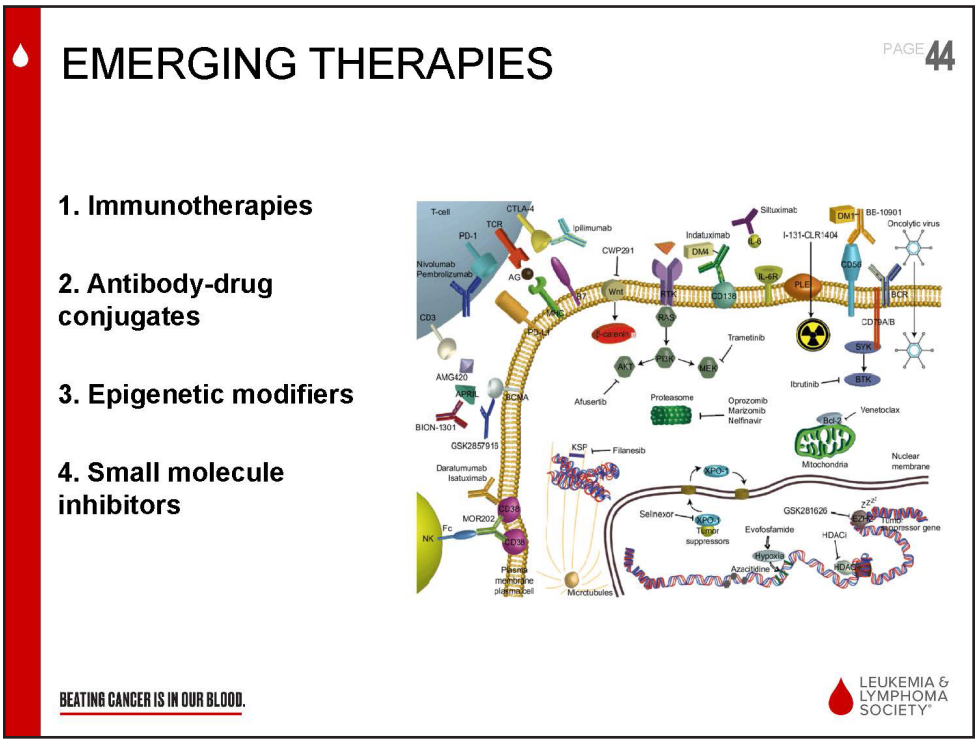
Unfortunately, checkpoint inhibitors or immunotherapy have been largely disappointing in aggressive non-Hodgkin's lymphoma. There are still various clinical trials ongoing, combining checkpoint inhibitors with other agents to potentially sensitize to checkpoint inhibitors. So, the story on immunotherapy is not completely told in aggressive non-Hodgkin's lymphomas, but as single agents they do not look like they are going to be sufficient.

There is an exception to this. There has been good effect seen in checkpoint inhibitors for relapsed/refractory primary mediastinal B-cell lymphoma. And, the 2 most common checkpoint inhibitors are pembrolizumab and nivolumab.



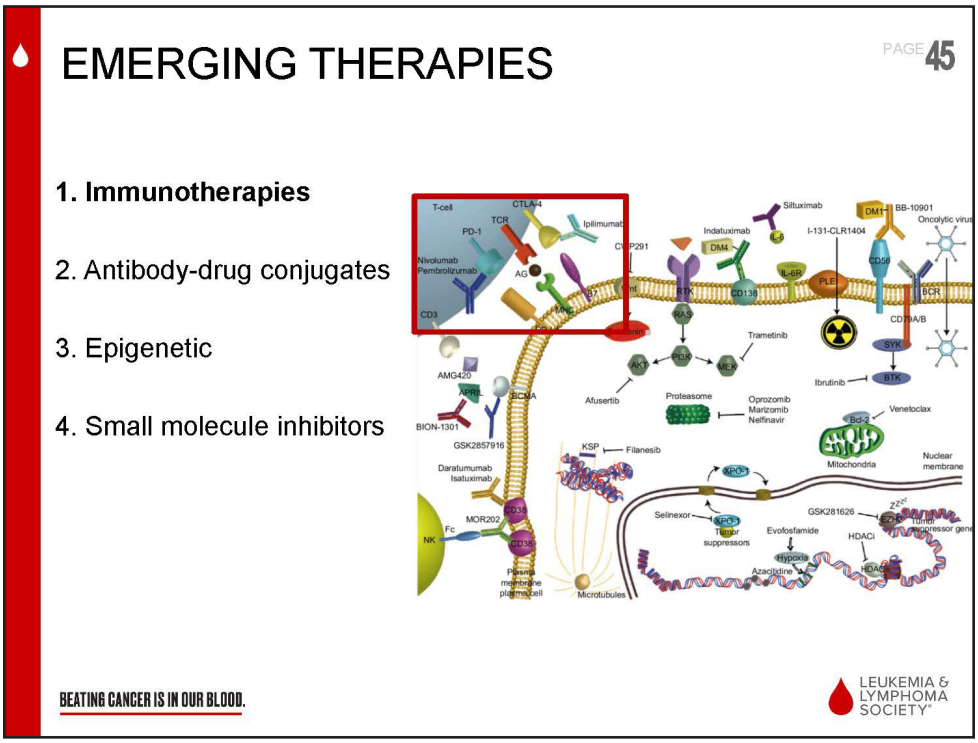
Slide 43: TREATMENT OF AGGRESSIVE NHL

Now, switching gears to promising clinical trials and emerging therapies. Before I get into this, I want to let you guys know this is barely scratching the surface of the emerging therapies for lymphomas. But in the interest of time, I can't review all of the research that is ongoing, so I tried to offer you guys some representative exciting things that are ongoing in the clinic and in the lab.



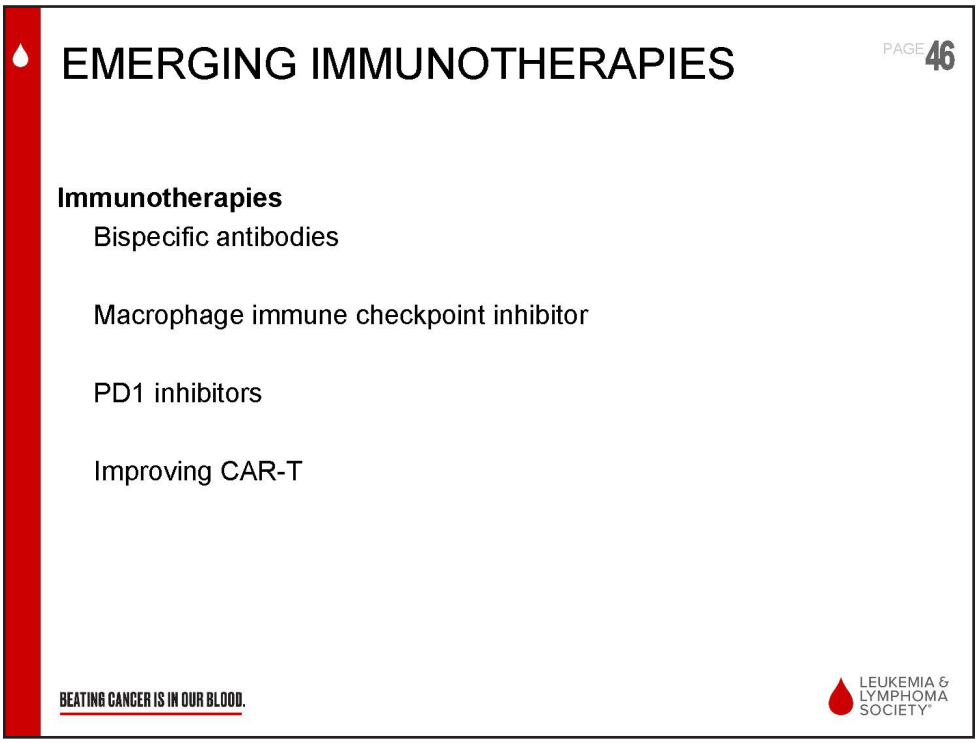
Slide 44: EMERGING THERAPIES

So, emerging therapies can be loosely grouped into 4 categories: immunotherapies; antibody drug conjugates, which you guys are familiar with, we have already discussed an older antibody drug conjugate; epigenetic modifiers; and small molecule inhibitors.



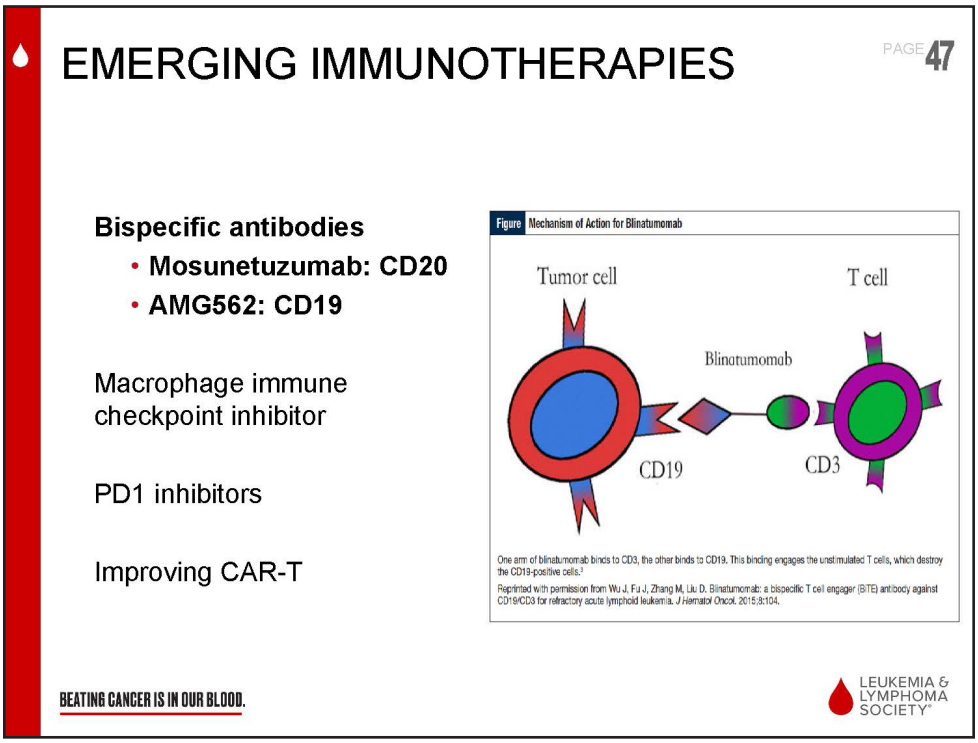
Slide 45: EMERGING THERAPIES

So, the picture to the right, I selected to try and impress upon you how challenging it can be to treat lymphoma. So, all of that busy activity in like two-thirds of the slide on the right, this is a lymphoma cell. The yellow area is the membrane of a lymphoma cell, and all that stuff on the inside are various signaling pathways that help a lymphoma stay strong and grow and replicate. The cell in the upper left-hand corner is the immune system T-cell.



Slide 46: EMERGING IMMUNOTHERAPIES

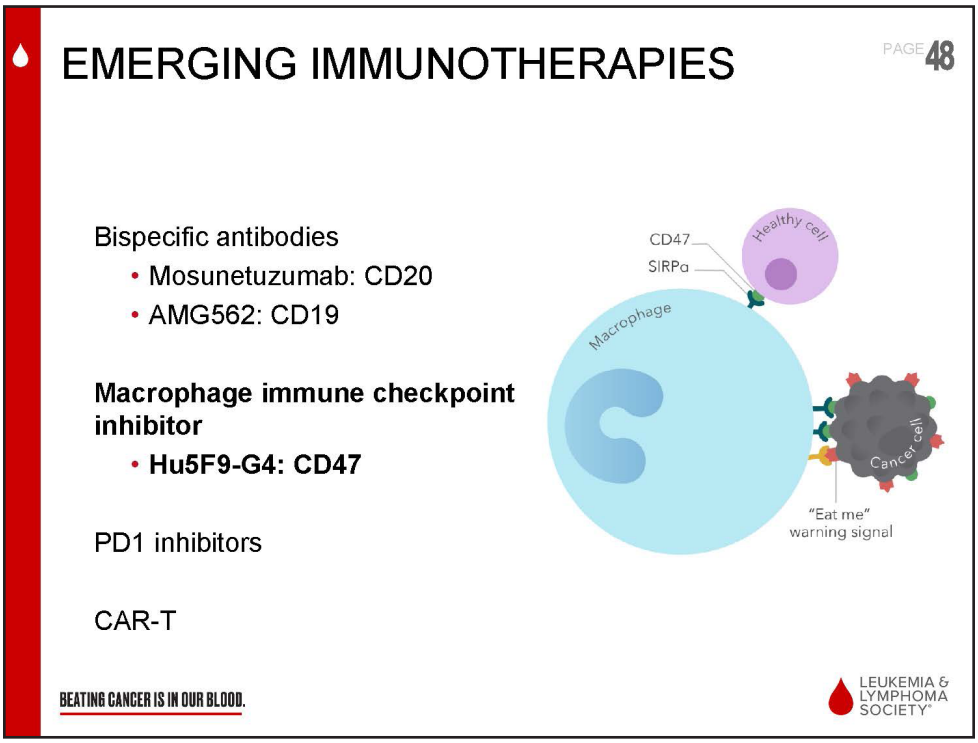
So, starting off with new immunotherapies, it is targeting the interaction between a patient's healthy T-cell and the lymphoma cell. These can be categorized as bispecific antibodies, macrophage immune checkpoint inhibitors, PD-1 inhibitors, which you are familiar with, and also improving on our current CAR-T technology.



Slide 47: EMERGING IMMUNOTHERAPIES

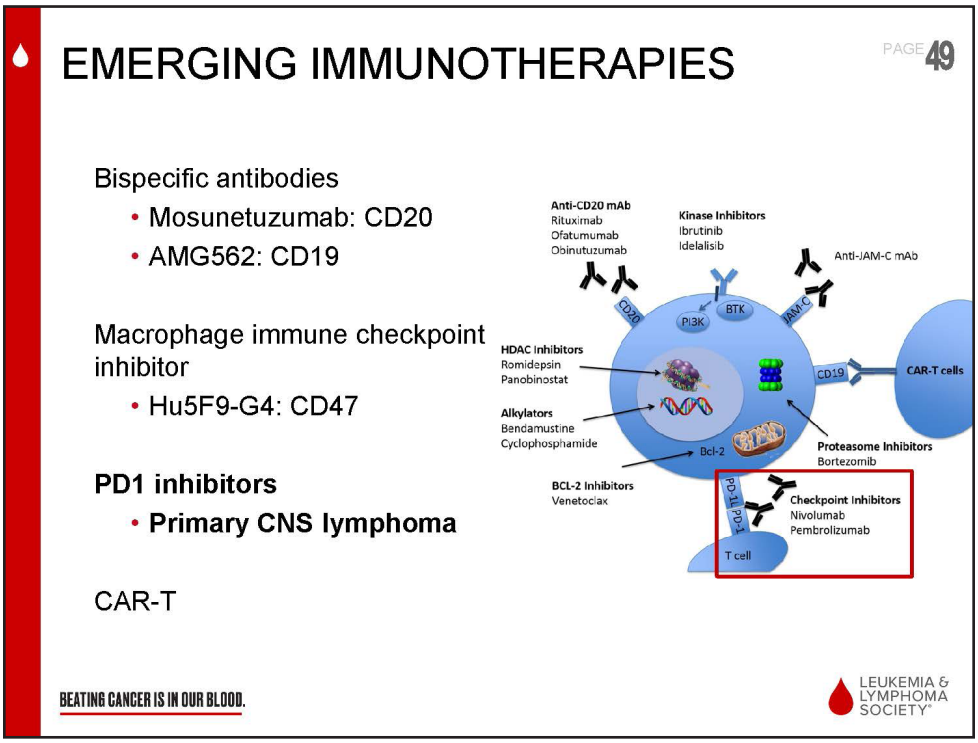
So, bispecific antibodies are an interesting developing way of treating lymphoma. So, it is utilizing the patient's immune system with a T-cell, and so it is bispecific, meaning that it has 2 binding sites. So, one arm of the antibody binds the lymphoma cell, commonly at CD19. The other arm of the molecule binds the T-cell, and it brings those 2 cells in close proximity to one another, so that the T-cell can help eradicate the lymphoma cell.

So, we're developing a bispecific antibody called mosunetuzumab that targets a CD20 protein expressed on the majority of lymphoma cells, and there is also AMG562 that targets CD19.



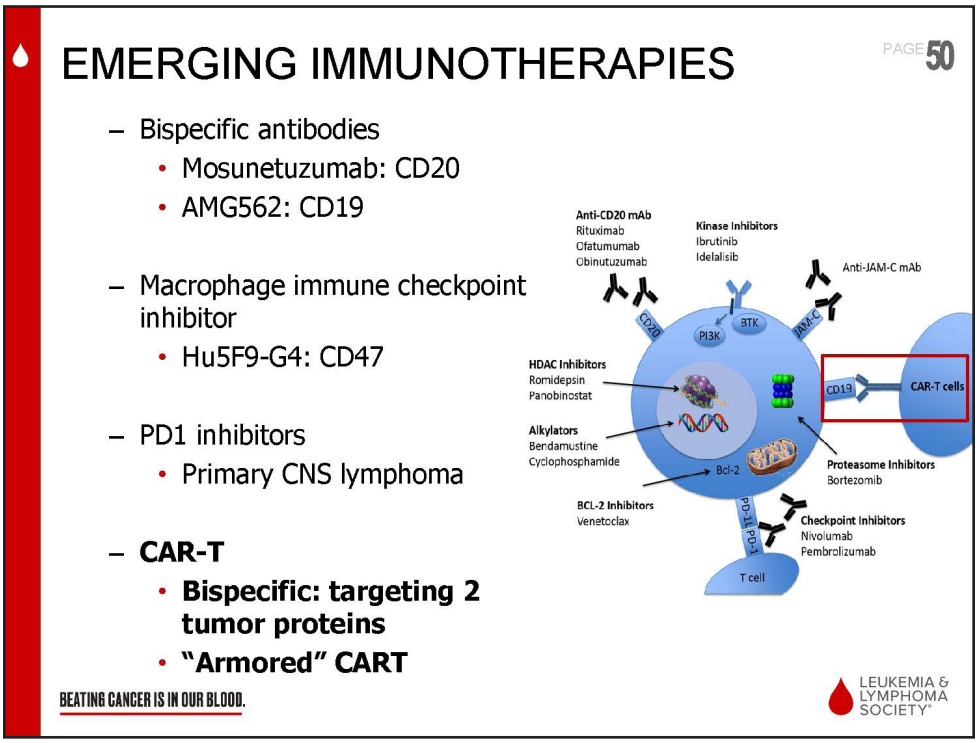
Slide 48: EMERGING IMMUNOTHERAPIES

Moving on to a macrophage immune checkpoint inhibitor. So, I have shown you guys numerous pictures of T-cells and mentioned patients' immune system T-cells many, many times. But, the T-cell is not the only cell within our immune systems. Our immune systems are extremely complex. Another important cell within our immune system is called the macrophage. So, the macrophage, one of its main jobs is to gobble up damaged tissue. So, not only has lymphoma figured out how to hide from our T-cells, it has also figured out how to hide from our macrophage cells. It does that by expressing a protein called CD47. That is essentially a signal, it has been nicknamed the "don't eat me" signal. It expresses this protein, the macrophage sees it, and is told okay, the cell is okay, I am not going to do anything to it. So, a medication called Hu5F9-G4 disrupts that binding. And, it essentially uncovers the lymphoma cell to the macrophage cell, allowing the macrophage to help eradicate lymphoma.



Slide 49: EMERGING IMMUNOTHERAPIES

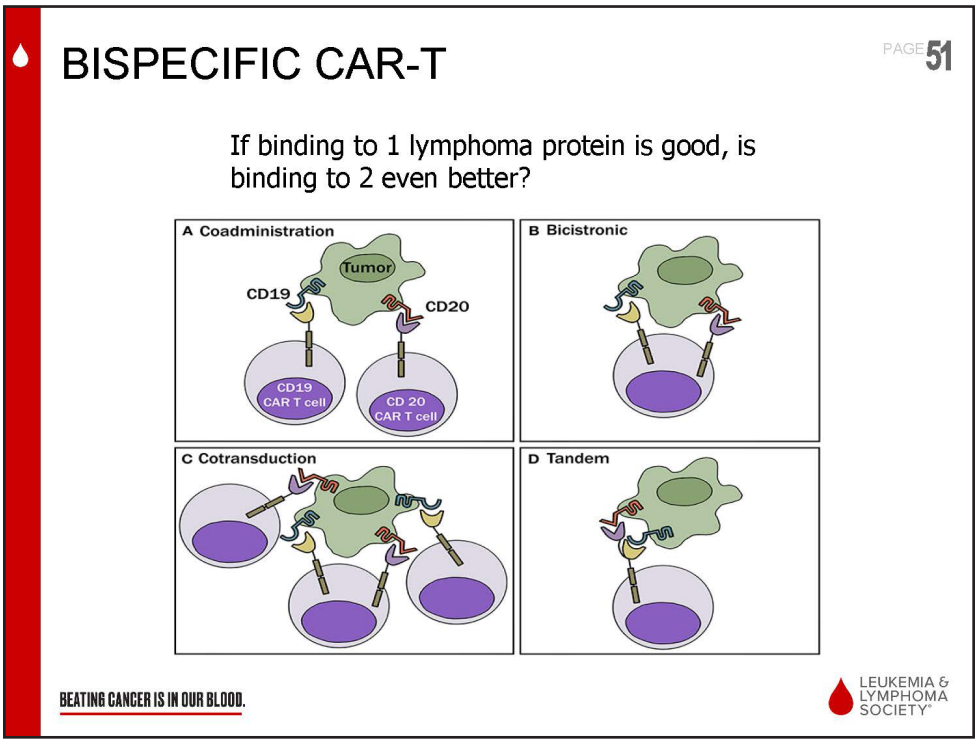
Moving on to PD1 inhibitors. An area of particular interest for PD1 inhibition may be in a variant of aggressive non-Hodgkin's lymphoma called primary CNS lymphoma.



Slide 50: EMERGING IMMUNOTHERAPIES

And, CAR-T. As I said, the current CAR-Ts that are FDA approved, we call those first-generation CAR-T cells. So, if you recall from the previous pictures, those CAR-T cells bind to 1 protein on a lymphoma cell called CD19. So, we are now looking at different technologies to see if we can make these CAR-Ts even stronger. So, we are looking at something called bispecific CAR-T cells. These CAR-T cells target 2 tumor proteins on the lymphoma surface, as opposed to the 1. And, there is also a category of CAR-Ts called "armored" CAR-Ts.

So there are many different ways that we can engineer a CAR-T cell to bind to a lymphoma cell, so the question is, if we are seeing good results with the current CAR-Ts that only bind to 1 lymphoma protein, then perhaps binding to 2 lymphoma proteins might be even better.

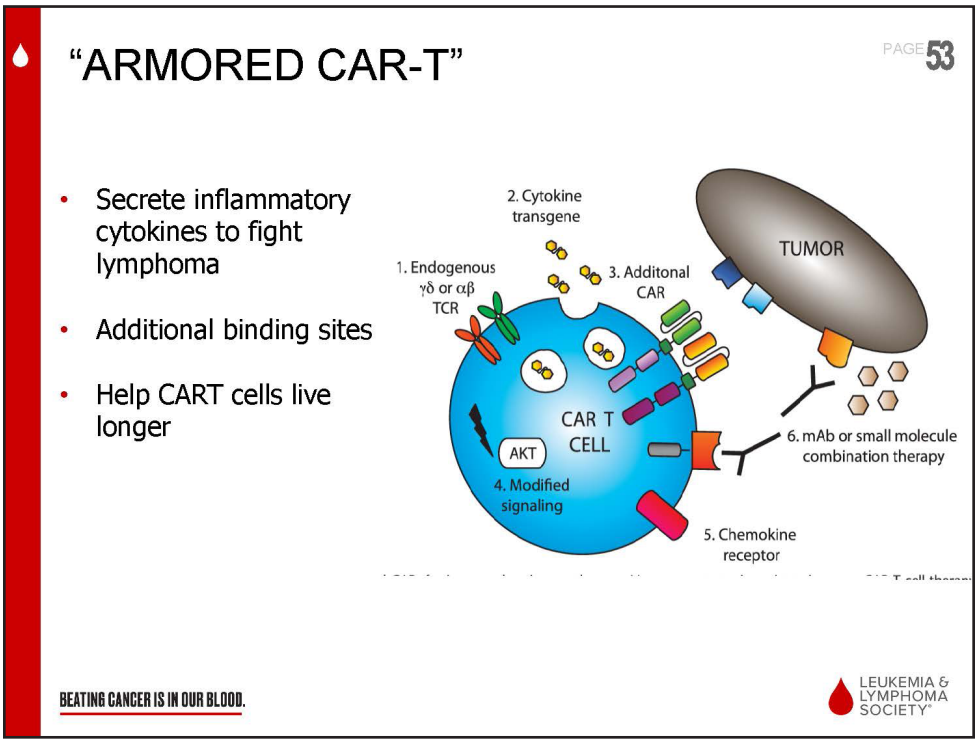


Slide 51: BISPECIFIC CAR-T

So, the picture you see here on the slide are all the various ways you can elicit multiple binding sites for a CAR-T cell, but I want to call attention to the image in the upper right hand corner. This is one of the more common ways, and we actually have a trial open investigating this strategy. So, the green cell is the tumor cell. The purple cell is the CAR-T cell. And, you can see there are 2 binding points for this strategy.

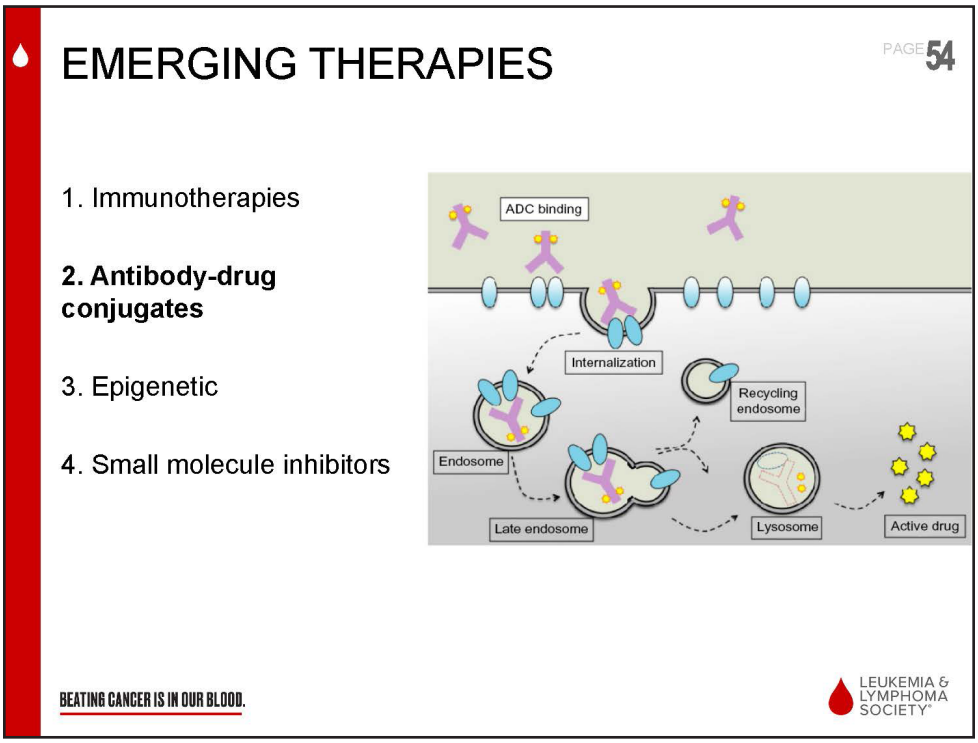
Slide 52: "ARMORED CAR-T"

Moving on to "armored" CAR-T cells. It got its nickname using armored vehicles, like what the military does to try and make vehicles stronger and effective weapons. We are trying to see if there are things that we can do to make a CAR-T more effective.



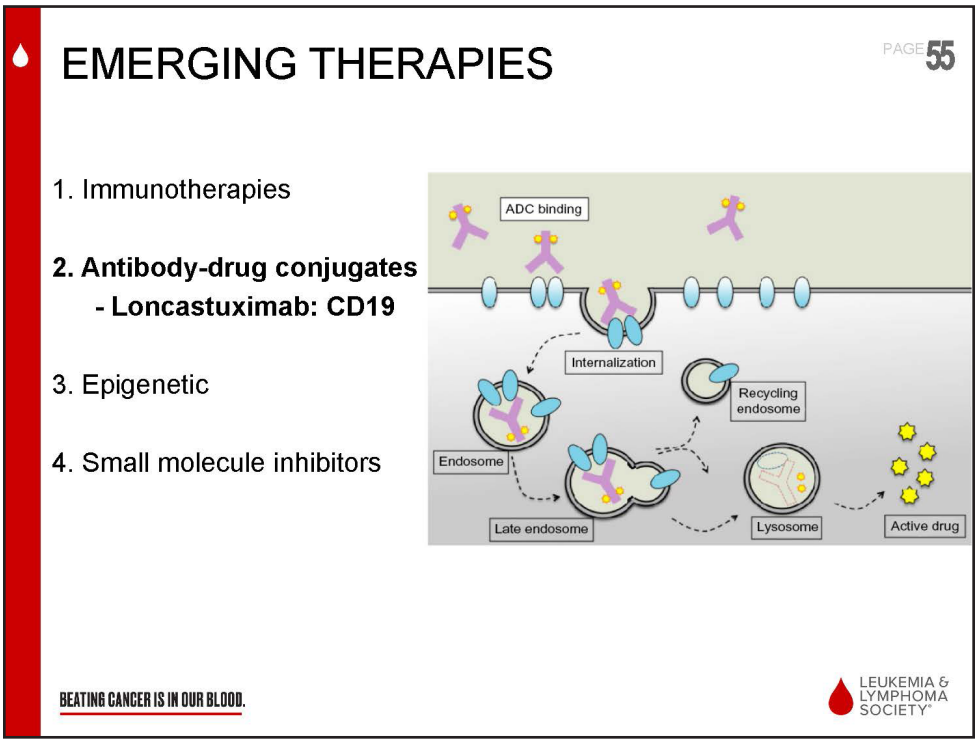
Slide 53: "ARMORED CAR-T"

So, some of the strategies to try and strengthen CAR-T cells include mechanisms that help them secrete even more inflammatory cytokines to fight lymphoma, to provide additional binding sites as we have previously discussed with the bispecific CAR-Ts, and then also strategies to help the CAR-T cells live longer and circulate in a patient's bloodstream longer. Keeping those active CAR-T cells around can help continue to eradicate a lymphoma cell, should one reemerge.



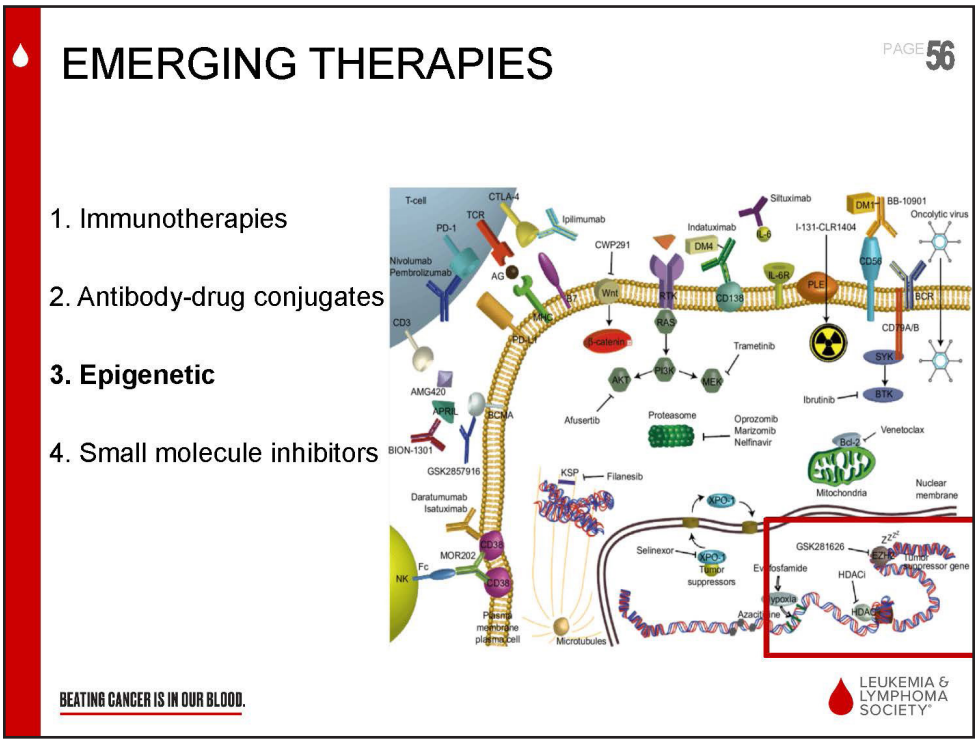
Slide 54: EMERGING THERAPIES

The next category are antibody drug conjugates, which we will not spend a lot of time on because we have already talked about the mechanism of this when we discussed polatuzumab.



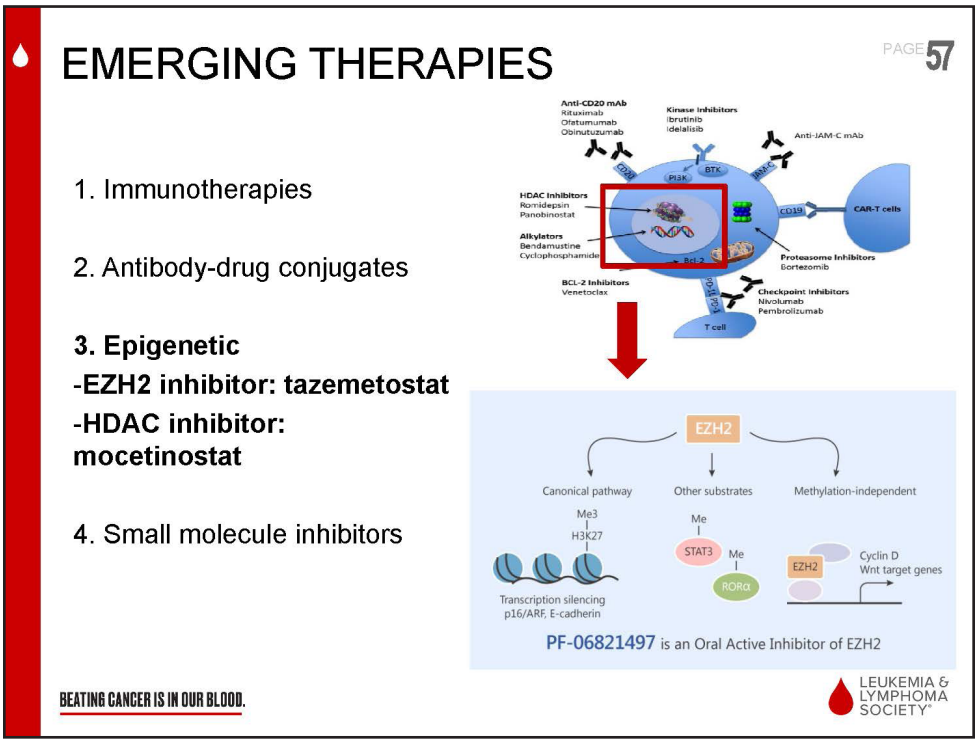
Slide 55: EMERGING THERAPIES

But, I just wanted you guys to be aware that polatuzumab is not the only antibody drug conjugate out there. There are several that we are looking at. And, the antibody drug conjugates can differ based on their binding sites, such as what I have listed here. loncastuximab binds CD19. They may differ in the subtype of chemotherapy molecule that are attached to them. Or, they may differ in the way that the chemotherapy is bound to the binding portion of the antibody drug conjugate. So, there is a lot of areas of active study for this category of treatment.



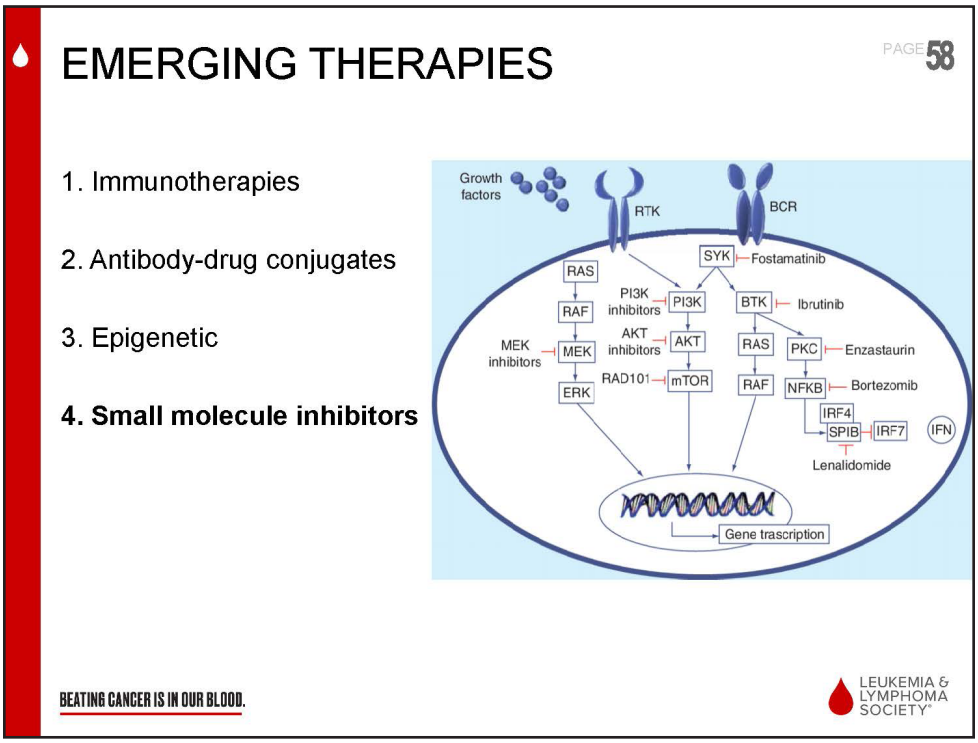
Slide 56: EMERGING THERAPIES

Moving on to the category of epigenetic modifiers. I find that this category of treatment is a little bit harder to explain to patients, so bear with me. If you take a look at the red box down in the bottom right hand corner, this is where the majority of epigenetic therapies work. Inside the nucleus at the level of DNA. So, DNA is folded in a particular confirmation and that dictates what proteins are produced. So, lymphoma cells have figured out how to hijack that system and alter the folding of the DNA within their nucleus, so that they can produce proteins that help them survive longer, reproduce faster, and grow. Epigenetic therapies act to try and correct that misfolding.



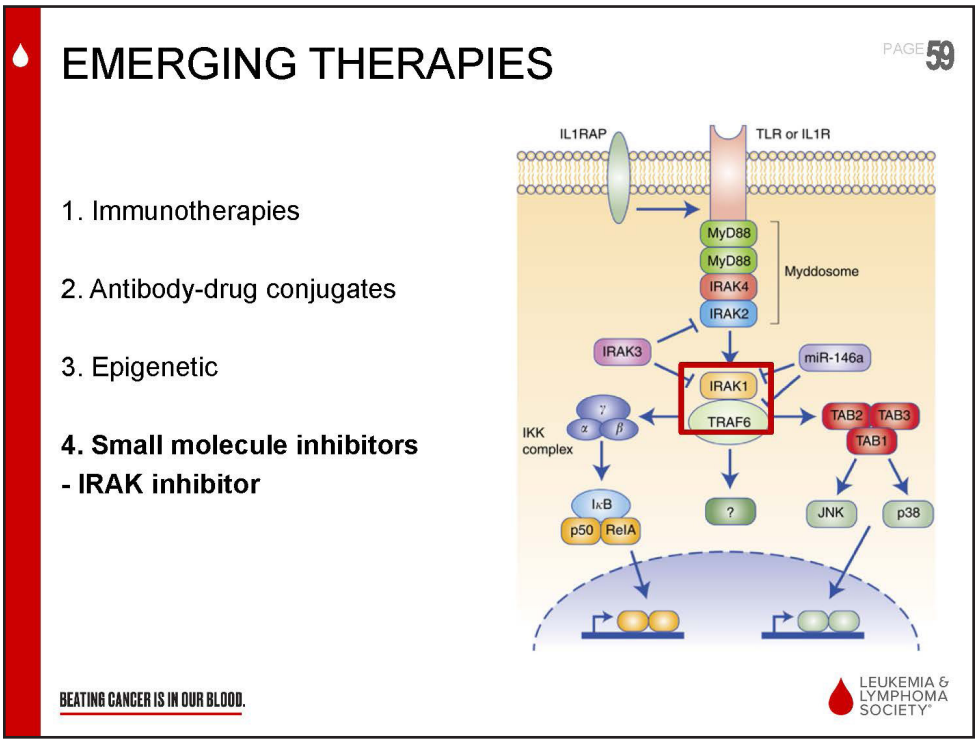
Slide 57: EMERGING THERAPIES

There are many epigenetic therapies undergoing clinical trial investigation, but I have 2 representatives listed here, an EZH2 inhibitor called tazemetostat, and an HDAC inhibitor called mocetinostat.



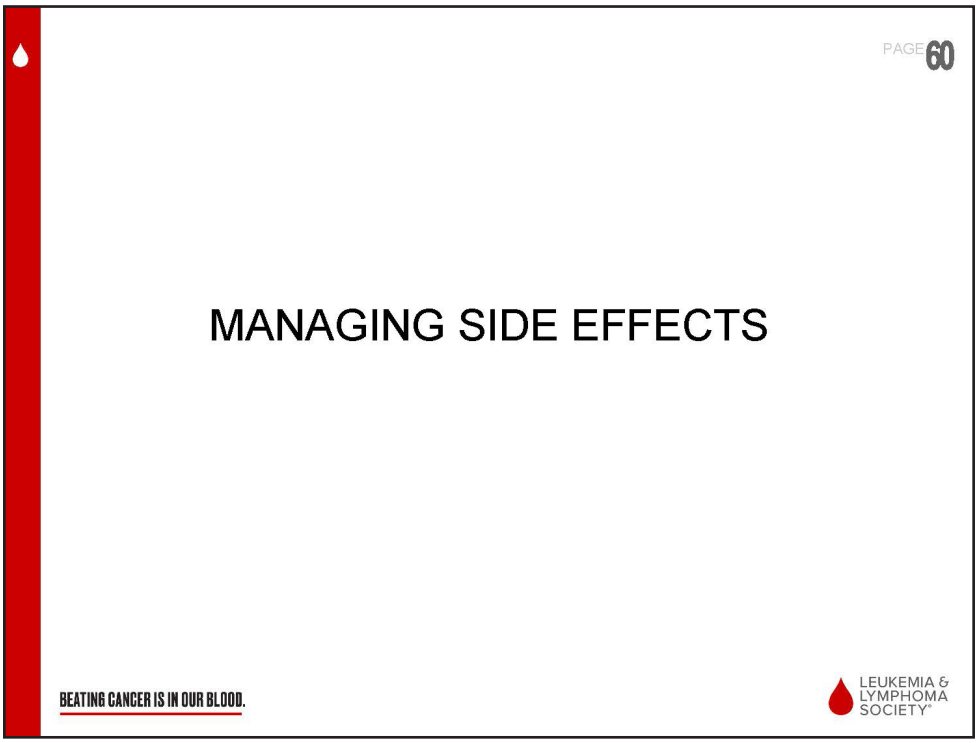
Slide 58: EMERGING THERAPIES

The fourth category are called small molecule inhibitors. Now, this is a very broad categorization and not only applied to lymphoma. Small molecule inhibitors, in general, interfere with signaling pathways inside a lymphoma cell. So, the picture to the right is a lymphoma cell. And, I chose this one to impress upon you guys how many different pro-growth pathways there are within a lymphoma cell. And so, there are many pathways where we can hopefully use small molecule inhibitors that bind certain proteins in these growth pathways, therefore disrupting signaling and preventing cell growth.



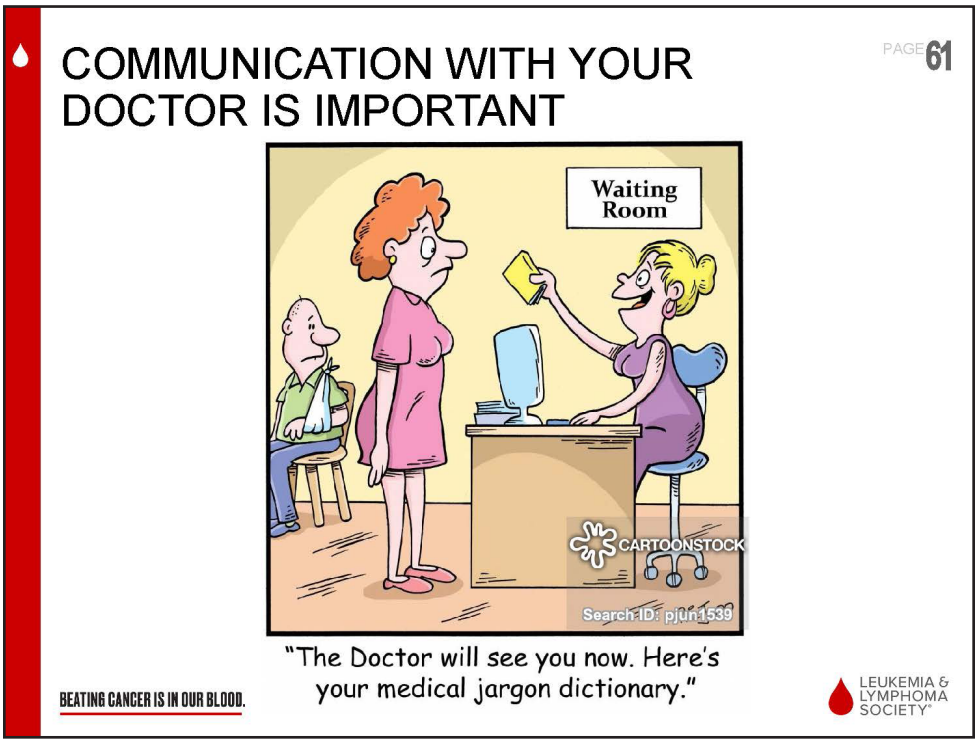
Slide 59: EMERGING THERAPIES

One that is undergoing active investigation is something called an IRAK inhibitor. And, you can see the pathway pictured to the right that IRAK is involved in. So, the yellow portion of this is a lymphoma cell, the cell surface is up at the top, and you can see there is a receptor that when bound, initiates activation of all those proteins that are downstream of it, MyD88, IRAK4, 2, etcetera. So, if you can disrupt that pathway, if you can disrupt those growth signals from reaching the nucleus, then that will help eradicate lymphoma.



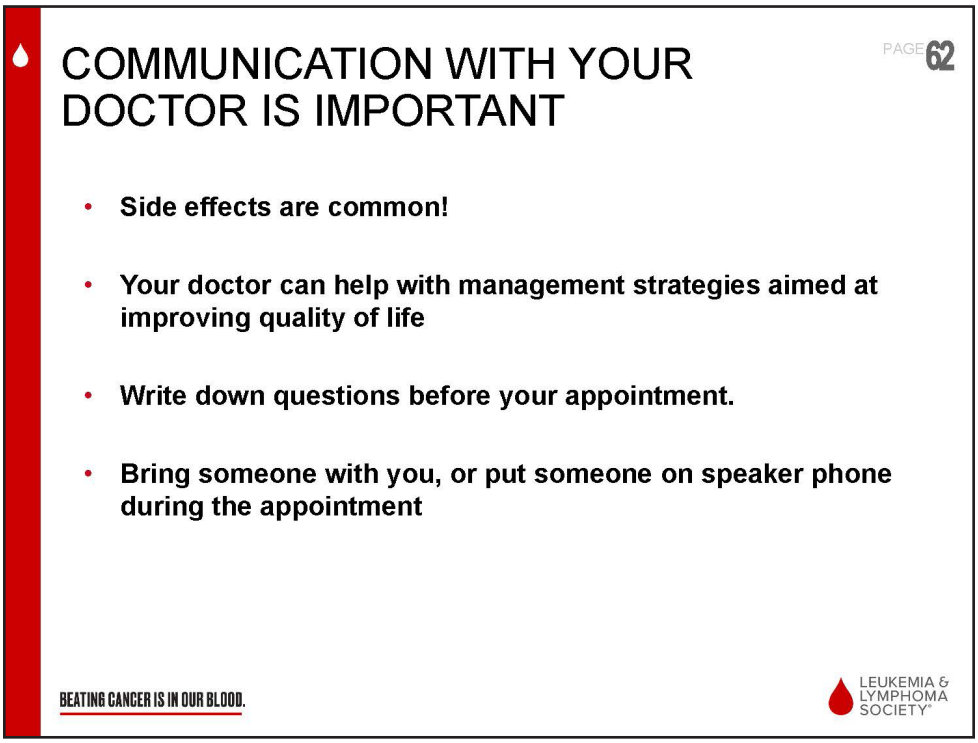
Slide 60: MANAGING SIDE EFFECTS

So, now switching over to managing side effects. This is an important part of treating lymphoma. I know we spend a lot of time on planning our treatment plan and discussing these things with you guys, but it is also important for doctors and the other participants in the care team to help manage side effects.



Slide 61: COMMUNICATION WITH YOUR DOCTOR IS IMPORTANT

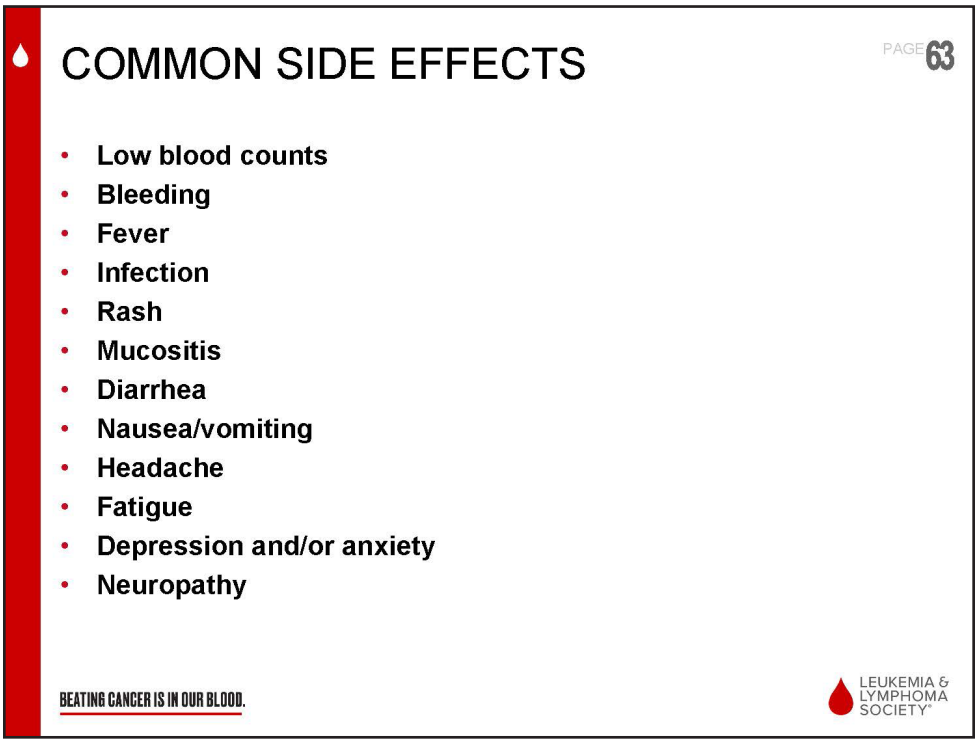
So, you can see the cartoon here. The woman at the front desk at the doctor's office is telling the patient that is checking in, "The doctor will see you now, here's your medical jargon dictionary." It is meant to be a joke, but I think in a lot of instances is actually fairly accurate. I think you can tell from the talk that we are having now, as well as conversations you have had with your doctor, that it is easy to get lost in the medical jargon. So, if there is something that you do not understand, it is important for you to let your doctor know, you are not clear, you do not understand what they are saying, and see if there is a better way to reword it.



Slide 62: COMMUNICATION WITH YOUR DOCTOR IS IMPORTANT

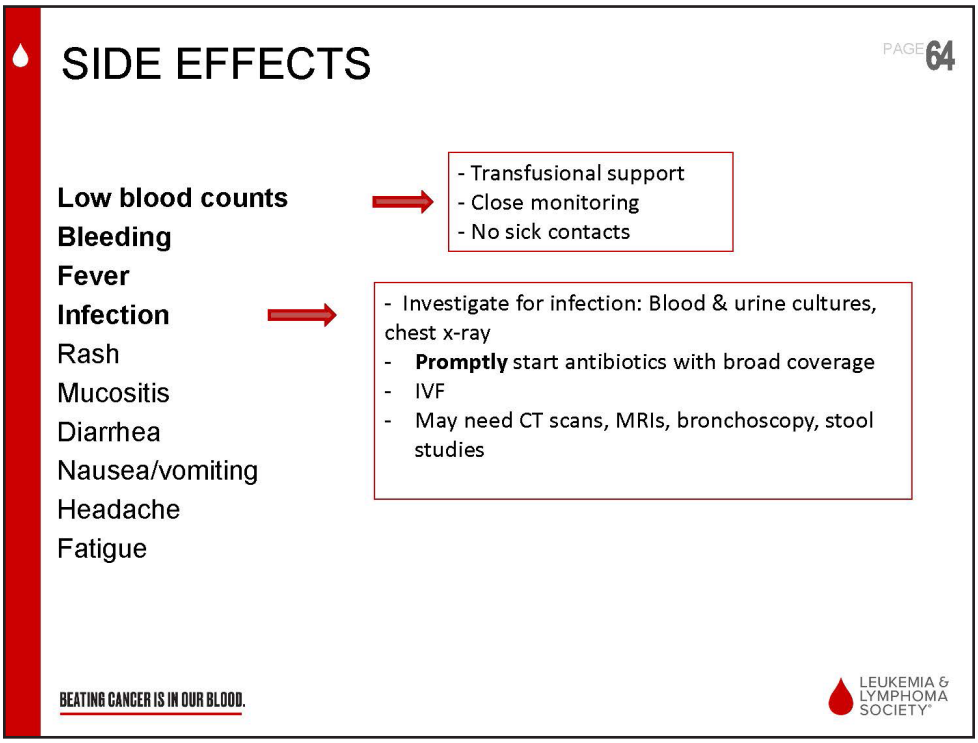
So, communication with your doctor is important. Side effects are very common, but if you do not communicate your side effects to your doctor, then they are not going to know how to best help you. I have had patients tell me they did not let me know that they felt bad because they did not think there was anything I could do to help them. Or, because they thought this is just how chemotherapy is supposed to feel. Most of the time those things are not true. There are many management strategies that a doctor or a nurse practitioner can prescribe or arrange for you that can help mitigate your symptoms and improve your quality of life while you are on treatment.

So, the bottom 2 bullet points are some tips to try and help you communicate most effectively with your doctor. Write your questions down before your appointment. I cannot tell you how many times I have had a patient come in and say, oh, I had so many questions for you, but now I cannot think of any of them. Another one is, bring someone with you, or if somebody cannot be with you, put them on the speaker phone during the appointment. A lot of times when you are at your oncologist's office, first of all, it is an intimidating place to be, just, you know, baseline. But in addition to that, you are getting a lot of information during those appointments. I think it is very difficult to digest all of the information and also have enough mental presence left to get your side effects dealt with or your questions asked. And, it can be very helpful to have someone with you.



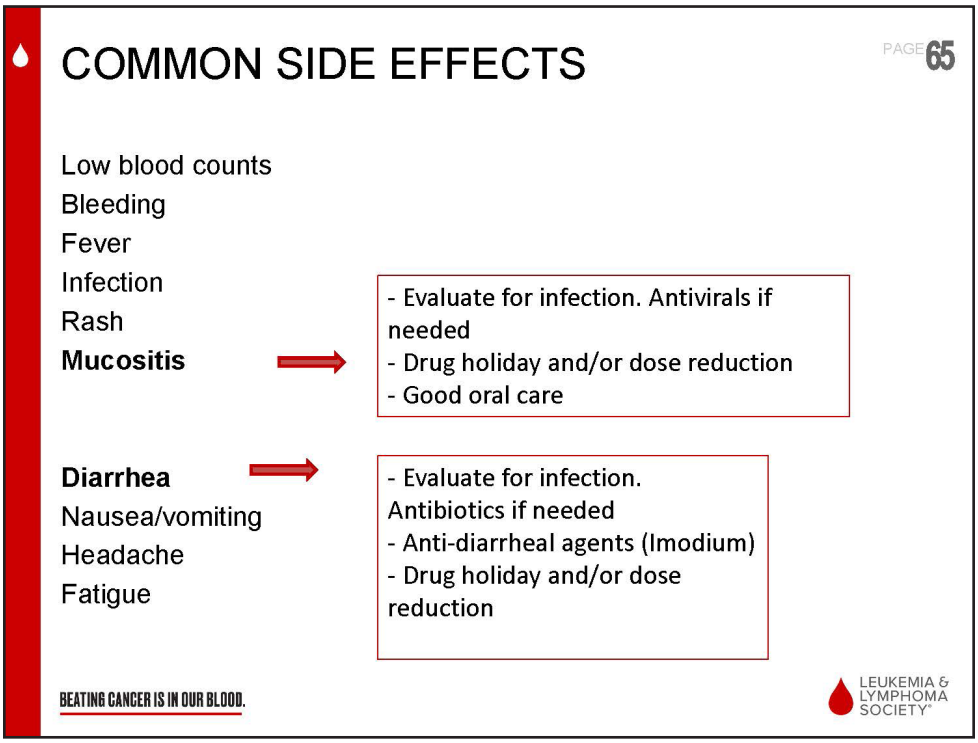
Slide 63: COMMON SIDE EFFECTS

So, common side effects are listed below. This is by no means a comprehensive list. These are just some of the more common ones, and can include low blood counts, bleeding, fever, infection, rash, mucositis, which is inflammation of the mouth, diarrhea, nausea, vomiting, headache, fatigue, depression and/or anxiety, which I think is an under-recognized concurrent diagnosis in our patient population, and neuropathy, which is numbness and tingling in the fingers and toes.



Slide 64: SIDE EFFECTS

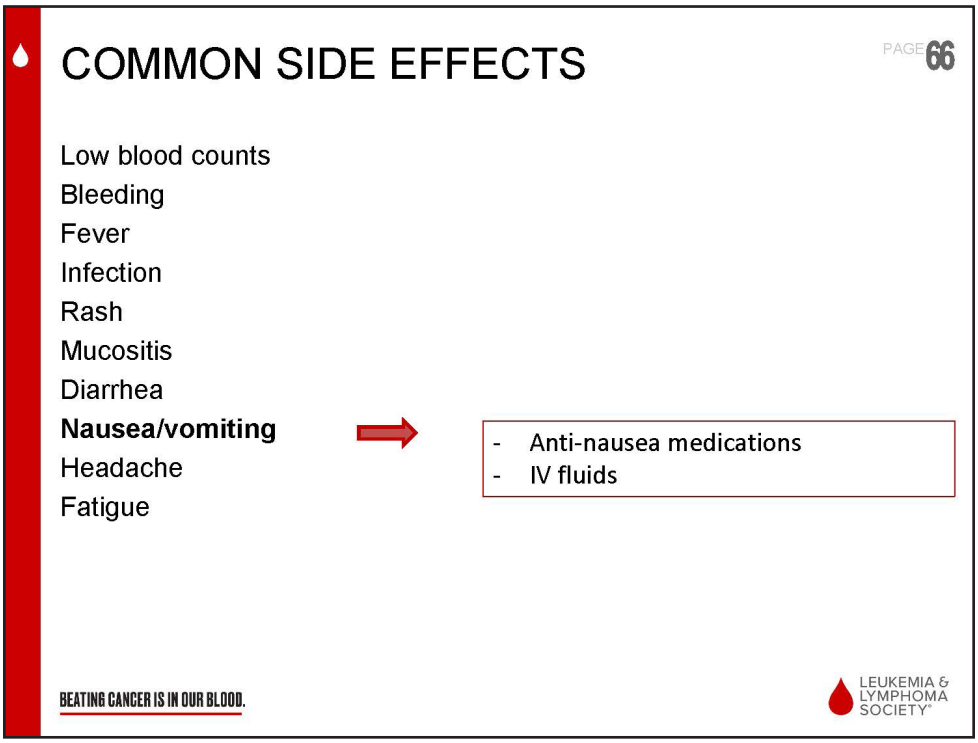
So, how can we manage these side effects? Well, if a patient has low blood counts and potentially bleeding complications, they may need red blood cell or platelet transfusions. They certainly need close monitoring. If they have fever and infection, your doctor may want to do some tests to see if they can figure out what is causing a fever, blood and urine cultures, a chest X-ray, and in this viral season, a viral panel. Treatment is going to vary depending on how severe the infection seems. Most patients will need antibiotics. You may need IV fluids if you are so sick that you are dehydrated. And again, depending on the severity, additional studies may be warranted, including CT scans, MRIs, bronchoscopies, or stool studies.



Slide 65: COMMON SIDE EFFECTS

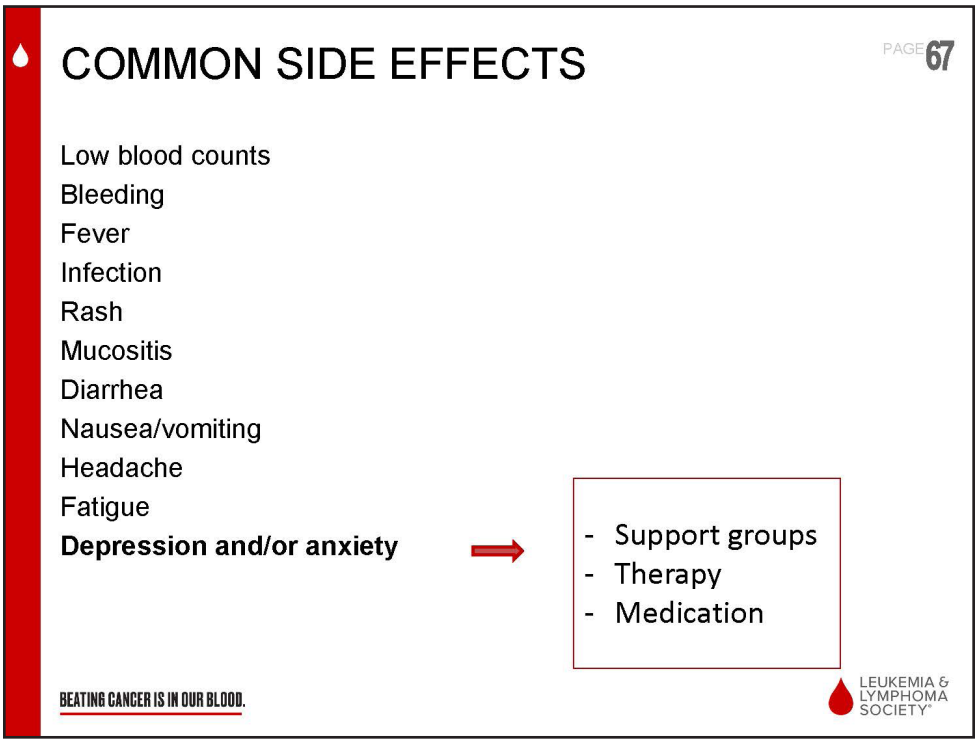
If a patient develops mucositis or inflammation in the mouth, there are symptomatic medications for pain relief that can be given, some kind of swish-and-spit type preparations, or even swallowing small amounts of these preparations. Good oral care will help. You also want to evaluate to see if the inflammation is being caused by an infection, and if so, appropriate medication should be given. In the rare instance a patient may need a drug holiday, and by that, I mean delaying the subsequent cycle of chemotherapy by a few days.

If a patient develops diarrhea you want to see if this is diarrhea due to infection and if so, give antibiotics. And, if it's not an infection and is just related to chemotherapy, then give them something to slow down the diarrhea, and they also may need IV fluids, depending on how severe the diarrhea is.



Slide 66: COMMON SIDE EFFECTS

Nausea and vomiting, fortunately, is less common these days than it was many years ago because we have really made a lot of progress in our pre-medications for nausea that we give prior to even giving chemotherapy. However, I always provide my patients with a nausea medicine to have at home with them in case they develop nausea anyway. In some patients the initial nausea medicines I recommend do not work and they may need something else. If nausea is severe, they may need IV fluids.

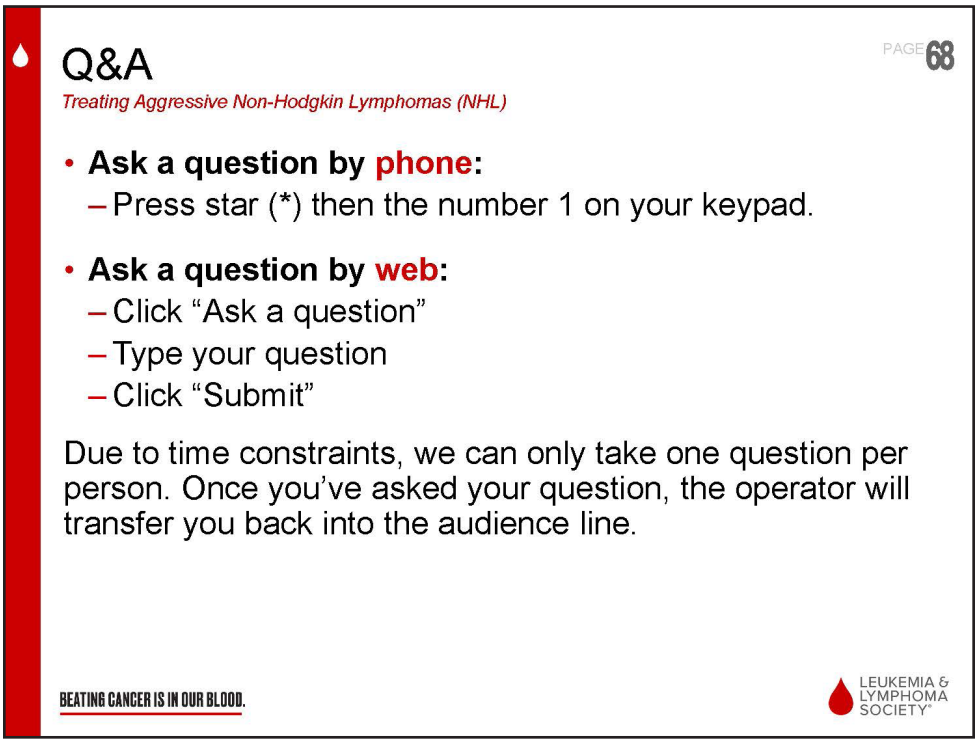


Slide 67: COMMON SIDE EFFECTS

Depression and/or anxiety. Do not hesitate to discuss these types of symptoms with your oncologist. I know our appointments are short and we have a long list of things that we need to accomplish during the visit, but addressing these issues is also important. And, we have access to a lot of resources to offer patients to help us address these types of things. I may not be the best person to address your depression or anxiety, but we can certainly get a therapist or a psychiatrist to help us.

Also, a lot of my patients enjoy support groups. It helps some people just to talk to someone else that is going through something similar.

So, with that I conclude my talk.



Slide 68: Q&A SESSION

Ms. Figueroa-Rivera:

Thank you, Dr. Mead. It is time for our question and answer portion of our program.

We will take the first question from our web audience. Doctor, Bob is asking what advances are being made in reducing toxicity of treatment options for aggressive non-Hodgkin lymphoma?

Dr. Mead:

A great effort that we are making is the example that I gave with the antibody drug conjugates, so that is almost like a targeted way to deliver chemotherapy. So, the chemotherapy is being released internally inside the lymphoma cell with minimal exposure of healthy tissues to chemotherapy. So, for polatuzumab, we are not seeing the same toxicity that we would be seeing in patients that are getting chemotherapy administered systemically, which has access, easy access, to both lymphoma cells and healthy tissues. So, that is one example.

Ms. Figueroa-Rivera:

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

Operator:

Certainly. Thank you, Lizette. We will hear from Sarah in South Carolina.

Sarah:

Yes, I would like to ask the doctor how do I go about massaging to relieve ascites due to the lymphoma?

Dr. Mead:

So, I think the question was, how do you go about doing massaging to alleviate ascites. I will say 2 things about that. So, the first is if you have ascites, massage may be a nice supportive approach, but if the ascites is severe you may actually need some fluid removed from the belly to provide you with maximum symptom relief. If the ascites is minimal, then perhaps massage alone will be sufficient. It is not something that patients necessarily do themselves. We have a group at UCLA called East-West Medicine that provides a lot of supportive approaches, such as therapeutic massage and other things like acupuncture. So, you may want to ask your doctor if they have access to supportive services like that.

Ms. Figueroa-Rivera:

Thank you for the question. And, our next question from our web audience Doctor, Barbara's asking about double-hit lymphoma and saying that every study seems to start with poor prognosis but provides little information on the profile. Any first-line treatment options and should the patient relapse, what is the current favorite second-line treatment?

Dr. Mead:

That is a great question and there is a lot of active research going on for this subset of aggressive non-Hodgkin's lymphoma, specifically for the reason that their prognosis, as it stands today, is relatively poor. Although, I would argue it is improving. So, in the talk I discussed front-line regimen for double-hit lymphoma and R-CHOP should really be avoided in this patient population. They need something a bit more aggressive. The most common, more aggressive regimen I use is dose-adjusted EPOCH-R. There may be some institutions that use something called hyper-CVAD, but I think EPOCH-R is kind of the more favored regimen. So yes, they do warrant a bit more of an aggressive front-line approach.

So, the question is to what do we do if they relapse, is evolving. Right now, we have a clinical trial open where we have a patient with double-hit lymphoma, we give them 2 cycles of EPOCH-R and we repeat their scans. If they have not achieved at least a partial response from the first 2 cycles of chemotherapy, then they may be a candidate to proceed directly to CAR-T therapy. We are looking at potentially changing their treatment approach earlier in the course of their front-line management.

As a word of encouragement, numbers are small and the follow-up is not terribly long just yet, but we are seeing some really nice responses in our double-hit population with CAR-T therapy that is used later on in their treatment, meaning if they relapse after EPOCH-R. So, we are making strides even within our double-hit population.

Ms. Figueroa-Rivera:

Thank you, Doctor. And, we will take the next question from our telephone audience, please.

Operator:

We will hear from Rachel in New York. Please go ahead.

Rachel:

My father has CLL and on Venclexta®. But someone who is dealing with so much in today's world, and he's losing so much weight with diarrhea. What do we do with somebody who can't go to the doctor's office? Right now, we are more focused on the diarrhea than we are on the cancer.

Dr. Mead:

Asking your doctor if home health would be an option, if there is a home health nurse that could come out and provide your dad at least with IV fluids, because it is important to keep up with the fluid loss if someone is having severe diarrhea. So, you could consider IV fluids. If an infection has not already been investigated, the doctor should check for an infection. An anti-diarrheal agent, such as Imodium®, may also be able to be considered. But it is important if you do experience diarrhea as a side effect of any treatment, that you be evaluated by your doctor to ensure that an infection is not being missed.

Ms. Figueroa-Rivera:

Thank you. And, we will take the next question from our web audience. Nancy is asking, if you have one type of blood cancer, are you more likely to get another blood cancer?

Dr. Mead:

That is a great question and not easily answered. A common misconception is that the majority of cancers are inherited, and it looks like that is not the case. It looks like a minority of cancers end up causing your family members to potentially have an increased risk of also developing a type of blood cancer. There are some exceptions. It does look like a subset of patients with CLL have a bit of an increased inheritable risk for other blood cancers. A small subset of patients with Hodgkin's lymphoma also has some type of familial risk. I think as we learn more about the way lymphoma develops and the different changes in the DNA that are clustered within certain lymphomas, this answer may change. But, as it stands right now, the majority of blood cancers are considered sporadic and family members are not at a particularly increased risk of also developing a blood cancer.

Ms. Figueroa-Rivera:

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

Operator:

Certainly. Next, we will hear from Carol. Please go ahead.

Carol:

Yes, I would like to know what clinical trials or what is being conducted when a person has primary immunodeficiency and cancer.

Dr. Mead:

There are none open where I practice, which is at UCLA, to the best of my knowledge. We have many, many clinical trials open, but none of which I can think that require a primary immunodeficiency and lymphoma to be enrolled.

Ms. Figueroa-Rivera:

And, I am going to let you know about our Clinical Trial Support Center after the Q&A session, and there are some clinical trial nurse navigators there that can actually assist you in finding out if a clinical trial is appropriate for you.

The next question, Richard asks, what constitutes aggressive versus non-aggressive?

Dr. Mead:

So, it is based on the clinical behavior and aggressive lymphomas are going to behave more aggressively in a patient, meaning they are going to grow faster, they are going to cause symptoms. These symptoms are normally manifested by fevers, weight loss, bad sweats at night, and profound fatigue. In general, if aggressive lymphomas are not treated quite quickly, a patient could potentially die of their lymphoma in a relatively short period of time. And, these cancers or the subset of cancers is considered potentially curable with treatment. Whereas, our non-aggressive lymphomas are kind of the opposite of that. They tend to grow slowly, not make patients feel so sick, they generally do not present with those symptoms that I mentioned, the fevers, night sweats, chills, and weight loss, and in some patients with the non-aggressive lymphomas, they may not even require immediate treatment up-front and monitoring may be appropriate in them. Whereas monitoring for an aggressive lymphoma is almost never appropriate.

Ms. Figueroa-Rivera:

Thank you. And, I know that we do have some folks on the line that have follicular lymphoma, which is usually an indolent or a slow-growing type of lymphoma but they are asking if follicular is ever aggressive or if it can change into an aggressive form of lymphoma.

Dr. Mead:

Unfortunately, the answer to both of those parts of the question is yes. So, even though follicular lymphoma is traditionally considered an indolent or a non-aggressive lymphoma, there are certainly a subset of follicular lymphoma patients that their lymphoma can behave badly.

We have looked at a lot of clinical outcome studies to try and figure out how to identify the subset of follicular lymphoma patients that may have a more aggressive clinical course. So, there are risk scores that we apply to patients, but they are imperfect.

And yes, follicular lymphoma can progress to something more aggressive. So, I had mentioned a subset of the aggressive non-Hodgkin's was histologic transformation of follicular lymphoma. That is when follicular lymphoma transforms into a more aggressive variant of lymphoma, generally diffuse large B-cell lymphoma. So, even though the textbooks would say that follicular lymphoma is quote-unquote indolent, certainly some patients do not have that experience.

Ms. Figueroa-Rivera:

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

Operator:

Certainly. Next, we will hear from Carol. Please go ahead, your line is open.

Carol:

Yes, what is being done in studies for CAR-T cells for mantle cell lymphoma?

Dr. Mead:

So, that is a great question. We participated in the ZUMA study, there is a CAR-T called Yescarta® that is FDA approved for the treatment of diffuse large B-cell lymphoma. Well, we have also taken that same CAR-T construct to see if it works in mantle cell lymphoma as well, and UCLA participated in that. That study is now closed to enrollment. They are working on analyzing the data. Based on the outcomes of that trial, the FDA will review the information to see if maybe we can expand the use of CAR-T cells into mantle cell lymphoma. That is not yet the case. The field is changing. As I said, they are analyzing the data. But, CAR-T may be expanded to include patients with mantle cell lymphoma, so it is an active area of investigation.

Ms. Figueroa-Rivera:

Thank you. And, our next question comes from Louisa, she is asking and she is stating that she has been in remission since March 1, 2011, congratulations, and she says, I was having PET scans for 5 years to see if there was a recurrence, however, my primary suggested I shouldn't do that because of the radiation exposure. Are there any blood tests or any other methods to make sure that my diffuse large B-cell non-Hodgkin lymphoma is still in remission? Thank you so much.

Dr. Mead:

So, you guys are asking really great questions. I agree with your primary about stopping the routine surveillance PET CTs at this point. Generally, continuing the radiation exposure that you get with PET CTs this far down the road is not really helpful. As to the question if there are alternative methods to watch a patient and monitor them for recurrence of lymphoma, that is also an area of active investigation. So, we are looking at something called cell-free tumor DNA. So, if you recall throughout the talk I pointed to the DNA, you know, calling it the brain of the lymphoma cell. That DNA can be shed into a patient's bloodstream and so when you do a blood draw, just like a routine lab, you would be able to collect cell-free DNA. So, we are looking to try and determine if this is something we are going to be able to apply to the clinic, because just because you can identify some circulating cell-free tumor DNA, as of yet a doctor does not know what to do with that information, meaning we do not know what threshold of cell-free tumor DNA indicates true

disease. If a patient has a very tiny amount circulating, does that necessarily mean that a relapse is impeding? There are many, many questions that are unanswered that the research community is currently looking into.

So, for a simple answer to your answer, right now, no, there is no standard approach to continue to monitor for relapse, aside from the scans, clinical exams, and basic blood work, but my answer may change to that question at some point in the future.

And, just to reassure you, risk of relapse 9 years after your achievement of remission is rare, so congratulations.

Ms. Figueroa-Rivera:

Thank you, Doctor. And, we will take the next question from the telephone audience, please.

Operator:

Certainly. We will hear next from Jeanette in Pennsylvania.

Jeanette:

Yes, hello. Dr. Mead, you just answered a very good question and I'd like to deal with that. You said that a 9 year, remission of the patient's condition, which was the large cell, large B-cell lymphoma is rare. Do you mean that in most cases the period is shorter?

Dr. Mead:

If I am interpreting the question correct, it was, is the period for risk of relapse shorter than 9 years. Yes, it is. Generally, what is considered the highest risk period for relapse is the first 5 years after diagnosis. I say that with caution because I have seen people relapse beyond the 5-year mark, but it's relatively rare. The highest risk period are those first 5 years.

Ms. Figueroa-Rivera:

Thank you. And, we will take the next question from the web. Gwendolyn is asking, is maintenance treatment needed once you've achieved remission?

Dr. Mead:

For the aggressive non-Hodgkin's lymphoma, no. Maintenance plays a role in some other types of lymphoma that we did not discuss today, but by and large we have not found maintenance therapy for the aggressive variants to provide patients with any benefit beyond what they receive with the standard first- or second-line therapy.

Ms. Figueroa-Rivera:

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

Operator:

Certainly. We will hear next from Marvin in New Mexico.

Marvin:

Doctor, I was diagnosed with mantle cell lymphoma about 3 years ago and went through the hyper-CVAD, R-CHOP and then 2 years of rituximab, and achieved total remission. But, I still have a lot of problems with fatigue and weakness and kind of some joint stiffness and muscle stiffness.

Ms. Figueroa-Rivera:

Just fatigue and the bone pain after treatment?

Marvin:

Yes.

Dr. Mead:

Yeah, so, side effects that kind of linger for a long period of time when a patient has required aggressive therapy like that can be very frustrating to deal with. If I have a patient that is having fatigue and joint pains and things like that, I do not immediately assume that it is due to prior toxicity from treatment. I do work a patient up for other causes. For the joint pain, does a patient have arthritis, those types of things. For fatigue, do they have problems with their thyroid. So, I assess for other underlying causes that might explain those symptoms that we could then target. If the work-up is otherwise negative and it looks like we are dealing with some type of treatment effect, the fatigue can be targeted, oftentimes not as effectively as I would like. I encourage patients to participate in physical therapy if appropriate, in group therapy if appropriate, make sure they have adequate good nutrition and remain hydrated, and just really help them from a supportive standpoint like that.

Ms. Figueroa-Rivera:

Thank you. And I know that a lot of other participants are also asking about neuropathy and, I know that you did mention neuropathy throughout your presentation, but is there something specific that people can do for neuropathy besides medications?

Dr. Mead:

Not really. There is not a supportive care mechanism outside of medications to really help with neuropathy. I monitor the development of neuropathy closely in my patients over the time course of treatment. In some instances, if neuropathy is severe, then one of the chemotherapy medications may require dose reduction, so I really put an effort to try and prevent the development of neuropathy in the first place. Sometimes, it is unavoidable. If the neuropathy does develop, some patients have said they have benefit in taking over-the-counter Vitamin B6. There is not a lot of great data to support that, but Vitamin B6 supplements are not terribly harmful, so it is worth a try. Patients could try a magnesium supplement. Sometimes that helps. And, the medication that I use, there are 2. There is something called gabapentin that can help, but unfortunately gabapentin can make people feel drowsy. And so, if that is the case, there is another category of medications called tricyclic antidepressants that might help with that as well. But, neuropathy can be very frustrating to try to help with. It is hard to get patients great relief from that, for that side effect.

Ms. Figueroa-Rivera:

The next question comes from the web. And, Barry is asking, I have completed my treatment and have questions about side effects. What kind of timing, do some of these side effects relieve themselves, the fatigue, the neuropathy.

Dr. Mead:

Yeah, the fatigue and the neuropathy can be 2 of the most long-lasting. The rest of the ones that I listed tend to resolve over a few weeks to months after the final cycle of chemotherapy. The fatigue and neuropathy, in the majority of patients, resolves along a similar time-line, but it is not uncommon for some patients to say they are experiencing fatigue and neuropathy up to 12 months after the completion of treatment. Particularly, the neuropathy. That can persist up to 18 months after you have received your chemotherapy.

Ms. Figueroa-Rivera:

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

Operator:

Certainly. We will move next to the Commonwealth of Virginia. Joe, Dr. Mead is ready for your question, Sir.

Joe:

Yes, hi. So, my question is relative to CAR-T treatment. What is the prevalence of cytokine release syndrome in CAR-T patients? And, have there been any casualties as a result?

Dr. Mead:

So, the side effects of CAR-T are graded on various grading scales. And so, the incidence of low-grade toxicity from CAR-T is quite high. Around 50 to 60% of patients can experience low-grade cytokine release syndrome (CRS). Fortunately, only a minority of them go on to develop the more severe cytokine release syndrome. Folks that do experience the more severe variant, they may experience very low blood pressure and significant difficulty breathing, that requires transfer to the ICU, so that they may need to be on a ventilator for a period of time, or they may require medications to help support their blood pressure as the cytokine release syndrome is calming down.

We also have interventions that we can do for these side effects, a medication called tocilizumab. And, some patients may require steroids.

There have been casualties documented from cytokine release syndrome. These are very, very low numbers and they are seen a little bit more frequently in our population receiving CAR-T for acute lymphoblastic leukemia as opposed to our lymphoma patients. So, with aggressive supportive care and vigilance from the healthcare team, deaths associated from CAR-T toxicity are very low.

Ms. Figueroa-Rivera:

Thank you. And, Alexis is asking, is EPOCH-R used for those with diffuse large B-cell lymphoma or is that R-CHOP?

Dr. Mead:

So, R-CHOP is more commonly used. Until a few years ago, you may have seen EPOCH-R used at various institutions and community centers. There was early phase data to support the use of this regimen in lots of different diffuse large B-cell lymphomas. So, a randomized trial was conducted, enrolling patients with diffuse large B-cell lymphoma, where a portion of them received R-CHOP and a portion of them received EPOCH, to kind of definitively answer this question of is EPOCH better than R-CHOP.

The results of the study showed that EPOCH in most patients was not better. So, R-CHOP is considered the front-line standard of care for the majority of patients with diffuse large B-cell lymphoma. Now I say the majority rather than all, because some lymphoma physicians still do use EPOCH-R for a small subset of diffuse large B-cell lymphomas that may have certain characteristics seen in their biopsy. But a type of lymphoma patient where it is certainly indicated, as I mentioned during the talk, are the high-grade B-cell lymphomas with the CMYC and BCL2 and/or BCL6 gene rearrangements, as well as patients with primary mediastinal B-cell lymphoma.

Ms. Figueroa-Rivera:

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

Operator:

Next, we will hear from Eddie in Texas.

Eddie:

I have recovered from 2004 through ‘06 of chemotherapy. At the present time, I have a high white cell count. It seems to be going up and I’m seeing my oncologist, about every 4 to 6 months. I wonder what I can do about that.

Dr. Mead:

So, an elevated white blood cell count can be the result of a lot of different things. Certainly, there are some cancers that can drive the white blood cell up, such as CLL, but there is a lot of non-cancerous reasons for the white blood cell

count to rise. It could be due to an underlying infection, it could be due to underlying inflammation from other causes such as, you know, osteoarthritis. So, it requires a work-up by your oncologist, looking to see which subtype of white blood cell is elevated, and then performing studies to see if they can determine the reason for the white blood cell elevation. So, what you can do about it is going to vary based on what is driving the white blood cell count up.

Ms. Figueroa-Rivera:

Thank you. And, our next question comes from Joseph, is asking about stem cell transplantation, the types available, and is qualification contingent on age and health. I hear discussions regarding cutoff in the mid-70s, however, I read online patients in their mid to late 70s that have had successful stem cell transplantations.

Dr. Mead:

So the types of stem cell transplants out there are largely categorized into 2 groups, autologous stem cell transplant, which is what we discussed in the talk where a patient receives their own stem cells, and an allogeneic stem cell transplant, where they receive stem cells from someone else. I deferred discussion for an allogeneic stem cell transplant in the talk because it really plays a minor role in the treatment of lymphoma and is fairly complex to explain, and just in the interest of time I did not discuss it. The auto stem cell transplant plays the largest role in the lymphoma population.

Speaking to your next question, is there an age cutoff? You are correct, that there is not a strict age cutoff. There have certainly been examples of doing autotransplants in patients that are in their late 70s. And, it is not so much chronological age that we are evaluating, although we do take that into account, but we also take into account a patient's functional status and their other comorbidities. So, someone that is 75, who bicycles multiple miles every day, has, you know, takes no medications for other healthcare problems, is probably a more appropriate transplant candidate than a 60 year old that has heart disease and bad diabetes and kidney disease and never leaves the couch, even though they are 15 years younger than the 75-year-old gentleman that I described.

Ms. Figueroa-Rivera:

Thank you. I will take the next question from our telephone audience, please.

Operator:

Certainly. Maria in California, Dr. Mead is listening for your question.

Maria:

Yes, I was treated 3 times for Waldenstrom's (Waldenström macroglobulinemia). And, the first one was rituximab and it was not successful. The second was Velcade, it was successful for 1 year. The third one I received about 15 months ago at City of Hope here in California and it was rituximab and bendamustine, and it has been 15 months and I am still clear, thank God. So, my question is, can I have that repeated if, God forbid, it should come back? Can I repeat the same treatment?

Dr. Mead:

I generally would not advocate for repeating bendamustine combined with rituximab. Rituximab is fairly non-toxic, but bendamustine is a chemotherapy and it is not without potential toxicity. If you are being treated in an institution like City of Hope, they just have a wealth of clinical trials open and available at that institution, which from my perspective, enrolling, on a clinical trial would be a better approach rather than trying to repeat an old chemotherapy.

Ms. Figueroa-Rivera:

Thank you. And, congratulations on reaching remission. Doctor, Wendy's asking, my husband has anaplastic large cell lymphoma, where does this type of lymphoma fall into, indolent, aggressive or very aggressive?

Dr. Mead:

I would categorize that as an aggressive lymphoma. There are subsets within the anaplastic large cell lymphomas, so-called ALK positive and ALK negative, that give physicians further guidance on how aggressive this particular lymphoma might behave. But, it is considered one of the more aggressive variants. It falls under the T-cell lymphoma umbrella, which we did not discuss today. And, in general, the T-cell lymphomas all behave aggressively.

Ms. Figueroa-Rivera:

Thank you. And, Michele is also asking, for a potential treatment option and where does primary central nervous system lymphoma fall into, what category?

Dr. Mead:

So, primary CNS lymphoma treatment is going to be age-dependent, and it is also institution-dependent because there is no number one gold standard of care. So, I keep mentioning that R-CHOP is standard of care for diffuse large B-cell lymphoma, but we do not really have like an R-CHOP correlate for primary CNS lymphoma. Most institutions are going to use a regimen that contains high-dose methotrexate. Here at UCLA, if a patient is fit and relatively healthy, we also incorporate a chemotherapy called thiotepa and we generally consider a bone marrow transplant as front-line treatment for primary CNS lymphoma, whereas for the systemic lymphomas the bone marrow transplant is not considered unless a patient relapses. And yes, primary CNS lymphoma would fall under the umbrella of aggressive non-Hodgkin's lymphoma.

Ms. Figueroa-Rivera:

Thank you. And, our last question today Doctor, in these uncertain times, what should patients, as well as their caregivers, be asking their physicians at this time about treatment, about treatment options, possibly, speaking with them in different ways, over e-mail or actually having some telemedicine appointments?

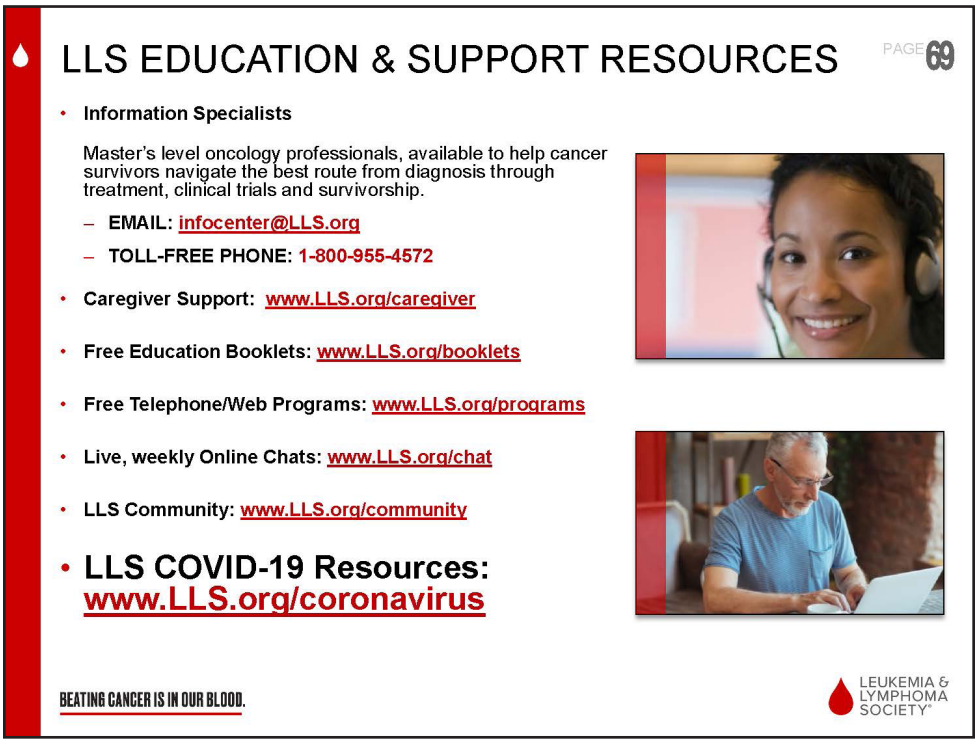
Dr. Mead:

So it is always going to be a balance of risk and benefit. And, for the aggressive non-Hodgkin's lymphoma you really do not have the luxury of time to delay treatment for the future. The majority of patients require treatment fairly quickly, so at least in my practice, for my folks that are newly diagnosed with an aggressive variant, you know, over the past few weeks, we are still proceeding with treatment as I would at any other time, just due to the aggressive nature of the lymphoma.

Ms. Figueroa-Rivera:

Thank you. And, thank you all for your questions today. I know that we did receive many questions and I will tell you about our Information Specialists in case we did not get to your question.

Again, Dr. Mead, thank you for your continued dedication to patients, and taking the time out, especially today, to speak with us about the aggressive non-Hodgkin's lymphomas and their treatments.



Slide 69: FREE LLS EDUCATION & SUPPORT RESOURCES

Ms. Figueroa-Rivera:

I do want to let everybody know that you can view the program slides and then the audio at LLS.org/programs. And if we weren't able to get to your question today, you may speak to an LLS Information Specialist at **1-800-955-4572** from 9 AM to 9 PM Eastern Time, or you can reach us by email at infocenter@LLS.org. And Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.

We also have a Clinical Trial Support Center (CTSC), where clinical trial nurse navigators, who are registered nurses with expertise in blood cancers, can assist you in finding out if a clinical trial is right for you, as well as keep you informed of any changes in trials due to COVID-19. And they could be found at www.LLS.org/CTSC. That stands for our Clinical Trial Support Center.

Again, our first webcast on COVID-19, *Your Questions Answered About COVID-19*, is available on our website at www.LLS.org/Coronavirus.

Slide 70: LLS EDUCATION & SUPPORT RESOURCES

I just wanted to let everybody know that we do have a new COVID-19 Patient Financial Aid Program. Thanks to the generosity of LLS Partners, eligible blood cancer patients will receive an individual one-time $250 stipend per patient to help with non-medical expenses, such as food, housing, utilities, transportation, and other needs. Patients do not need to have a COVID-19 diagnosis and there are no income criteria, to qualify. You may get more information about this program by calling **877-557-2672** or going to FinancialAssistance@LLS.org.

Slide 71: THANK YOU

Again, we'd like to acknowledge and thank Genentech & Biogen, and Pharmacyclics, An AbbVie Company & Janssen Biotech for support of this program.

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

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