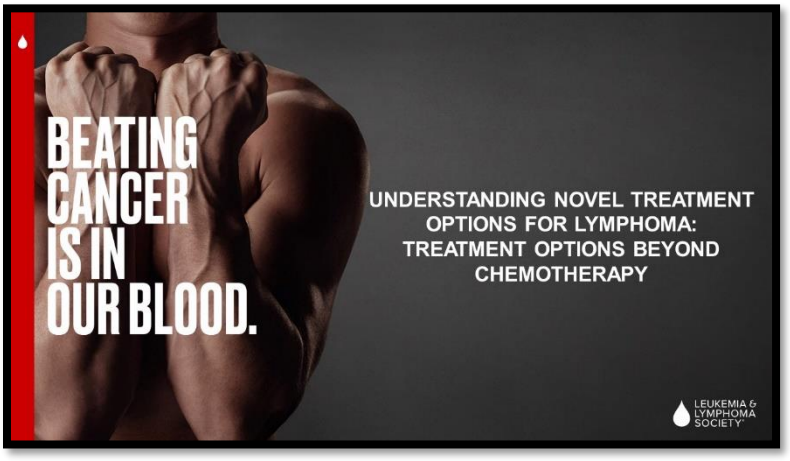


Elissa Baldwin: Hello everyone and welcome to *Understanding Novel Treatment Options for Lymphoma: Treatment Options Beyond Chemotherapy*. My name is Elissa Baldwin, with the Patient Education team at The Leukemia & Lymphoma Society, and I will be your moderator today. We will have a Question & Answer session after the presentation, where our guest will answer questions that came into our LLS Information Resource Center and Online Community.

Special thanks to Dr. Jonas Paludo for sharing his time and expertise with us today, and thank you to the Mayo Clinic for sponsoring this program. Before we begin, our President and CEO, Dr. Louis DeGennaro, will make some remarks.

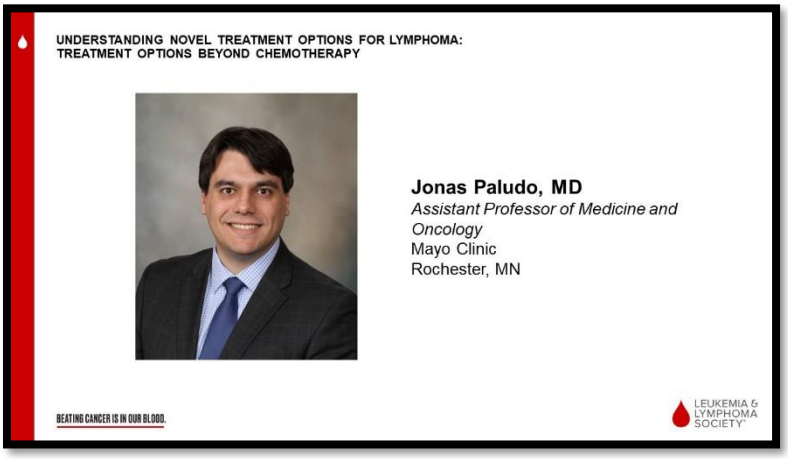
Dr. Louis DeGennaro: I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1 billion in scientific research to find better treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support. We also support blood cancer patients in their local communities through our chapters across the country and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We're committed to working tirelessly toward our mission every single day until we find a cure.

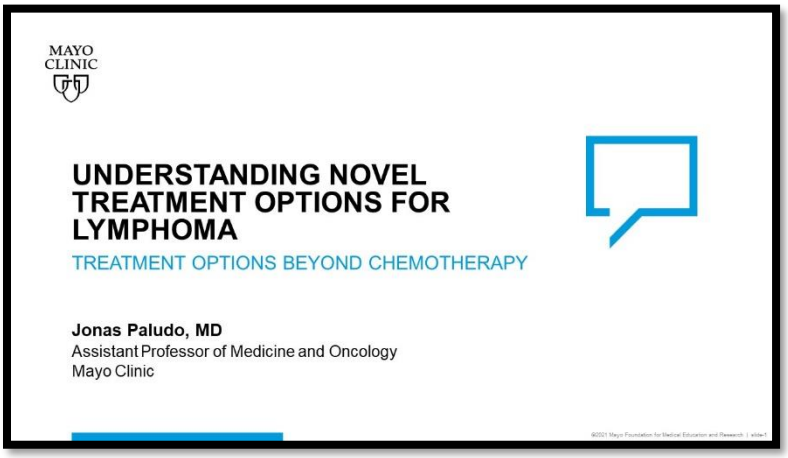
We're fortunate to have esteemed key opinion leaders to present our programs. They each have volunteered their time and we appreciate their dedication to supporting our mission and commitment to caring for patients living with blood cancers. Thank you for joining us today.

Elissa Baldwin: Thanks to Dr. Lou for his remarks and thank you for watching as you continue to face your blood cancer diagnosis.



I am now pleased to introduce Dr. Jonas Paludo, an Assistant Professor of Medicine and Oncology at Mayo Clinic in Rochester, Minnesota. He completed his medical degree at UFCSPA in Brazil, followed by Internal Medicine Residency, Hem/Onc Fellowship, and Advanced Lymphoma Fellowship at Mayo Clinic. He is currently a member of the Lymphoma Cell Therapy and Stem Cell Transplantation Disease Groups within the Division of Hematology. His research work focuses on translational and outcomes research in lymphoid malignancies and implementation of novel technologies in the management of patients with cancer. He is the principal investigator in several clinical trials, ranging from early therapeutic trials to platform projects exploring the use of wearable devices and remote patient monitoring.

On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Paludo I am now privileged to turn the program over to you.

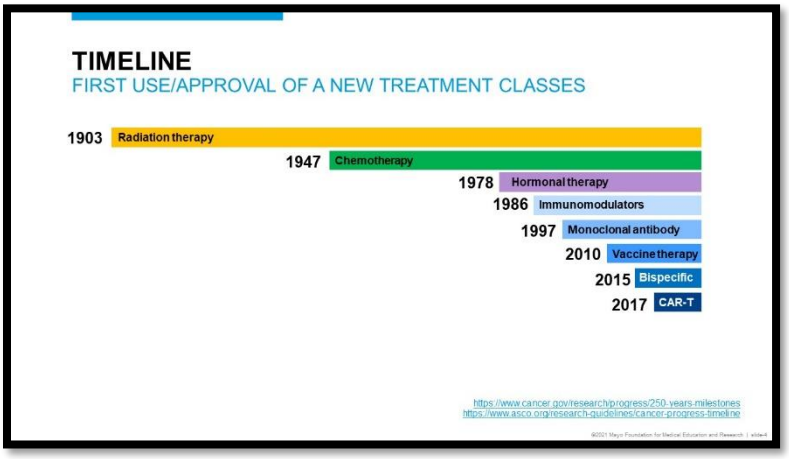


Dr. Jonas Paludo: Well, thank you for that introduction and thank you for the opportunity to discuss certain options beyond chemotherapy. Today, we will be focusing most on immunotherapeutic agents. Our goal today is to review how some of these drugs work in the context of how our immune system fights cancer.

So, I have divided our review today in three different topics. We'll start with a timeline of cancer treatment development to review how things have been developed in the last few decades. Within a review our immune system works and how it fights cancer, but also how cancer can get away from our immune system. And then we'll dive into the immunotherapeutic agent options and review how they work in conjunction with our immune system to fight cancer.

Have a couple of disclaimers. One, I'll be talking about some drugs, but by no means is a complete list of cancer treatments. And I'll be focusing most only on lymphoma because of my background in lymphoma cell therapy. But the same principles discussed today applied to other cancers and other diseases.

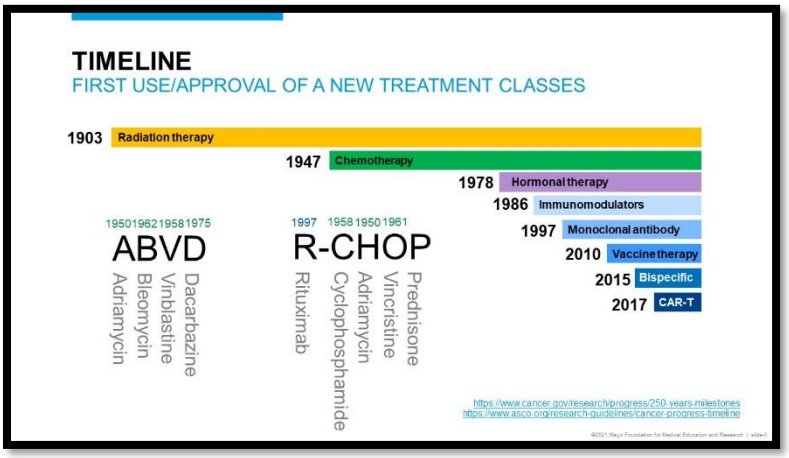
So, moving on to our timeline of cancer treatment development.



So, in 1903 was when radiation therapy was first used for the treatment of cancer. That was the first non-surgical treatment for cancer almost 120 years ago. It took about 40 to 50 years before chemotherapy came in play.

There was a 1947 when antimetabolites drugs were introduced, shortly followed by the use of nitrogen mustard from what was learned during World War II, a cousin of methotrexate, which is fairly commonly used today's date for treatment of lymphoma and other malignancies.
In ‘78, hormonal therapy drugs are introduced. In ‘86, immunodulatory drugs were introduced, and that was with the approval of interferon alpha. Was not until 1997 when the first monoclonal antibody was approved by the FDA and there was a Rituximab, commonly used in be so malignancies today.

A few years later, we have the approval of vaccine therapy for the use in patients with metastatic prostate cancer, and then bispecific antibodies came later in 2015. And finally, about four years ago, we had the first approval of a CAR T-cell therapy product.

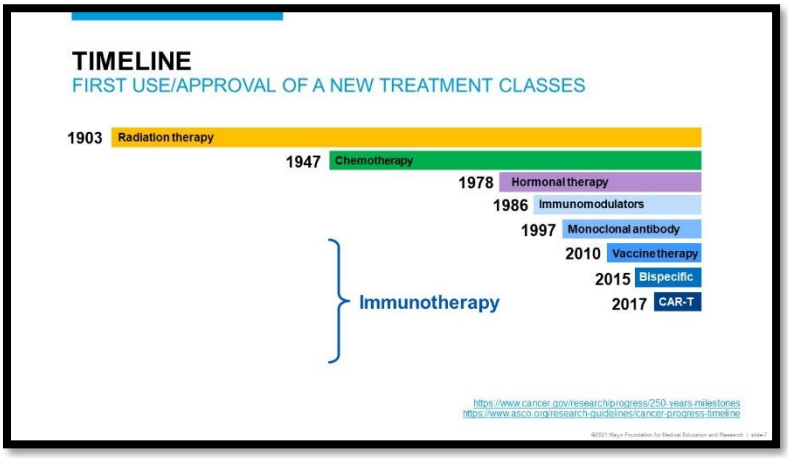


Here I list a couple very common regimens used in the management of lymphoma. So I have ABVD and R-CHOP. ABVD stands for Adriamycin, which it’s drug class was introduced in 1950. The B is for Bleomycin, that was introduced in ‘62, Vinblastine, ‘58 and Dacarbazine in 1975. So, these drugs have been around for almost five decades.

R-CHOP, which used to be CHOP in the past, has C for Cyclophosphamide, which it's drug class was introduced in 1958. H is Adriamycin. The same Adriamycin as the ABVD, but with a different letter. O is Vincrisine, introduced in 1961. And P is for Prednisone, which is not really chemotherapy drugs but also have some anti-cancer activity and has been around for close to 100 years.

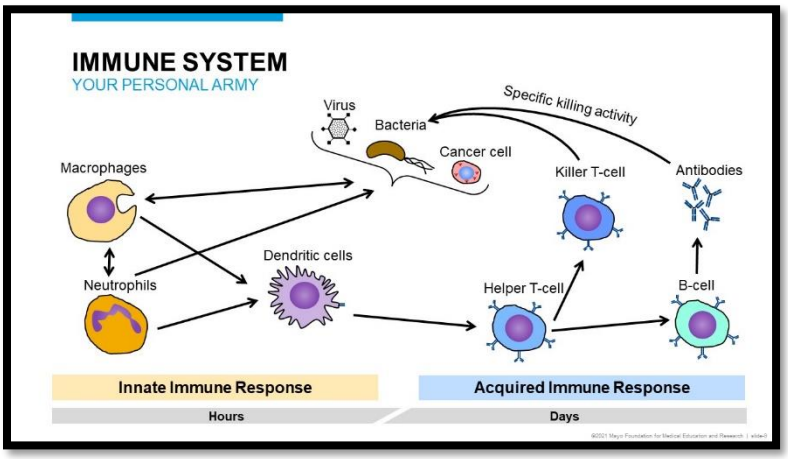
After 1997, with the approval of Rituximab, it was that CHOP and became R-CHOP. I think the goal of going over this chemo regimen is to show that older drugs don't lose efficacy, because they get older or because they get old. These regimens are still very effective and a very important part of the treatment of patients with lymphoma. Of course, new drugs are important and are needed, as not every patient responds well to chemotherapy. But chemotherapy still has an important role in the cancer management.

Have here a slide just to show how drugs have been approved for non-Hodgkin lymphoma. Just to give you a magnitude of how many drugs are out there. Of course, not all of these drugs are approved for all types of non-Hodgkin lymphoma. Some drugs are used for some subtypes. Other drugs are used for other subtypes. But just give an idea of how many drugs are out there.



Then going back to our timeline and, as I mentioned at the beginning, we'll be focusing on the immunotherapeutic agents, which are these drug classes highlighted in blue here.

Alright, well, moving to our second part. So now we have reviewed the timeline, let's talk about how the immune system works, how it fights cancer and how cancer can get away from it.



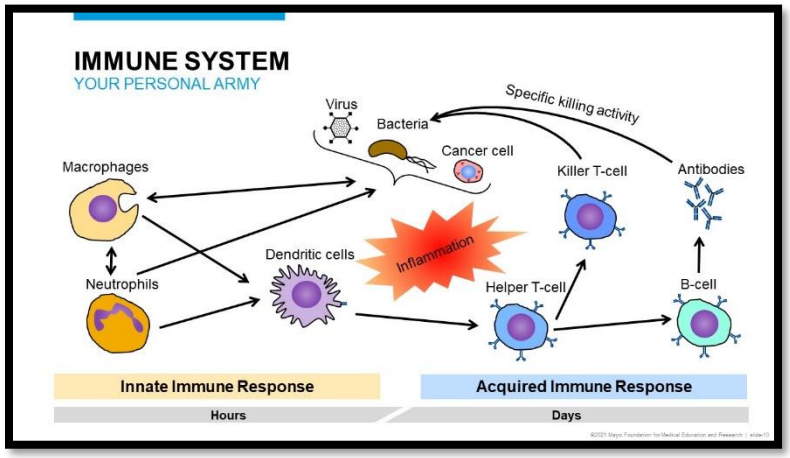
So, we can think about your immune system as your personal army. It's ready to fight a war to protect us from harm. It is army, we have different soldiers and different divisions. And, of course, there's also the enemy, which is what we're fighting against, such as virus, bacteria, parasites and cancer cells, among others. One of the divisions of our personal army of the immune system is the innate immune system. It provides the first line of defense. It attacks anything perceived as a threat, some broad and quick immune response that is mounted in a matter of a few hours.

It doesn't have precision against the attack and also, it does not create a memory. Some of the cells that belong to the innate immune system highlighted here as the macrophages, the neutrophils, and dendritic cells. The dendritic cell is very important because it communicates with the other division of this army, which is the acquired immune system. That provides the acquired immune response, which comes late. It can take a few days to develop and to be mounted, but it does provide a more precise response and also developed memory.

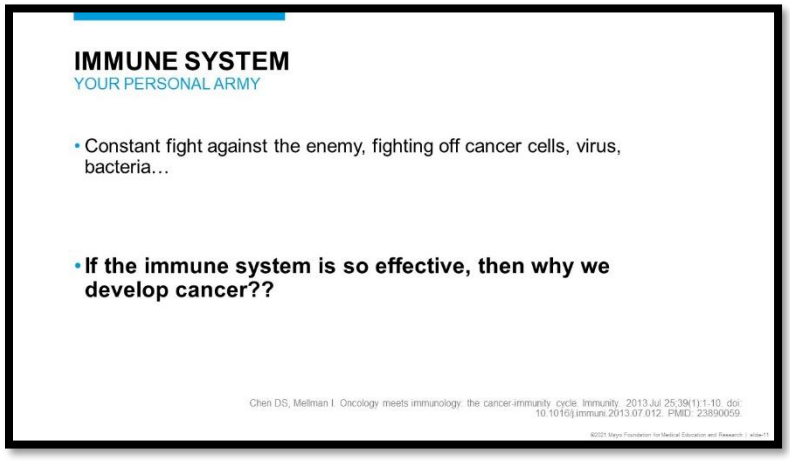
Most of the cells in the acquired immune system are T cells and B cells. Of course, there are other cells are not listed here, but these are the most important ones. We have helper T cells to

help coordinate the attack. We have the killer T cells, also known as cytotoxic T cells that provide the actual killing of cancer cells. We also have B cells that will then develop a maturity to plasma cells and produce antibodies. And we'll hear a lot about antibodies later that in this review, but antibodies are proteins that are naturally produced to bind specific markers, also known as antigens in the enemy - in virus, bacteria and also cancer cells. So, both antibodies in killer T cells, they provide a more specific killing activity, and they also provide a memory for the immune system.

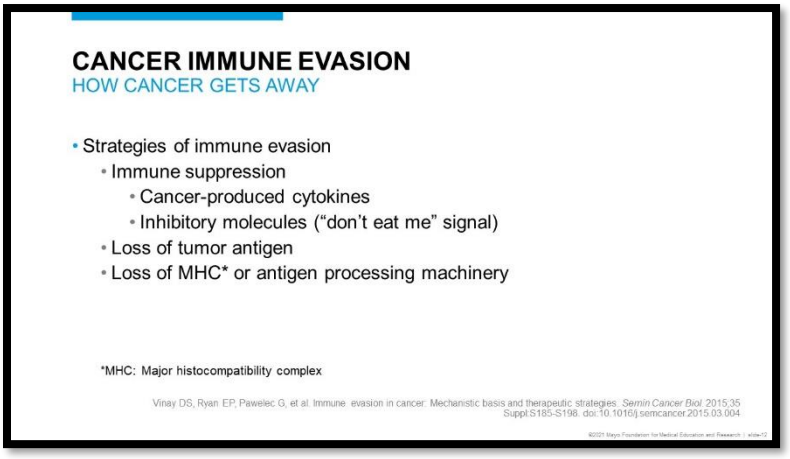
Now, no battle, no army can work without a good communication system and the communication system of our immune system are called cytokines. Cytokines are proteins. They are produced by the immune cells. They are released and are helpful in activating and suppressing the immune system. They are needed to start the immune response, but also to stop it once the battle is over.



Now we don't see the fight being fought, but we can certainly feel it and the way that we feel a fight is being fought is by inflammation. So, when cytokines are being released and our being used to help guide immune response against a cancer cell or bacteria or virus, those cytokines cause inflammation, which we feel that as fever chills, as night sweats, fatigue, have no appetite. Like when you feel when you have the flu, those symptoms that you're having when you have the flu are secondary to inflammation that's been triggered or caused by cytokines.



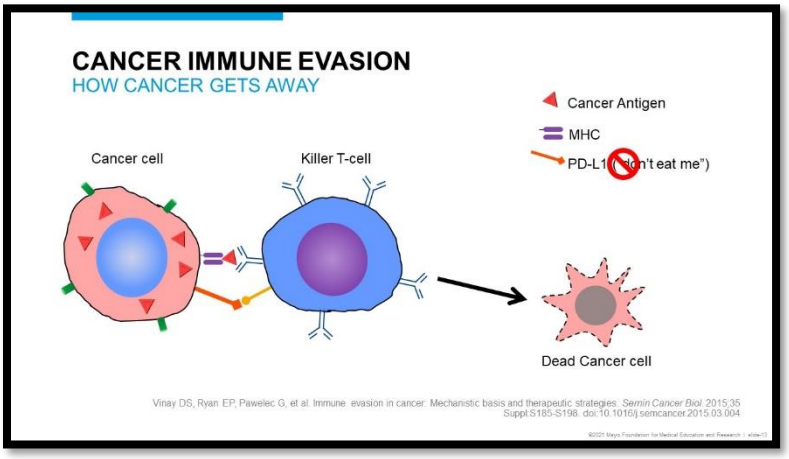
So our immune system is fighting a battle all the time and honestly our immune system is a very effective, wins almost every battle. And as a matter of fact, every day that we don't die from an infection is because our immune system is winning the battle. But if our immune system is so effective, here was the most important question, then why do we develop cancer?



Because cancer is quite smart and cancer can find a way to get away for an immune system and that's what we called cancer, immune evasion. Some ways how the immune system can get away, sorry how the cancer cells can get away, is by immunosuppression. So, cancer cells can produce cytokines. You're hacking the communication system and you're telling the immune system, "hey the battle is over, we're all friends here, you can stop fighting me". That's one way for cancer cells can get away.

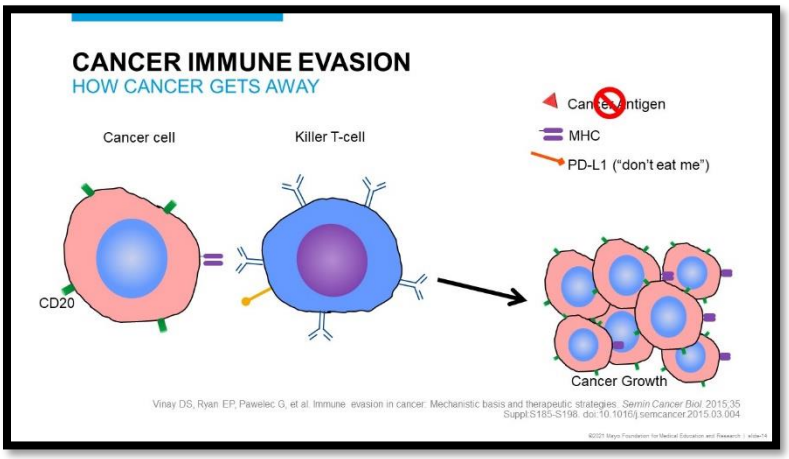
Cancer cells can also produce or express immunodulatory molecules or inhibitory molecules sometimes known as the "don't eat me" signal molecules or "don't destroy me" signal. Which is normally used by normal cells to tell the immune system, "I'm your friend, don't attack me". Cancer cells can use that and exploit that on their behalf. Other ways cancer cells can get away is by losing or not making the tumor antigens changing tumor antigens, so that they become invisible to the immune system.

And other ways that you can lose or they can stop making the MHC protein or major histocompatibility complex protein, which is a key part of the immune recognition and we review this in more detail in the next few slides.

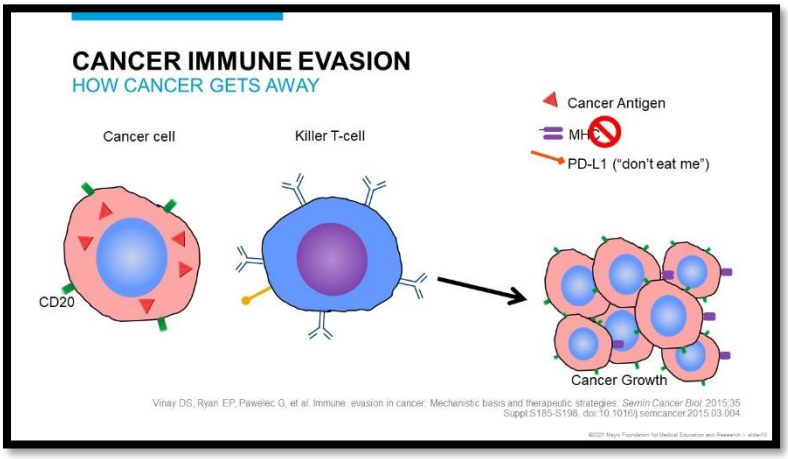


But first, let's review what is needed for a killer T cell to destroy a cancer cell. This will be important as we go along and talk about immunotherapeutic agents. A few things have to be in place. One, first and foremost, we need that MHC protein that's on the surface of the cells, normal cells and cancer cells. That protein is very important because that's the protein that holds and presents the antigen to the outside.

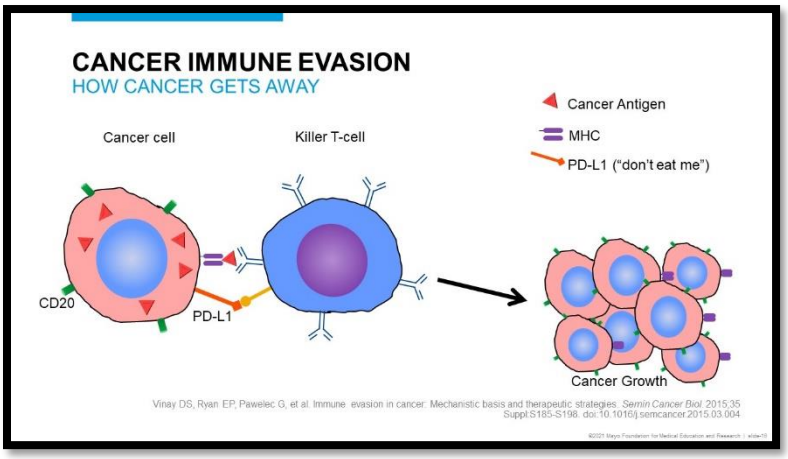
Of course, we need the antigen on the MHC protein and when they are all together, that's what is recognized by the killer T cell receptor to make that positive connection to say this is abnormal, I have to destroy this cell. However, you also cannot have the “don't eat me” signal, or that “don't destroy me” signal. And I'm representing that here is the PD-L-1, but there are others that we'll review later. So you cannot have that to have effective killing of the cancer cell. So again, you need the antigen, you need the MHC protein, and you cannot have “you don't need” me signal.



Alright, so moving on. So, of course, if the cancer cells, they stop making cancer antigen or they lose that or they change that and you don't have that antigen, you don't have that positive connection with the killer T cells, cancer cells can continue to grow and escape the immune system.

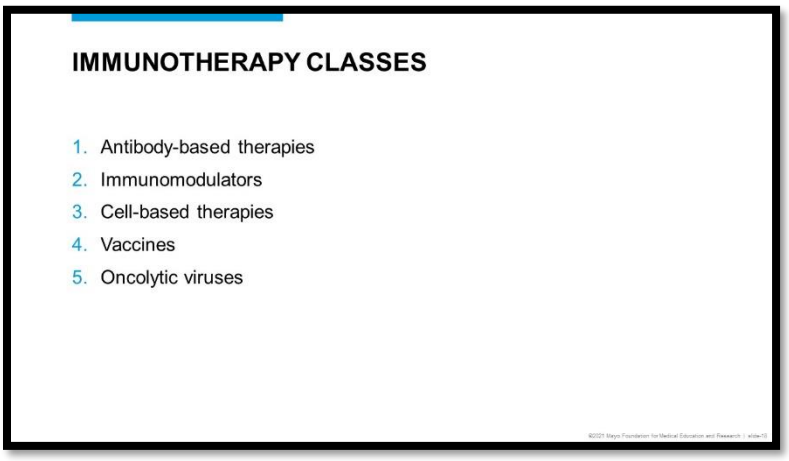


You may have the antigen, they may have the antigen, but you don't have the MHC protein. Again, you don't have what you needed for that connection, for that interaction. Cancer cells, again, free to grow. They are looking visible to the immune system.



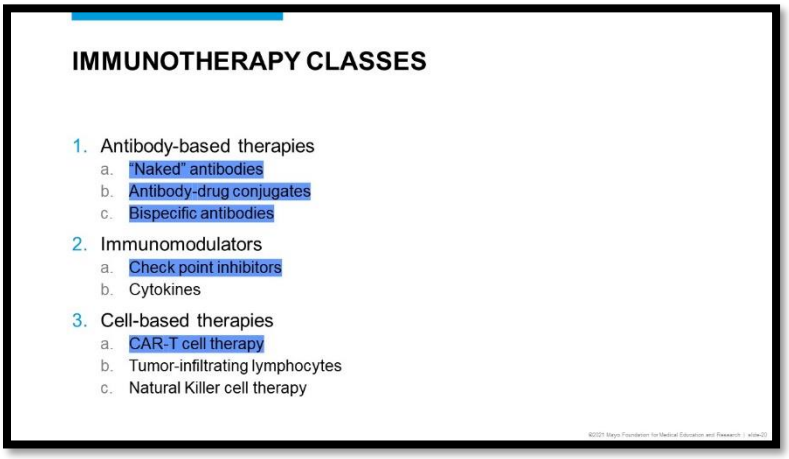
Or if they have both the antigen and the MHC protein, but they don't have, they also have the PD-L-1 or that “don't eat me” signal, for example. And also will stop the cancer cell, the killer T cell from destroying the cancer cell and that will allow the cancer cells to grow into more to develop.

Alright, so now we have reviewed a few different strategies of how cancer cells can get away from the immune system. So now let's look into different types of immunotherapeutic agents and how they actually have been designed to circumvent some of these ways that cancer cells can bypass and get away from the immune system.

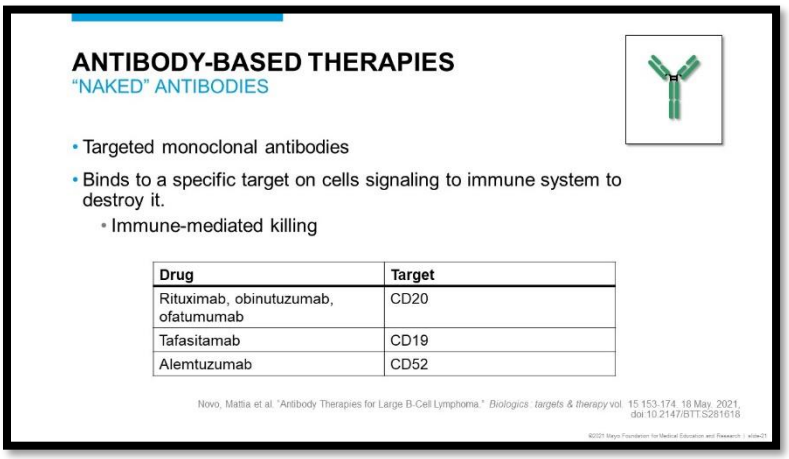


So we have at least five different you know immunotherapy classes available today. We have antibody-based therapies. We have immunodulator drugs, cell-based therapies, vaccines and oncolytic viruses.

For sake of time today, will be focusing on the top three of these classes that include different types of drugs. For example, in antibody-based therapies, we have what are called “naked” antibodies, we have antibody-drug conjugates and bispecific antibodies. For the immunodulator drugs, that includes check point inhibitors, which will be reviewing today, but also cytokines that have been used for a long time. In the cell therapy base or the cell-based therapy, classes we’ll be talking about CAR T-cell therapy today, but we also include tumor-infiltrating lymphocytes, natural killer cell therapies, among others.

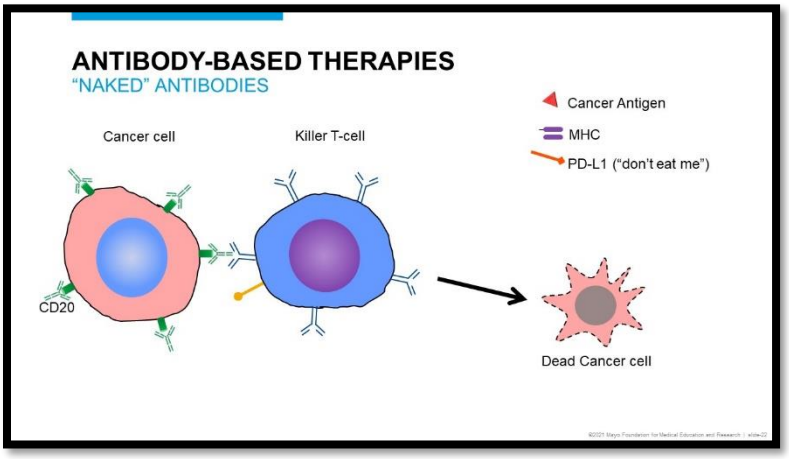


So I have highlighted in blue here the ones that will be reviewing today.



Right, moving to the first one. So, among the antibody-based therapies, let's talk about what it called “naked” antibodies or simple antibodies, also known as monoclonal antibodies. So, as I mentioned earlier, antibodies are normal proteins produced by our own immune system that tags the enemy, so that it can be destroyed by the immune system.

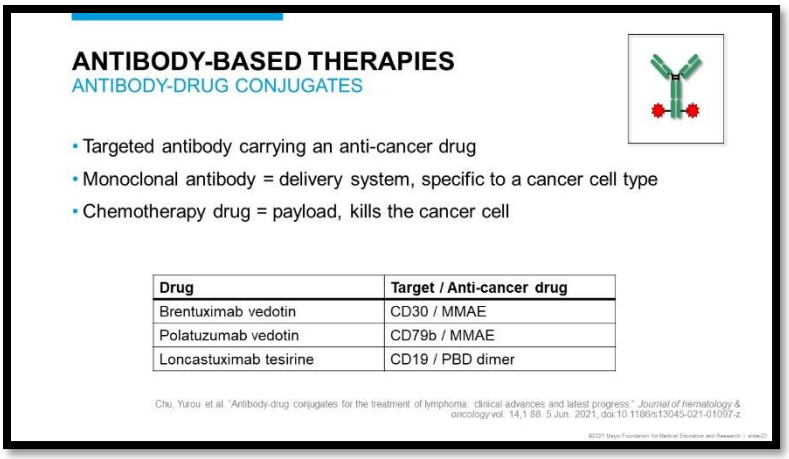
So here, we are using the same principle. So, these antibody drugs, “naked” antibody drugs, are designed to bind or to a marker on cancer cells. That will then signal for the immune system or for the immune cells that they are abnormal. The immune cells will come in and destroy them, as the immune mediated killing process, which is one way how monoclonal antibodies work.
I have listed a few drugs here that are used in lymphoma, such as Rituximab, as I mentioned, the first monoclonal antibody approved in ‘97, obinutuzumab and ofatunumab. All these three drugs, they bind or the target a marker call CD20. Tafasitamab targets CD19 and Alemtuzumab targets CD52. CD19 and CD52 are very common markers on B cells. Therefore, they work for B cell malignancies or B cell cancers.



Now, what are those CD20s? What are those markers? So, a normal B cell has, in every cell has different markers on their surface. B cells have CD19, CD20, among others. When a normal B cell becomes a cancer B cell or malignant B cell, those markers persist. They remain on the cell and that's how we can exploit that. And using antibodies to bind those markers that are also in the cancer cells. So, if you use a Rituximab and using our B cell cancer cells, as an example here.

Rituximab will bind to those surface markers, CD20 in this case, and that will signal to the killer T cell, this is abnormal come here and destroy yourself. As you can see, by using this strategy, we don't depend on cancer cells to make cancer antigen. We don't depend on cancer cells to have the MHC protein. You can bypass those limitations. You're still susceptible to the "don't eat me" signal. But if all that's present, then that's how the cancer cells are destroyed.

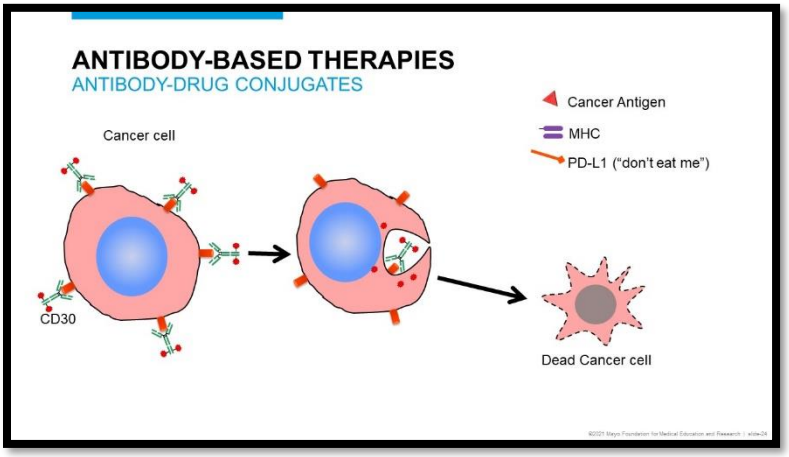
As I mentioned, C20 is a normal marker in normal B cells, so one of the side effects of these treatments is that you end up also destroying or killing some normal B cells. However, once the drug is out of your system, your body and your bone marrow is making new B cells to replace the ones who are destroyed in hopefully by the time, all cancer cells are gone and they won't be coming back.



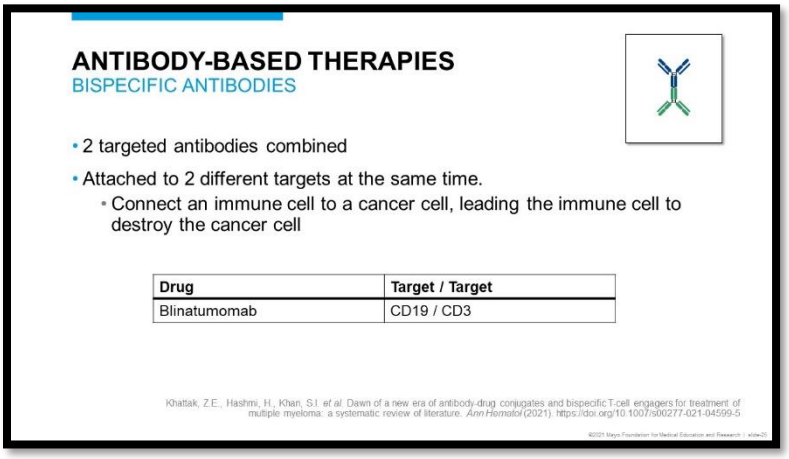
Moving on to the second immunotherapy drug. Now we're talking about antibody-drug conjugates. These are two for one drug. You have a monoclonal antibody, again designed to bind to a specific marker on cancer cells. Attached to it, you have an anti-cancer drug, usually a very strong chemotherapy drug.

The monoclonal antibody is a delivery system to bring the chemo drug where it needs to be in the cancer, in the cancer cells. And the chemo drug is what does the work of killing the cancer cells. Some examples of these drugs is a brentuximab vedotin, which is a monoclonal antibodies targeting CD30, which is commonly seen in our Hodgkin lymphoma and also in some types of T cell lymphomas.

The anti-cancer drug is MMAE,or monomethyl auristatin E, is a very strong chemotherapy drug that when it's used on its own and alone is very toxic. When you see us combine with the monoclonal antibody, that it's precise delivery system limits of toxicity. Polatuzumab vedotin targets CD79b, which is common in B cells. It has the same anti-cancer drug. Loncastuximab teserine targets CD19, also B cell marker or B cell cancer marker. Everybody has a different anti-cancer drug and this case you use a PBD dimer.

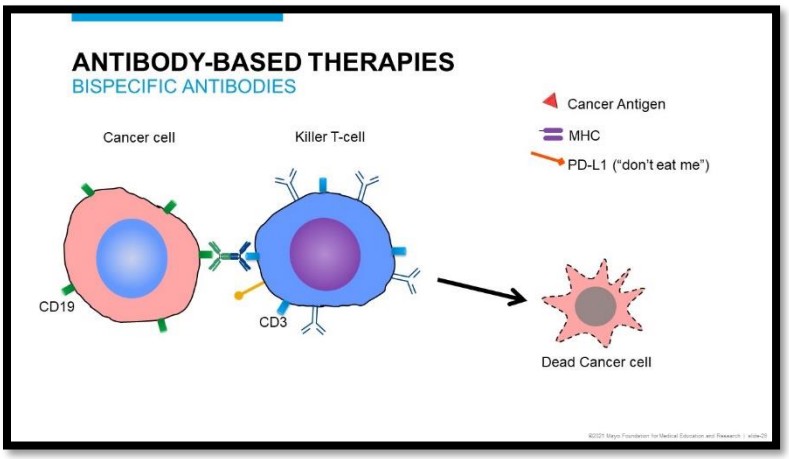


So how they work again. I'm here using an example of a Hodgkin cancer cell that has a CD30 mark on the surface, the antibodies bind onto it and after it binds to it, it gets internalized in the cell and the chemotherapy is released when the actual killing of the cancer cell. And one of the, for this treatment to work, it doesn't depend on having a cancer antigen, it doesn't depend on have the MHC protein and it doesn't really depend also on the "don't eat me" signal.

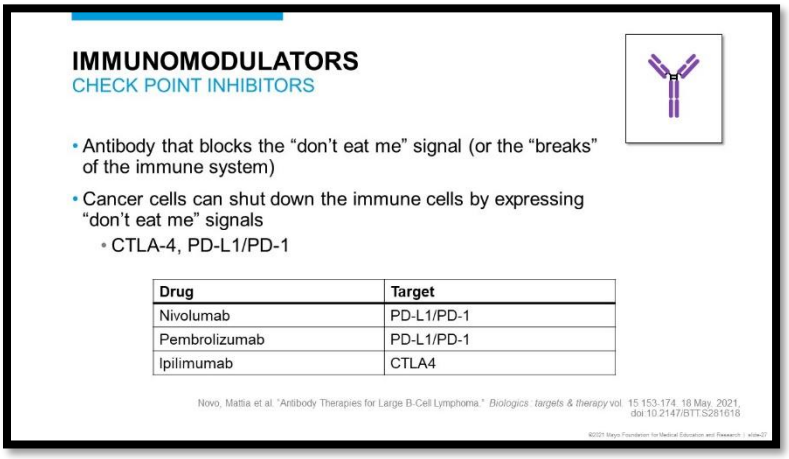


Moving to the next drug class, bispecific antibodies, which I guess the name is already suggesting what it is. It is an antibody that binds to two different markers. On one end, it is binding to a cancer marker. On the other end is binding to a T cell or immune cell marker. And the goal is that it will approximate or bring the two together, the cancer cell and the T cell, so that it facilitates the killing of the cancer cell by the immune cell.

When an example of this drug class is a blinatumomab. So blinatumomab was the first bispecific antibody approved on one end specific to CD19, designed to bind to B cancer cells, on the other end it binds to CD3, which is a common surface marker for killer T cells.

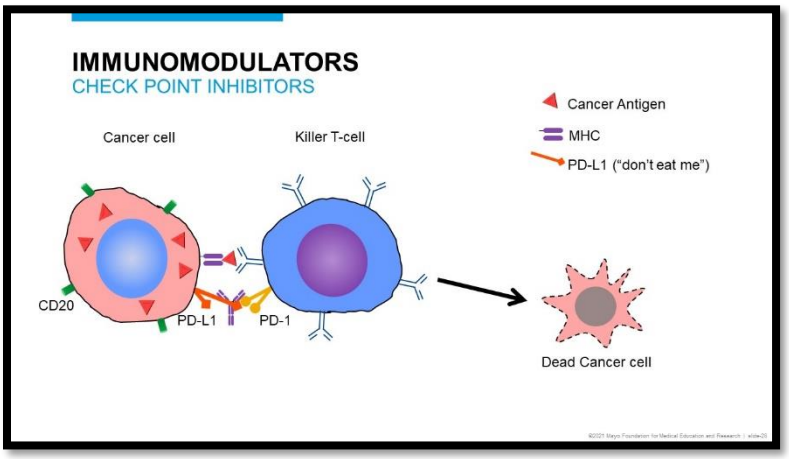


So again, going back to our example: you have a cancer cell, it has a CD19 on the surface. The bispecific antibody is binding to that one. And on the other end, is connected to a T cell. Bring the two together, so the killer T cell can do the killing, can kill or destroy the cancer cell. Similar here, it doesn't depend on the cancer antigen or MHC, but it can be affected by the "don't eat me" signal, if that is present.



Alright, moving to our next type of drug class, are the immunomodulators. So, here we'll be talking about check point inhibitors. Check point inhibitors are also monoclonal antibodies. But they are different, they are not binding to a marker on the surface of the cells, so that you can be signaling to the immune system like we talked about Rituximab. The check point inhibitors are designed to block that "don't eat me" signal, also known as the brakes of the immune system. As I mentioned earlier, cancer cells can shut down the immune system by expressing these "don't eat me" signals.

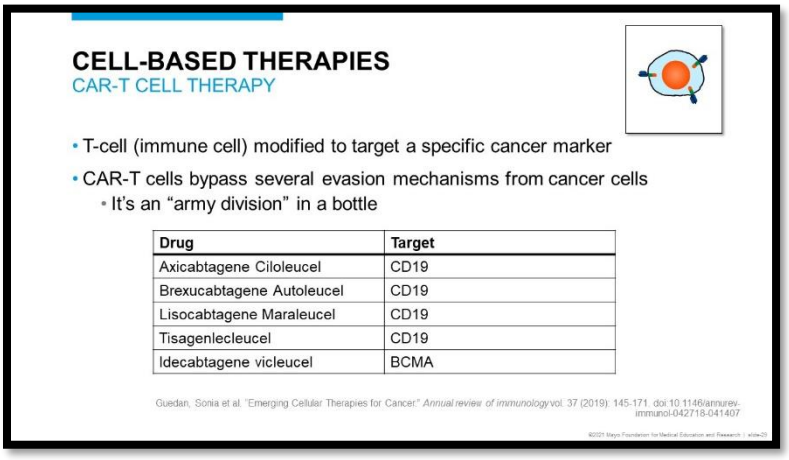
Some of those "don't eat me" signals that we know of, there are several, but I put here CTLA4 as one of them, and the PD-L-1/PD-1 pair as another one. Nivolumab and Pembrolizumab are two common drugs and they work by disrupting or blocking the PD-L-1/PD-1 direction. Ipilimumab, which was the first checkpoint inhibitor approved, it binds to the CTLA4 "don't eat me" signal.



So, again, we're back to our example. Now, you need to have that antigen, that cancer antigen. They have that MHC protein. If you also have that "don't eat me" signal connection here between the PD-L-1/PD-1, the cancer, the T cell cannot do its work. So, by using a check point inhibitor, we are breaking that connection, releasing that brake so that the killer T cell can destroy the cancer cells.

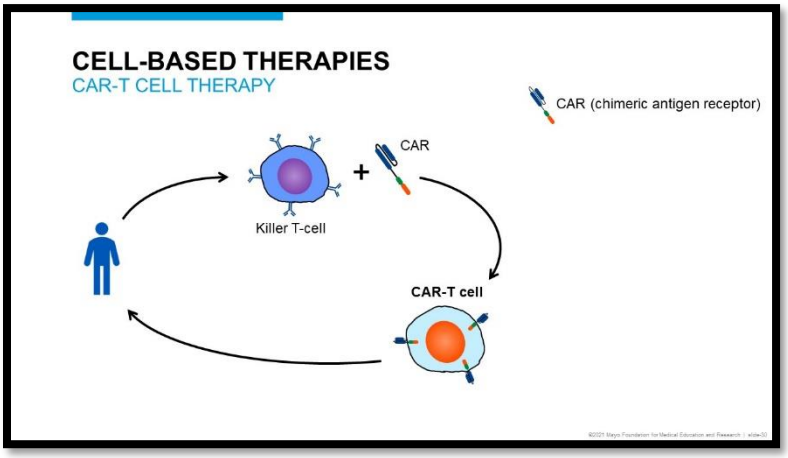
Now, the reason why “don't eat me” signals exist, as I mentioned earlier, so that normal cells can tell the immune system, "I'm your friend, don’t destroy me”. When you block that, you lead to one of the most common side effects of checkpoint inhibitors, which is that your immune system, now without the brakes and going full speed against the cancer cells, can sometimes misfire and attack normal cells. Sometimes it happens on the skin and you can see that as presenting as a rash. It can sometimes attack the gut or the GI tract. And one of the common side effects of these drug is diarrhea. Sometimes can affect your lung or other organs, but essentially the most common side effects of checkpoint inhibitors is that our immune process, because now your immune system is working without the breaks.

These drugs are very important. They have really revolutionized the treatment of several cancers, of course, including Hodgkin lymphoma, but also melanoma, lung cancer, bladder cancer, among others.



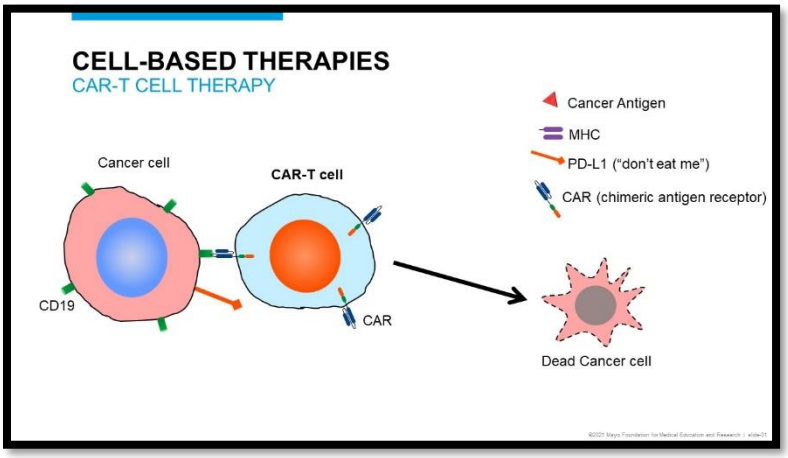
Alright, moving to our last one, now into the cell-based therapies. We will be talking about CAR T-cell therapy. So, CAR T-cells, they are a T cell, a killer T cell, part of our immune system - those are modified to bind and target a specific cancer marker. CAR stands for Chimeric Antigen Receptor, which is essentially a design built in receptor, on one end sticking to the outside of the cell, recognizing the cancer cell, and on the other end, is taking inside of the T cell, has all the machinery necessary to activate that cell and does not depend on any other signals.

You can think we can think about CAR T-cells as an army division in a battle. Several drugs have been approved in the last few years. As I said, the first one was only approved 2017. And almost all of them target CD19, so they have been used for B cell malignancies, including B cell leukemias and lymphomas. The most recent one was approved against the BCMA, which is a marker seen in multiple myeloma cells.



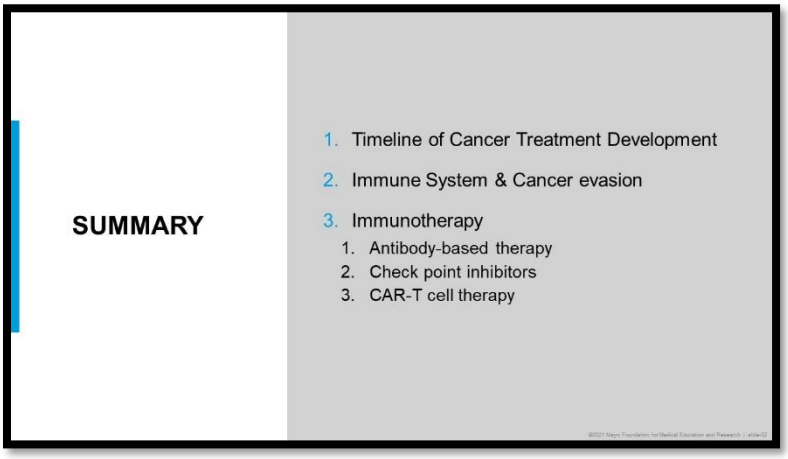
How CAR T-cells are made? So, the products approved to date are autologous products, meaning that they are made from the patient cells back to the same patient. We usually start the process by collecting normal T cells from the patient through an apheresis process, which is essentially a filtering of the blood and removal all of the cells that we want. So, with the apheresis, we take T cells out of the patient, send them to the lab, to the manufacturing facility. There, the T cells will be modified to express is a special receptor, this CAR receptor, then becoming a CAR T-cell.

They are shipped back to us. That process takes about three weeks. Then come back to us, and then we infuse those CAR T-cells back to the same patient where the T cells came from to begin with.

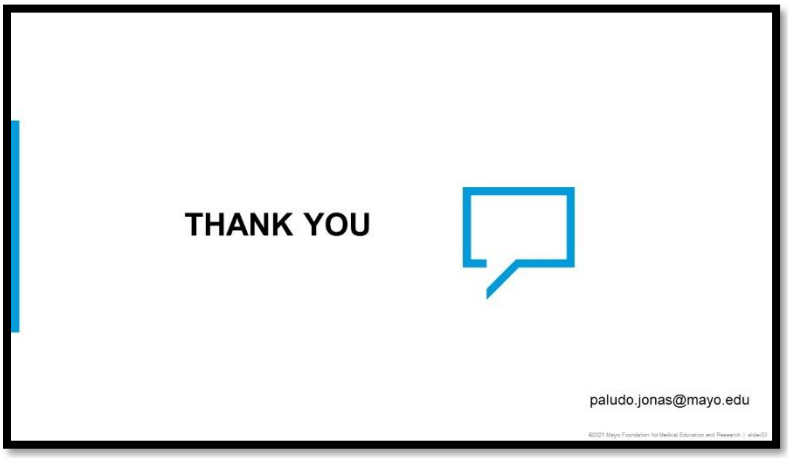


When the CAR T-cells are re-infused, now we're infusing millions and millions of CAR T-cells, they will find the cancer cells, they will bind to the marker they are designed to bind. And they are going to use that pre-activate state to start the killing process of the cancer cells. Now, as I mentioned in the very beginning, one of the communication systems of this army of the immune system is using cytokines. Now, when you have millions of CAR T-cells coming in at once and starting the process of killing the cancer cells, they are releasing a lot of cytokines. And that is one of the most common side effects of CAR T, is called cytokines release syndrome (CRS),

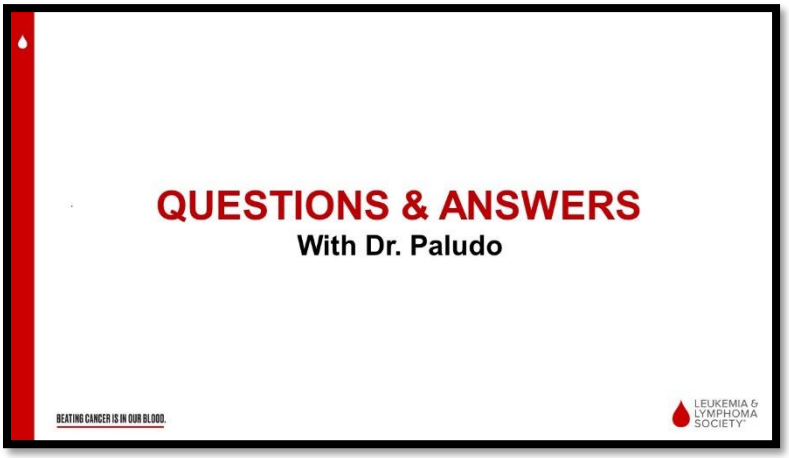
which is usually presenting as high-grade fevers, chills, fatigue, no appetite, sometimes even lower blood pressure. And it's treated by blocking some of those cytokines on some other medications. But here you have the CAR T-cell. It's connected with the cancer cell and it's destroying it.



Very well, so just to summarize, we have briefly revealed a timeline of cancer treatment development. Highlighting how many new treatments have been developed in the last couple of decades. Also showing that most of the new treatment developments have been related to the immunotherapy or immune system. But also, not forgetting the cancer chemotherapy drugs, they may be old, but they are still very effective. They have an important role in treatment of cancer. With a review our immune system works and how cancer cells can get away from it. Diving into the immunotherapy options, we reviewed some of them in how they work to bypass those weaknesses.



So, I want to thank you all for your attention today and I'll be happy to go over some of the questions as well. Thank you.



Elissa Baldwin: Thank you, Dr Paludo for your very informative presentation. It is time for the question and answer portion of our program. We will start with our first commonly asked question.

How do doctors know which treatment is best for a patient, now that we have more treatment options?

Dr. Jonas Paludo: It's an excellent question and it's a very individualized decision, to be honest. One, it depends on what kind of cancer we're dealing with. For example, what kind of lymphoma we're dealing with, what prior treatments have been used before, and how the cancer has responded to those treatments.

And we try to use treatments that work in different ways, that attack the cancer from different angles. So, for example, if we have used the chemotherapy-based treatment and the cancer didn't respond well at all, we usually try to then use another chemo reg or treatment regimen that does not involve chemotherapy or is not chemotherapy heavy. Again, to try to, for example, to use or harness the immune system, in that sense, to come from a different angle and try to attack the cancer cells from that for that way

So, it depends on the cancer type. It depends on the markers on the cancer cells. It depends on how the cancer has responded to prior treatments. And, of course, all of that is based on what we know from prior clinical trials, and how drugs have responded before, and how drugs have worked before and also what kind of side effects are commonly seen with different drugs and what kind of side effects we're trying to avoid the most.

For example, if someone has received a treatment before that has caused the peripheral neuropathy. And that being significant or try to avoid a treatment next that will also cause peripheral neuropathy, so try to avoid know doubling of the side effects.
But it's a very individualized decision based on clinical trials data, based on disease specific, based on prior treatment and response.

Elissa Baldwin: Thank you. Is there a certain order doctors have for moving through these different types of medications?

Dr. Jonas Paludo: There's some, there's some order. There are some preferred treatments that we used first. Of course, with cancer treatment in general, we always go with the better

treatments, or the best treatments first. We always use the most effective treatments first. So, there are some treatments that are preferred as the first line or frontline treatment. Of course, every cancer is different. After that, there is some data on how we go with the second line of therapy or the second-best treatments. But once you get to the third line or later, then that's very, it becomes more subjective. Most of the treatments in a third line or later, in general, they are quite similar. So, it's a matter of selecting based on different side effects and based on prior treatments used. So, there is an order, but that order is mostly present for the first and second treatments. When you get a third or later, it is more of a subjective selection.

Elissa Baldwin: Our next question: do patients always have to start with the oldest approved treatment before they can qualify for a newer treatment?

Dr. Jonas Paludo: Good question and the answer is no. You don't have to start with the older, or the oldest treatment. Actually, as data becomes available and clinical trials have been concluded and reported, sometimes we learned that a new treatment is better or more effective, or better tolerated than older treatment and that becomes our first option. So that's true for several different lymphomas, for example, as we learn that some new treatments work better than the old ones. Then that treatment becomes the first or the preferred first option, and that older treatment remains as an option to be used later, if needed. So, it's really based on clinical trial data, as we just decide which one of these comes first.

Elissa Baldwin: Our next question is, do doctors need to do genetics and genomics testing before they choose a treatment that is best for the patient.

Dr. Jonas Paludo: Excellent question. The short answer it depends on what cancer we're dealing with. The long answer is that, if I consider lymphoma, for example, for most lymphomas, we don't have to have a genetic testing done at the beginning of the treatment. But as we move along and as we go along in other treatments are required; a genetic testing can be helpful in helping us select the next treatment.

Now there are so many lymphomas, for example, and I'm going to use Waldenstrom macroglobulinemia or lymphoplasmacytic lymphoma, as a good example where our genetic tests may come into play. Sometimes some of these lymphomas, some of Waldenstroms, have mutation on a gene called MYD88. And that is a genetic test or mutation that can help us decide which treatment to use next. If we're going to use, for example, a BTK inhibitor treatment or not.

So that's one of the few examples where our genetic testing may be helpful at the beginning of the treatment. But, most of the other lymphomas, you don't need to have one at the beginning, but as you move along, as you get more treatments and you go on between two or three, four

lines of therapy, that's when a genetic testing may be helpful to help us find a specific target that we can use a treatment for. Now, that is not common and sometimes we don't find a specific target or specific marker on genetic testing, but usually, when we do one it will be a little later in the treatment course.

Elissa Baldwin: Our next question is regarding side effects. Do all of the newer treatments have less side effects than traditional chemotherapy?

Dr. Jonas Paludo: Good question and the short answer to that is no. So, new drugs or new treatments, do not always have less side effects than older drugs. Again, sometimes, we are often looking for a new treatments, because they work in a different way, because they work after other treatments have failed and sometimes, they come with more side effects. We have CAR T-cell therapy as a good example, is one of the very new treatments it comes with a lot of side effects or quite significant side effects that require intense monitoring.

But we still use them and they are still very effective, because they can, they're very active against cancer. So, it's always a balance. When your treatment comes along, it's a balance between how active and how effective they are and how much side effects they produce, or they cause. Another point I want to make to this question is, and they hear this very often. Now, we have a lot of treatments for cancer these days, that are in the form of a pill, that you can take every day. And sometimes, there is a misconception that just because you're taking a pill that it's easier or have the less side effects than an IV drug or IV chemo therapy. That's not always the case. Even some oral medications that we use today may have as much side effects as older drugs that are used IV. They're just, they're just different.

Elissa Baldwin: Our next question: How do I know if these types of treatments are approved for my type of lymphoma? Aren't there many types of non-Hodgkin lymphoma?

Dr. Jonas Paludo: Yes. that's an excellent question. There are probably more than 60 to 70 types of non-Hodgkin lymphoma. You can think of them as a big family, you have close relatives and you know further out relatives. Some of those non-Hodgkin lymphomas are more similar to each other and they may be treated with the same drugs. And some non-Hodgkin lymphoma are more different in each other and they may not be able to treat with the same drugs.
Now, so you can, I mean one way that you can find which drugs are approved or not, the FDA website [fda.gov], cancer.org website, the LLS website [LLS.org], have information about which drugs may be approved for a cancer or not. But at the end of the day, there's so many types of non-Hodgkin lymphoma. There's so many different drugs and treatments, including can be improved in the last few years, that the best is to rely on your doctor and your physician that has been updated on that information.

Elissa Baldwin: Next question. Are there clinical trials still open that are testing these treatments that you spoke about?

Dr. Jonas Paludo: Absolutely, there are several clinical trials still open and looking at those treatments, at these types of treatments and in different treatments. For example, there are other types of bispecific antibodies that I didn't mention today that are currently being investigated in clinical trials. There are other types of immunotherapy agents like bispecific antibodies, antibody drug conjugates, monoclonal antibodies, CAR T-cell therapies that are still being investigated in clinical trials. Including, for example, CAR T-cell therapies, that are not autologous that doesn't come from the same patient back to the same patient. So, there are including other clinical trials looking at other drugs that work in different ways, not necessarily with the immune system, but there are several trials open still looking at drugs like this.

Elissa Baldwin: Thank you. It looks like radiation therapy is one of the oldest treatments, but it is still part of my treatment regimen. Has it been changed during the years to be more efficient?

Dr. Jonas Paludo: Absolutely. So, radiation therapy has changed a lot in the last 120 years. Especially the way that is delivered in a more precise way. In the past, radiation therapy used to be given at higher doses in bigger areas, which was causing more side effects and more complications. There are different types of radiation therapy today, especially different types of delivering of the radiation therapy today in a more precise and focused area, so that you minimize toxicity and side effects. And also different types of radiation therapy provide even more precise and delineated area of treatment.

If we're trying to spare important organs, for example, if you have a tumor next to your heart or another important area, to try to avoid a radiation therapy to do any damage. So, several different improvements have been made, especially in the last three decades, two to four decades, that's when we were used to be really has made quite a significant number of advancements.

Elissa Baldwin: Thank you. Our next question: will CAR T-cell therapy replace stem cell transplants in the future?

Dr. Jonas Paludo: Excellent question. I don't, I don't know yet. We don't know yet. There have been a few studies comparing CAR T-cell therapy directly against in stem cell transplant. I think the results will be available later in the year at the ASH [American Society of Hematology] annual meeting in December this year, so I don't have the results. I don't know yet, but I guess the jury's out there. We'll find out soon.

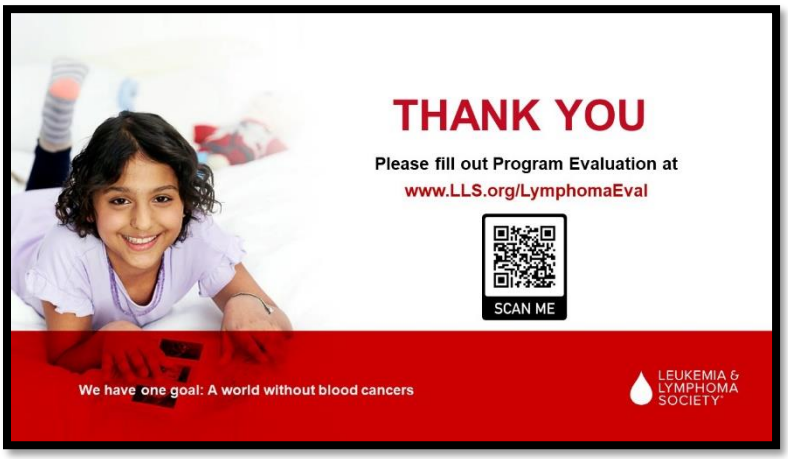
Elissa Baldwin: And now for our final question of the program: where do you see the future of lymphoma treatment headed?

Dr. Jonas Paludo: I think, if I just look at it, if I think about a timeline of cancer driven development and, as we can see that most of the new drugs and treatments have been developed in that they are somewhat related to the immune system. I think in the future and the future of treatment cancer and lymphoma treatment, will be probably more focused on immunotherapeutic agents, so treatments that work with your immune system to fight cancer

cells. So, I imagine we're going to be moving towards that direction in the future. I don't think chemotherapy drugs will ever be forgotten. I think they also have a role in how to treat cancer patients, but will probably want to be putting more focus on immunotherapy.

Elissa Baldwin: A special thank you again, Dr. Paludo, for sharing your expertise with us, and for your continued dedication to cancer patients.

If we were not able to answer your question during this program, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9am to 9pm ET.



We also encourage you to please complete the program evaluation, which can be found at LLS.org/LymphomaEval or by scanning the QR code on your screen with your smartphone. Completing the evaluation will help us to continue to provide the engaging and informative programming that would benefit you the most.

Dr. Paludo, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for watching this program. Take good care.