Slide 1: CAR T-CELL THERAPY AND BLOOD CANCERS

Slide 2: WELCOMING REMARKS

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society I'd like to welcome all of you. We have over 6,000 people participating from across the United States, as well as over 25 other countries. Thank you so much for joining us today.

Dr. Keren Osman from the Tisch Cancer Institute at Mount Sinai Hospital in New York will be discussing the advances in CAR T-cell therapy for blood cancers.

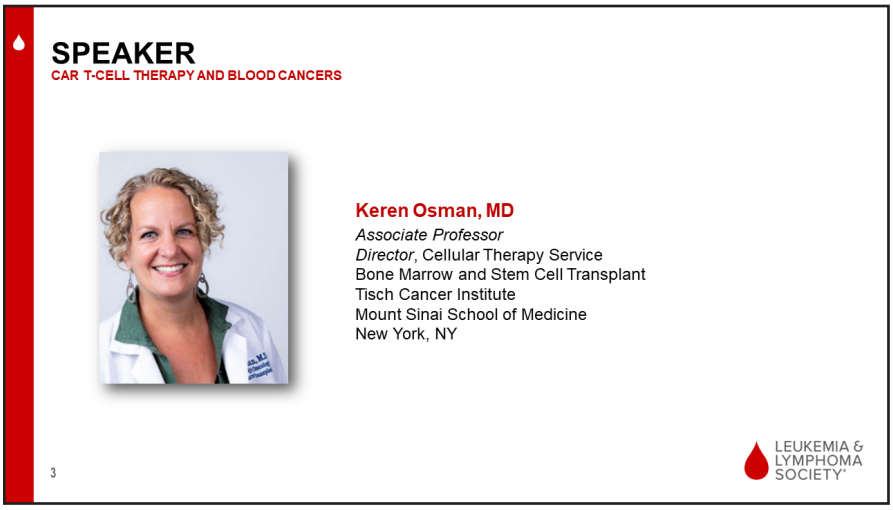
The Leukemia & Lymphoma Society funds leading edge research for every type of blood cancer, including leukemia, lymphoma, myeloma, MDS, MPNs, and other rare types of blood cancers. As the largest nonprofit funder of cutting-edge blood cancer research to advance cures, LLS has invested more than $1.6 billion dollars in cancer research since we started in 1949, leading to breakthroughs in immunotherapy, genomics, and personalized medicine that are improving and saving the lives of patients. In the last 6 years, LLS has helped advance more than 70% of the 110 blood cancer treatment options approved by the FDA.

LLS helps you navigate cancer treatment and ensures that you or your loved one has access to quality, affordable, and coordinated care.

Research will help us achieve an end to cancer. In the meantime, patients and caregivers need help before, during, and after a cancer diagnosis. LLS is the leading nonprofit that does just that.

Please continue to inform us of what you need during this time and please continue to let us be here for you.

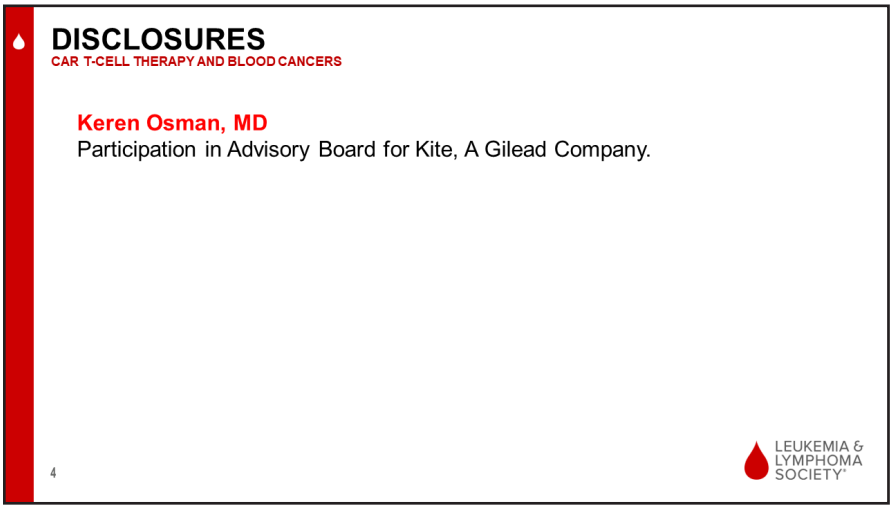
For this program we would like to acknowledge and thank Allogene Therapeutics; Bristol Myers Squibb; CRISPR Therapeutics; Janssen Oncology and Legend Biotech; Kite, a Gilead Company; and Novartis Oncology for their support of this program. I'm now pleased to introduce Dr. Osman, Associate Professor and Director of the Cellular Therapy Service, Bone Marrow and Stem Cell Transplant at the Tisch Cancer Institute at the Mount Sinai School of Medicine in New York, New York. Dr. Osman, I'm privileged to turn the program over to you.



Slide 3: FACULTY

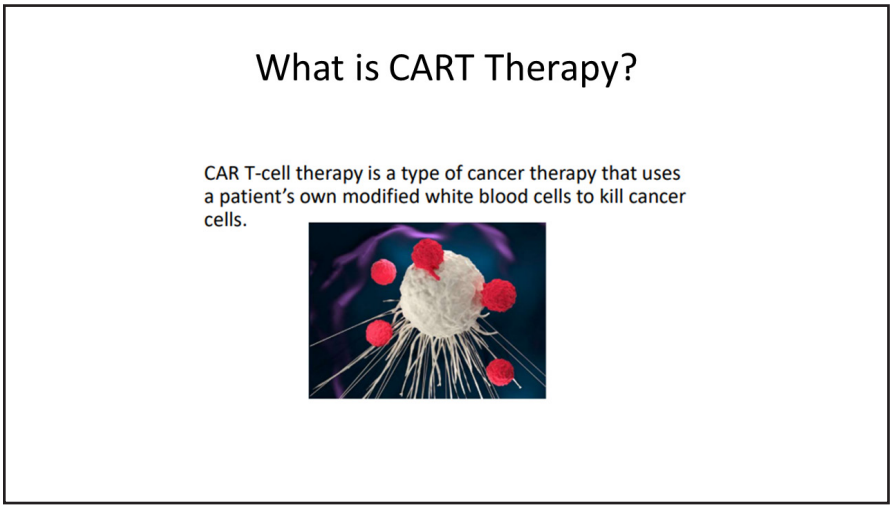
Dr. Keren Osman:

Thank you and thank you for inviting me to speak to everybody. We're going to be speaking about CAR T-cell therapy for blood malignancies today.



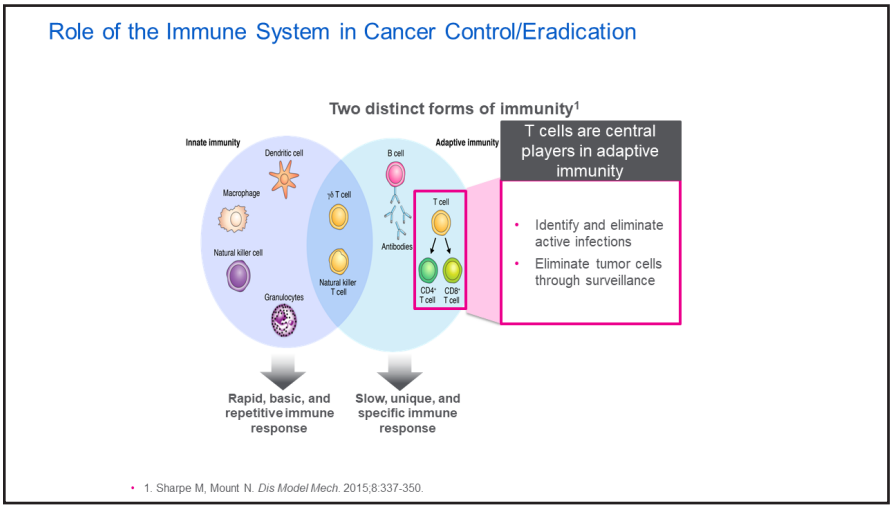
Slide 4: DISCLOSURES

My only disclosure is that I have participated in advisory board for Kite in the past.



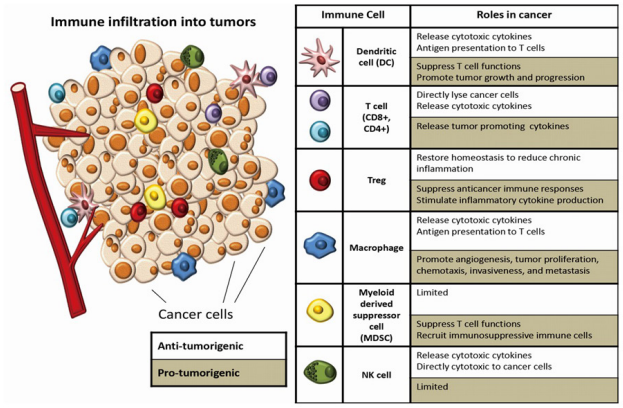
Slide 5: WHAT IS CART THERAPY?

The first question is really, What is CAR T-cell therapy? And the most simple way to put it is that CAR T-cell therapy is a type of cancer therapy that uses the patient's own white blood cells in order to kill cancer cells. But in order to understand how we got to this place, I want to kind of go back and speak about why this even ever came up as an idea or a treatment that we could use for cancer.



Slide 6: ROLE OF THE IMMUNE SYSTEM IN CANCER CONTROL/ERADICATION

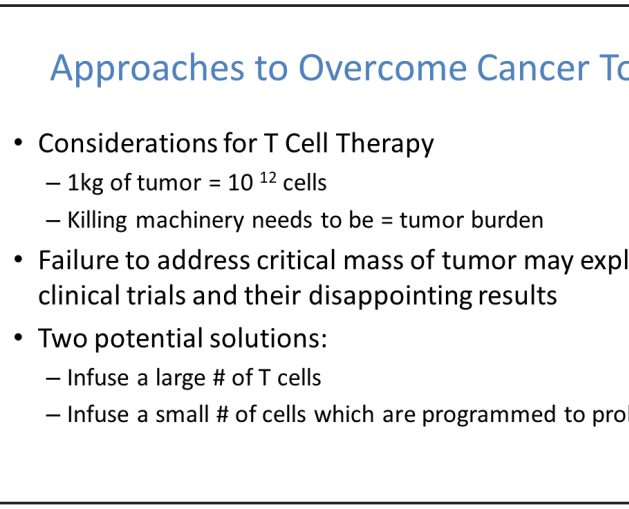
So, we know through many, many years of research that the immune system plays a very important role in cancer control and eradication. If you think about the immune system, there are really 2 major kinds of distinct forms of immunity, what we call innate immunity and what we call adaptive immunity. Innate immunity is something that happens quickly and is a repetitive immune response characterized by certain cells that you may have heard if you're getting treatment for cancer, in particular the granulocytes, or your doctor may refer to them as neutrophils. The other arm of the immune system is what we call the adaptive immune system and that is made up of B cells and T cells. These cells' job is to make antibodies, so you make an antibody against, let's say, COVID-19 or any other viral infection, either through vaccination or through previous exposure, and the T cells' job is to actually kill, whether it's microorganisms or in the case of what we're going to talk about today, they actually play an important role in eliminating tumor cells through surveillance.



Immune Cell		Roles in cancer
	Dendritic cell (DC)	Release cytotoxic cytokines Antigen presentation to T cells
		Suppress T cell functions Promote tumor growth and progression
	T cell (CD8+, CD4+)	Directly lyse cancer cells Release cytotoxic cytokines
		Release tumor promoting cytokines
	Treg	Restore homeostasis to reduce chronic inflammation
		Suppress anticancer immune responses Stimulate inflammatory cytokine production
	Macrophage	Release cytotoxic cytokines Antigen presentation to T cells
		Promote angiogenesis, tumor proliferation, chemotaxis, invasiveness, and metastasis
	Myeloid derived suppressor cell (MDSC)	Limited
		Suppress T cell functions Recruit immunosuppressive immune cells
	NK cell	Release cytotoxic cytokines Directly cytotoxic to cancer cells
		Limited

Slide 7: IMMUNE INFILTRATION INTO TUMORS

The interplay between the immune system and cancer is very important and that is that the immune system can regulate cancer by identifying it and eliminating, but the cancer cells are themselves quite brilliant at also influencing the immune system to tolerate them. So here in this slide you can see that the role of the T cells is to directly lyse (breakdown) cancer cells and release toxic cytokines in order to kill tumor cells. But tumor cells can actually evolve and force T cells to release actually tumor-promoting cytokines, in other words, molecules that will promote and help the growth of tumor cells. And as we go down this list you can see that the immune system can be both antitumorigenic, in other words, stopping the growth of cancer, but can also facilitate the growth of cancer cells. And so, the challenge to us as oncologists and immunologists is to try to figure out how to move the immune system into the category in which it will actually eliminate cancer and not promote its growth.



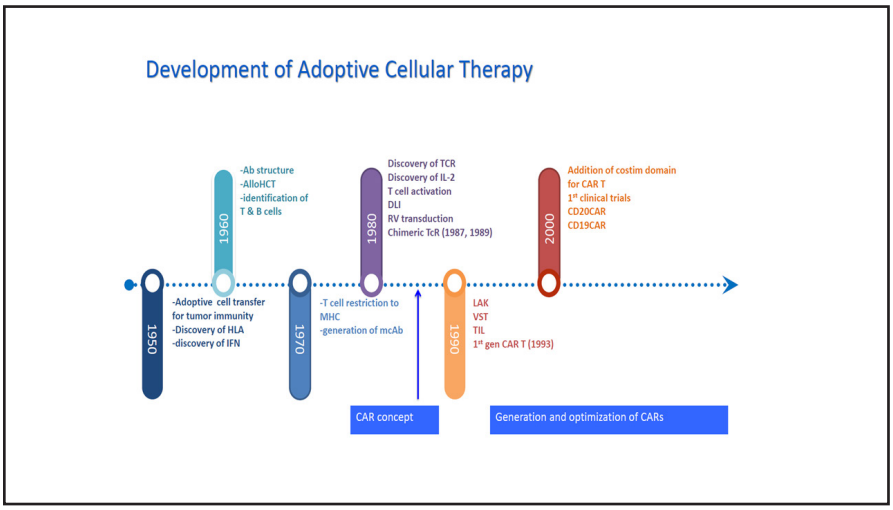
Slide 8: APPROACHES TO OVERCOME CANCER TOLERANCE

So, as a bone marrow transplanter and as somebody who has studied immunology, over the years people have really tried to figure out what are the approaches to actually overcome cancer tolerance, in other words, to push the immune system to kill cancer as opposed to help it grow.

There were many considerations for T cell therapy. If you think about a kilogram of tumor that is 10^{12} cells, that's a lot of cells. We know that the killing machinery needs to be somewhat equivalent to the tumor burden. However,

the failure to address this critical mass of tumor may explain why certain clinical trials in the past have had really disappointing results. If you give a cancer vaccine or you give certain other immune therapies in small numbers, you're not able to eliminate what is a really large amount of tumor.

One of the potential solutions was to infuse a really large number of T cells, however, that is a very difficult thing to do. The idea for CAR T-cells came about with the idea of infusing a very small number of T cells, but that those T cells would be programmed to proliferate and to grow and to sort of takeover in the immune system of the cancer patient.

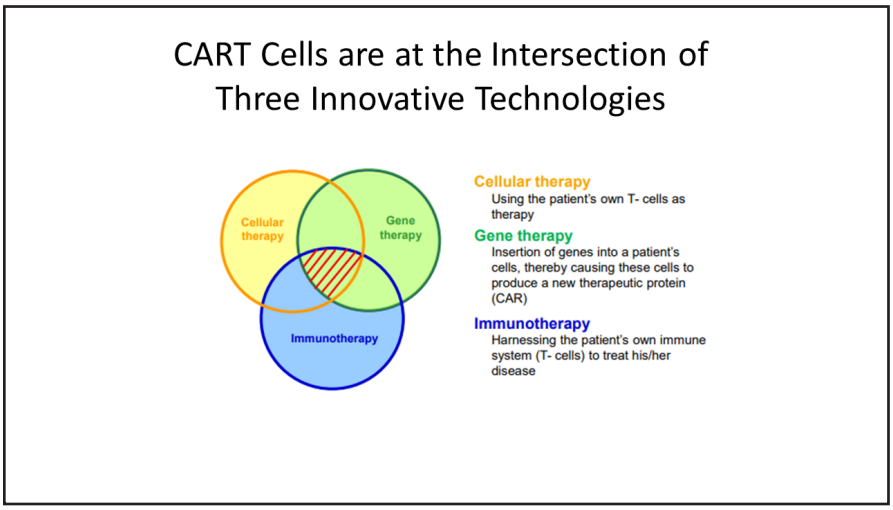


Slide 9: DEVELOPMENT OF ADOPTIVE CELLULAR THERAPY

In this slide I'm showing the kind of evolution of how we have thought about cellular therapy since the 1950s. CAR T-cells didn't emerge out of nowhere, they've kind of been something that has evolved over time as we have all struggled with the idea of how to move the immune system to fight cancer. So in the 1950s that is when we discovered HLA (human leukocyte antigen) antigens, which for any of you who have had an allogeneic stem cell transplant, you know that is an important matching criteria for making allogeneic transplants.

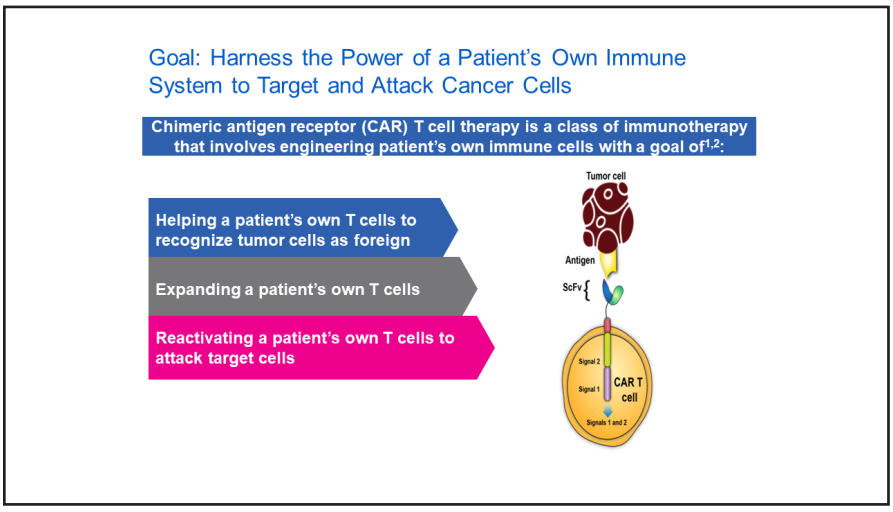
In the 1960s is when we began to do allogeneic transplants and we began to identify the role of T and B cells in fighting cancer in the immune system. In the 1970s we discovered and were able to create monoclonal antibodies, which are now used very often in the treatment of certain malignancies. You may be familiar with such monoclonal antibodies as rituximab and daratumumab, so the idea for monoclonal antibodies was really born in the 1970s.

The idea for a chimeric antigen receptor concept really came about in the late 80s, early 90s, and the first generation CAR T-cells were designed in the 90s. We really only began to test them in patients sometime in the early 2000s. And now we are optimizing them and expanding them for use in many different malignancies.



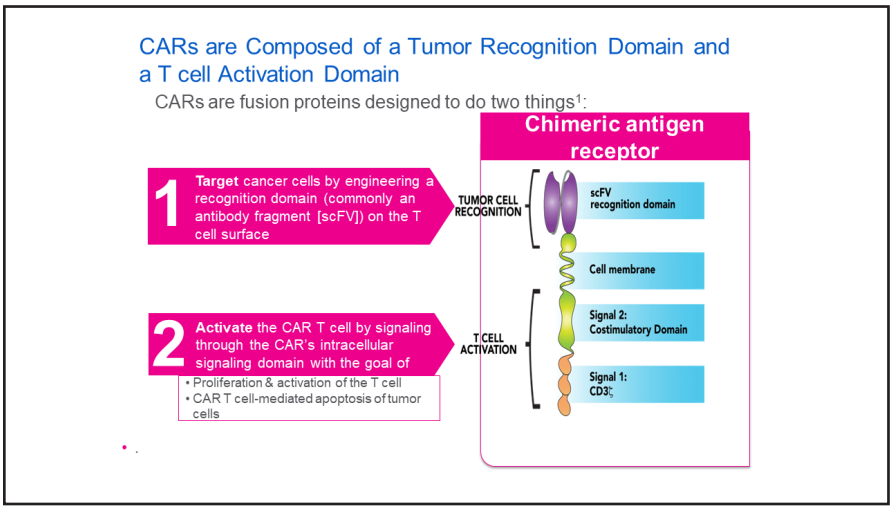
Slide 10: CART CELLS ARE AT THE INTERSECTION OF THREE INNOVATIVE TECHNOLOGIES

So, to kind of understand where it fits in the process of immune and innovative technology, CAR T-cells are really kind of at the intersection of 3 major innovative technologies in the treatment and in the use of the immune system to treat cancer. Cellular therapy is using the patient's T cells as a therapy. Gene therapy, which many of you may have heard of, is a way of inserting genes into patients' cells and then changing the way that those cells behave, and make the cells produce a new protein. And immunotherapy is a way of harnessing the patient's own immune system to treat his or her disease.



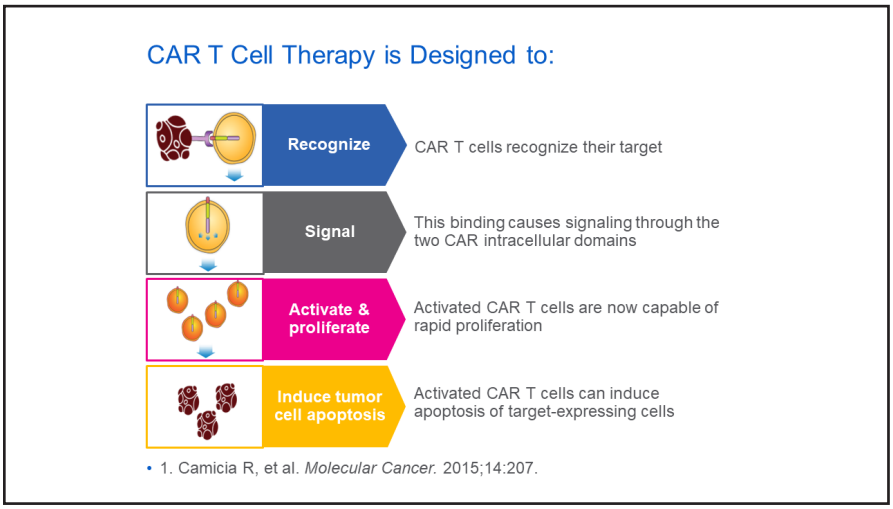
Slide 11: GOAL: HARNESS THE POWER OF A PATIENT'S OWN IMMUNE SYSTEM TO TARGET AND ATTACK CANCER CELLS

So the goal of the CAR T-cell is to harness the power of the patient's own immune cell to attack, to target and attack cancer cells. And this is a cartoon that shows you how the CAR T-cell is set up. It is a T cell which has a B cell antigenrecognizing protein on it that allows the T cell to recognize the tumor cells as foreign, and through what we call a costimulatory domain, allows the expansion of the patient's own T cells and activates them to target cancer cells.



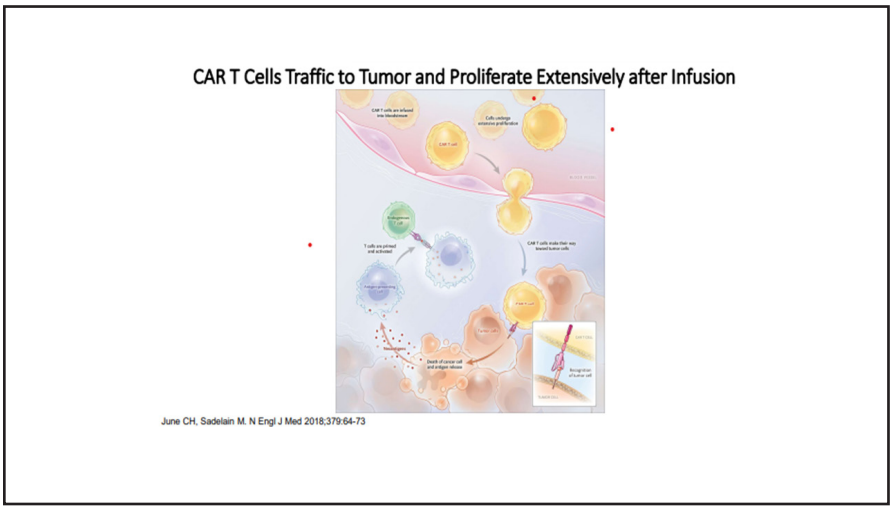
Slide 12: CARS ARE COMPOSED OF A TUMOR RECOGNITION DOMAIN AND A T CELL ACTIVATION DOMAIN

A kind of up-close look at this structure shows you that at the very top where the number 1 is, is this tumor cell recognition domain, commonly known as an antibody fragment on the T cell surface. This is something that is normally on the B cell and is what allows the B cell to recognize antigens and to make antibodies. That is a link through the membrane of the T cell and there is what we call costimulatory domain. And then, if you look at number 2, once that links to the tumor antigen, to the protein, abnormal protein on the surface of the tumor cells, it activates the CAR T-cells by signaling through the intracellular signaling domain with the goal of making those T cells proliferate, in other words, make many, many, many more of them and cause death of the tumor cell.



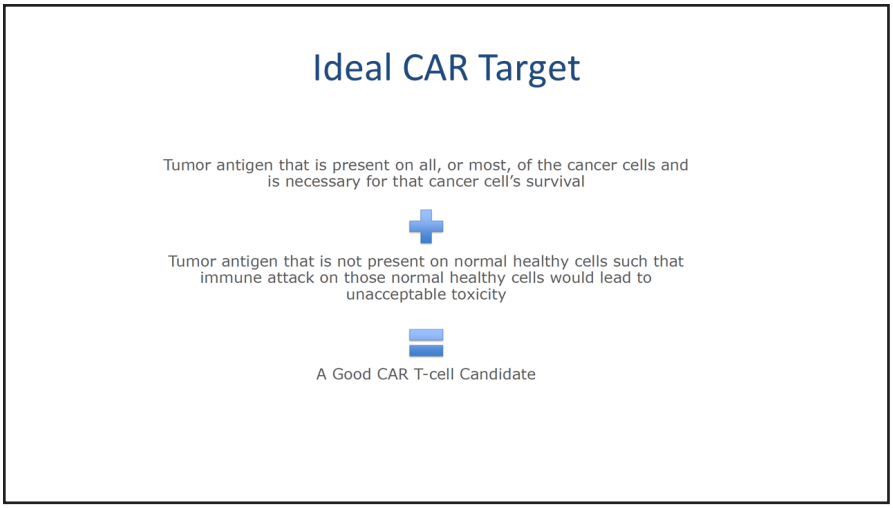
Slide 13: CAR T CELL THERAPY IS DESIGNED TO:

The CAR T-cell therapy is therefore designed for the tumor, for the CAR T-cells to recognize the target, the binding then causes signaling through the intracellular domain, the activated CAR T-cells are now capable of proliferating very rapidly, and cause death or what we call apoptosis of the cells that express the target, in other words, the cancer cells that express that very particular tumor antigen.



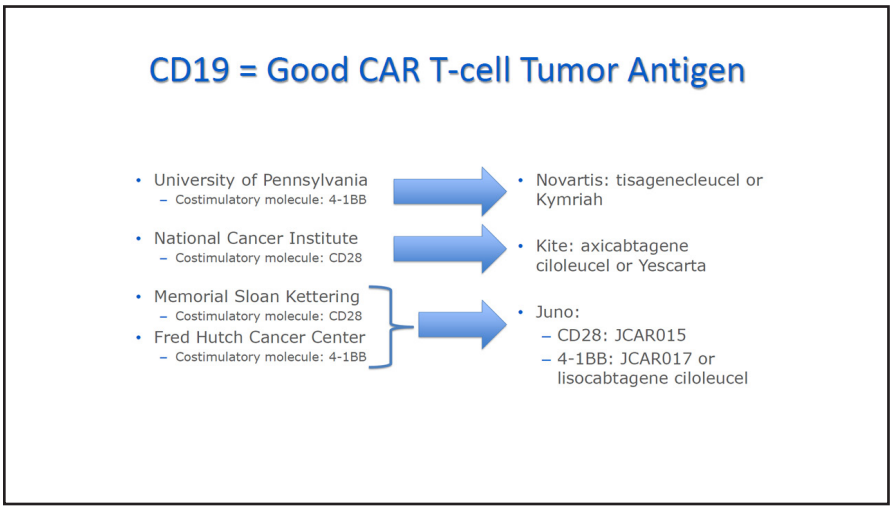
Slide 14: CAR T CELLS TRAFFIC TO TUMOR AND PROLIFERATE EXTENSIVELY AFTER INFUSION

This is a cartoon showing you how CAR T-cells traffic to the tumor and proliferate after infusion, and so you can see the CAR T-cell there, moving through the bloodstream to where the tumor is engaging, and therefore destroying and killing the tumor cell.



Slide 15: IDEAL CAR TARGET

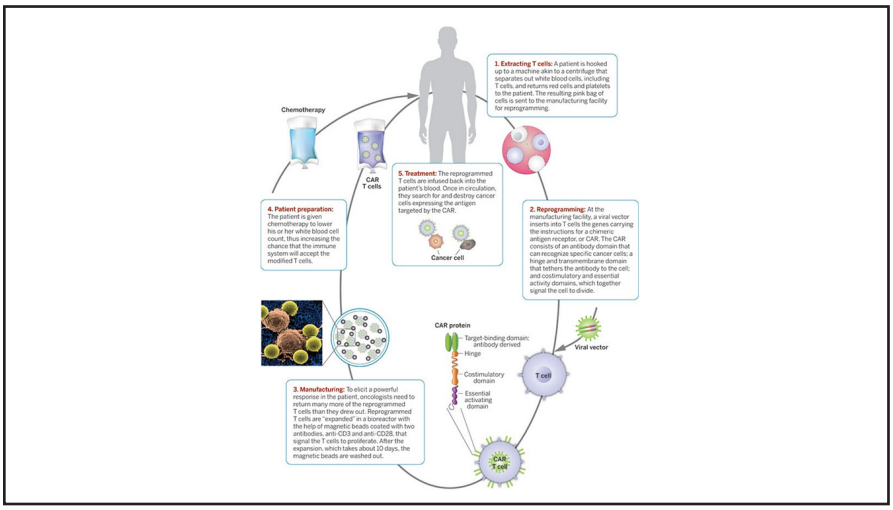
So now that we've spoken about what they are and how they work, how do we figure out which are the kind of tumors that would benefit from CAR T-cells? Well, the tumor antigen has to be present on all or most of the cancer cells that are responsible for the cancer cells' survival. That means that there has to be something on the surface of the tumor cell that makes it recognizable to the T cell, to the CAR T-cell, and that is important for its growth and proliferation. That special antigen should be pretty unique to the tumor cell and therefore not present on normal healthy cells, so that when the immune attack happens we don't also destroy normal healthy cells in the patient's own body. And so the combination of those 2 factors would make a perfect candidate for targeting by CAR T-cells.



Slide 16: CD19 = GOOD CAR T-CELL TUMOR ANTIGEN

The first antigen that was identified as an excellent CAR T-cell antigen was CD19. Here you can see all the different hospitals and scientific institutes that targeted CAR T-cell against CD19. CD19 we know is present on B cells, both present on cells for patients who have ALL (acute lymphoblastic leukemia) and also for patients who have various types of lymphomas and we will speak about that a little bit later.

The University of Pennsylvania developed the very first one in conjunction with Novartis, called Kymriah® (tisagenlecleucel), and it was first tested for ALL in children. The National Cancer Institute developed Yescarta® (axicabtagene ciloleucel) with the company Kite, and then in a combination of Memorial Sloan Kettering and Fred Hutchinson Cancer Center, they developed, liso-cel (Breyanzi®) through a company called Juno. All CAR T-cells directed against CD19.



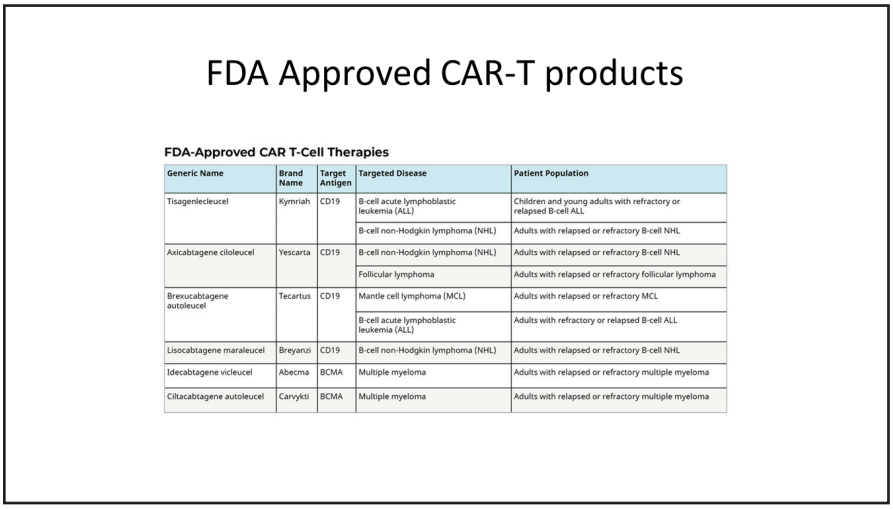
Slide 17: UNTITLED

Okay, so how do we then make these cells for patients? The very first step is to extract T cells from the patients themselves. The patient is hooked up to a machine that looks like a dialysis machine or a centrifuge and that is called T cell harvest. For anybody who's had stem cells collected, it's a very similar process except that there is no need in this particular situation to mobilize, in other words no injections are needed, it is a collection that happens over one day, not over multiple days, and does not require any special preparation for the collection of the T cells.

Once the T cells have been collected, those are shipped to the manufacturing facility by the hospital that is treating the patient, and that facility then introduces what we call a viral vector, this is the part of this process that is like gene therapy that enters into the T cell and tells the T cell to begin to make these other CAR T proteins. Then over this period of time, this reprogramming or viral induction causes the T cells to have the CAR T protein expressed on their surface.

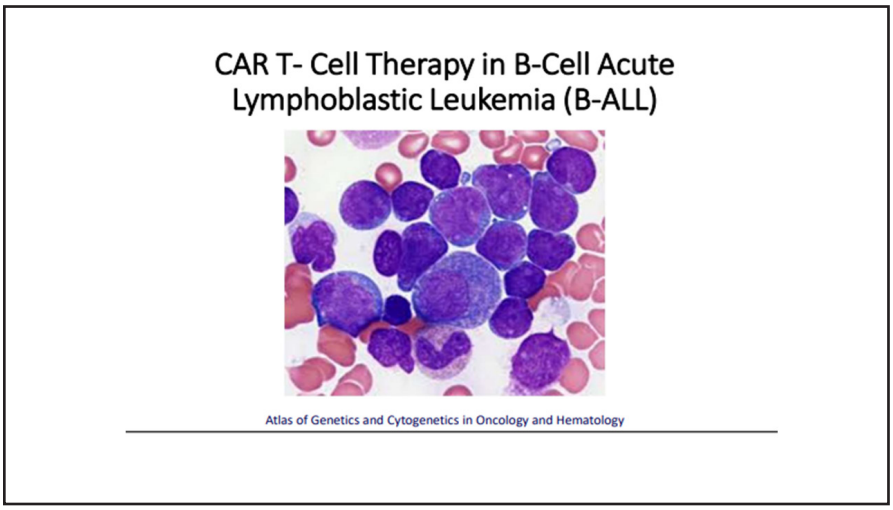
Then comes the portion of manufacturing where the CAR T-cells are then kind of taught to make a powerful response within the patient's body. They are grown, cell culture is done, and certain cytokines (proteins) are added in the culture medium, to make sure that the cells will be viable and able to respond to the patient's own tumor.

At that point the manufacturing facility will usually contact the hospital and let them know that the cells are ready and when the cells arrive in the center or are shipped, that is when the physicians and nurses begin to prepare the patient to receive the CAR T-cells. The patient preparation has to do with reducing the number of normal T cells in the patient's body through a mild chemotherapy that we sometimes refer to as lympho-depleting chemotherapy. It's almost always the same combination of drugs that is given to the patients, and that is only to change the ratio of the number of T cells that are in the patient and allows for the new infused CAR T-cells to be kind of the dominant T cells. Once the lympho-depleting chemotherapy is given, usually 2 days after that, the CAR T-cells are then infused and then we wait for them to do their job.



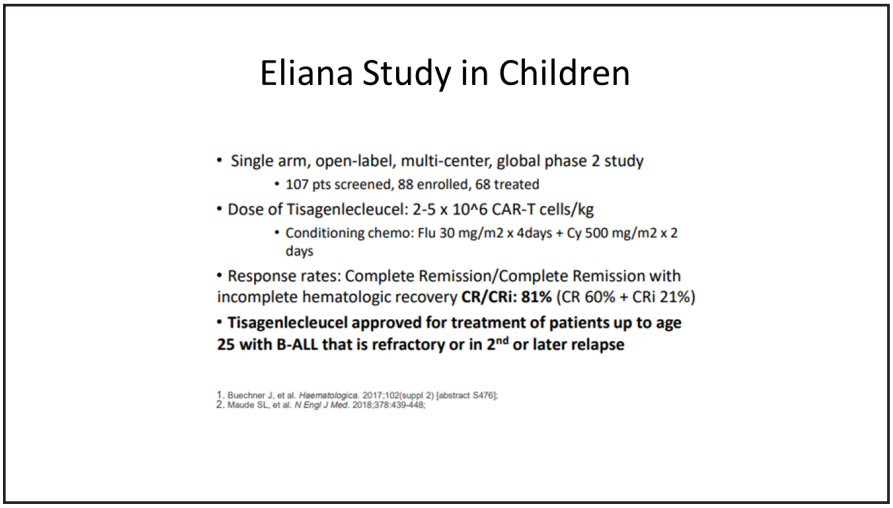
Slide 18: FDA APPROVED CAR-T PRODUCTS

Currently we have FDA approved CAR T products for multiple different diseases. We have FDA approved products for B cell ALL, for B cell non-Hodgkin's lymphoma, those are the Kymriah CD19 CAR T-cells. We have Yescarta, which is approved also for B cell non-Hodgkin's lymphoma, and for follicular lymphoma. We have Tecartus® (brexucabtagene autoleucel), which also targets CD19, which is FDA approved for mantle cell lymphoma and for B cell ALL in adults. Liso-cel, as we spoke about, is also a CD19 directed product approved for adults with relapsed/refractory B cell non-Hodgkin's lymphoma. And we have 2 products which are approved for the treatment of multiple myeloma, Abecma® (idecabtagene vicleucel) and Carvykti™ (ciltacabtagene autoleucel).



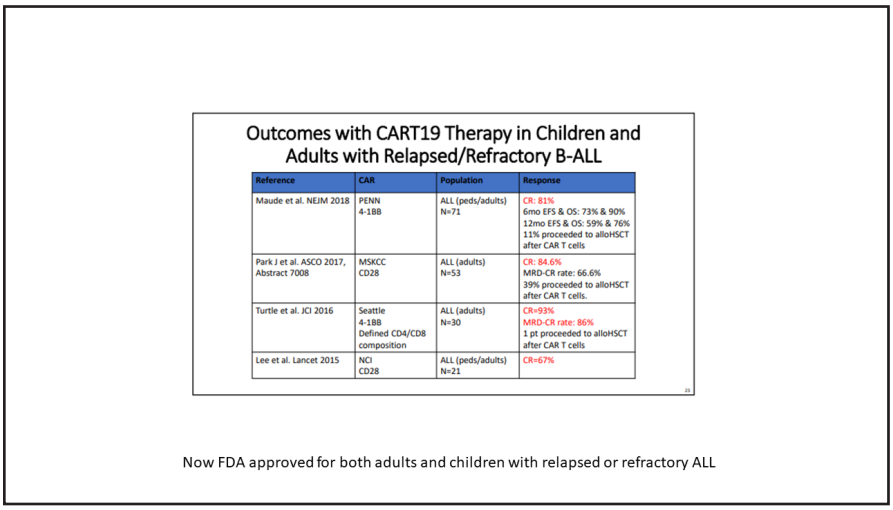
Slide 19: CAR T-CELL THERAPY IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL)

Just to give you a background on all of the different ones, the first CAR T-cells that were approved for use in humans were those for B cell acute lymphoblastic leukemia.



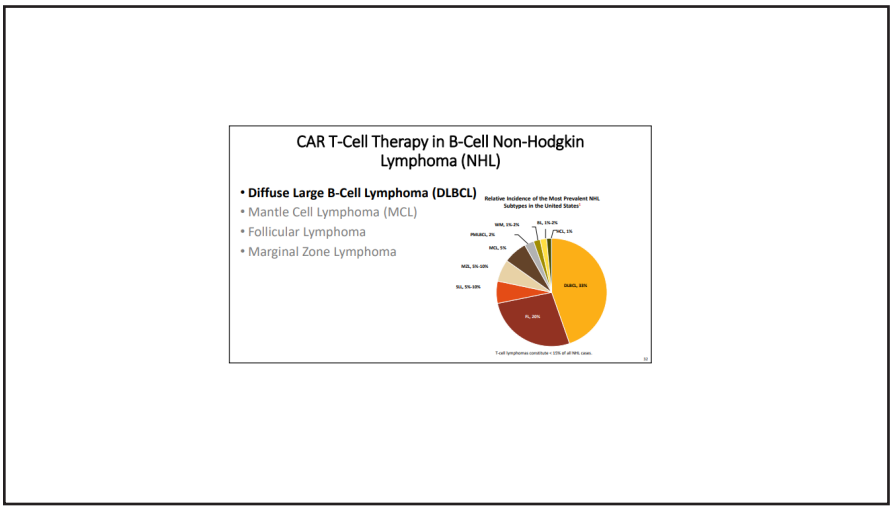
Slide 20: ELIANA STUDY IN CHILDREN

The first approval was actually for children with B cell ALL. And that was a landmark study called the Eliana Study that was done in children: 107 patients were screened, 88 were enrolled, 68 patients were treated, the dose was 2 to 5 times 10^6, so about 2 million cells per kilogram with what we call lympho-depleting chemotherapy, fludarabine (Fludara®) and Cytoxan® (cyclophosphamide) which is really pretty much identical for use in all CAR T-cells. The response rate for patients who had relapsed, especially children after allogeneic transplant, was extraordinarily high. The total response rate with remission was 81%, with a complete response of 60%, and almost complete response of 21%. And therefore, it was approved for children up to age 25 with B cell ALL that was refractory or in second or later relapse. This really was able to save the life of many, many children who had ALL.



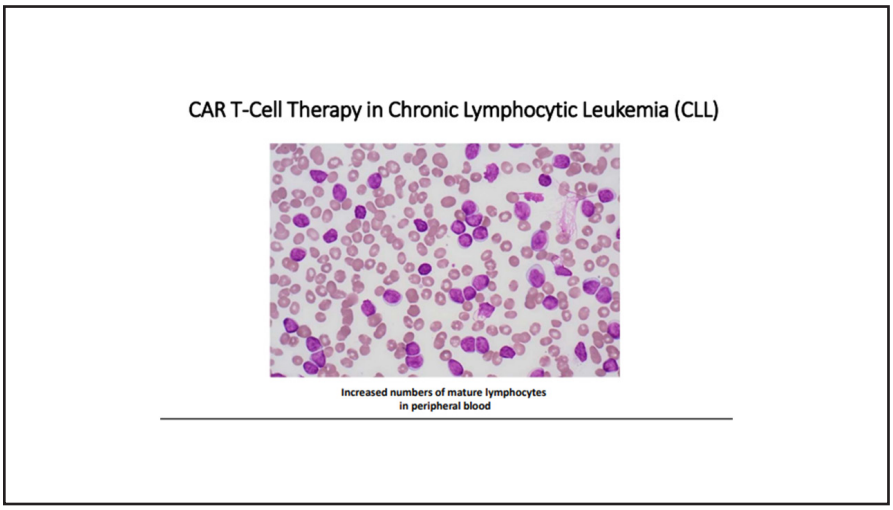
Slide 21: OUTCOMES WITH CART19 THERAPY IN CHILDREN AND ADULTS WITH RELAPSED/REFRACTORY B-ALL

Because we knew that the target was CD19, this technology then became expanded to other diseases. And here you see that the CD19 therapy in children was then also studied in adults. The reason it took so much longer for the FDA approval to happen in adults was because luckily, it's a very, very rare disease, but many different centers reported on this and therefore CD19-directed therapy is now also approved for adults with relapsed/refractory B cell ALL.



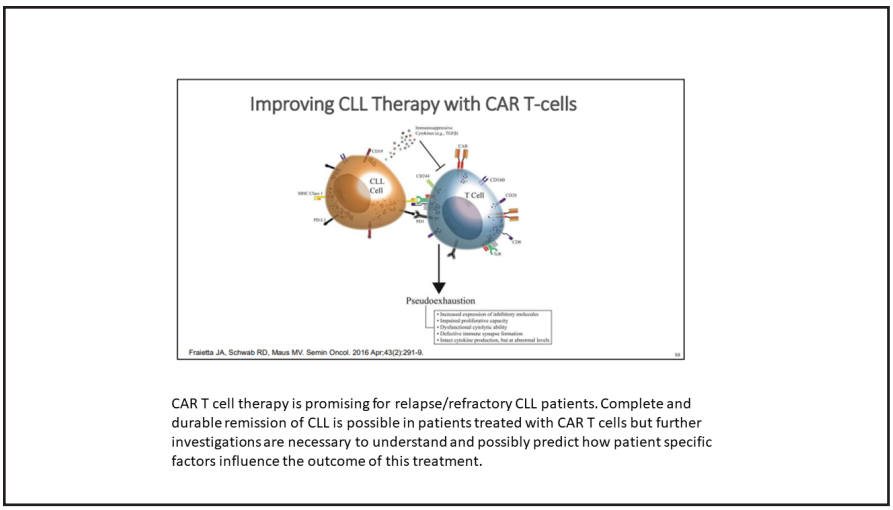
Slide 22: CAR T-CELL THERAPY IN B-CELL NON-HODGKIN LYMPHOMA (NHL)

CD19 is also expressed on different types of lymphoma because they come from the B cells which are very, very similar to the B cells that cause ALL. And so over the last several years, CAR T-cells have now been FDA approved for treatment in B cell non-Hodgkin's lymphoma, and diffuse large B cell lymphoma was the first indication for CD19-directed cells. That was followed with approval for mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma. So currently, you can see in this pie chart how many different types of lymphoma comprise the non-Hodgkin's lymphomas and how many of those lymphomas have the FDA label for the use of CAR T-cells in those various diseases.



Slide 23: CAR T-CELL THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

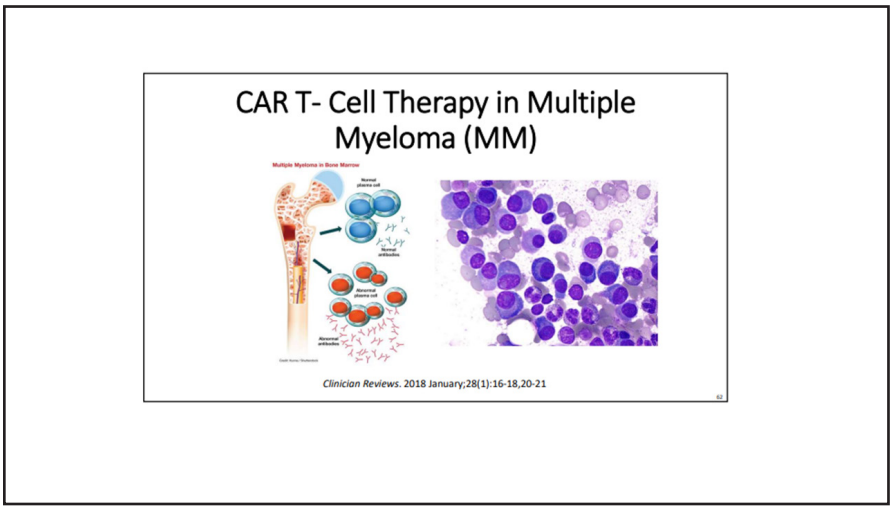
Another disease that also expresses CD19 is chronic lymphocytic leukemia (CLL). CAR T-cells are not yet FDA approved for patients with chronic lymphocytic leukemia except those who had CLL which then transformed into diffuse large B cell lymphoma through a mechanism called the Richter's transformation.



CAR T cell therapy is promising for relapse/refractory CLL patients. Complete and durable remission of CLL is possible in patients treated with CAR T cells but further investigations are necessary to understand and possibly predict how patient specific factors influence the outcome of this treatment.

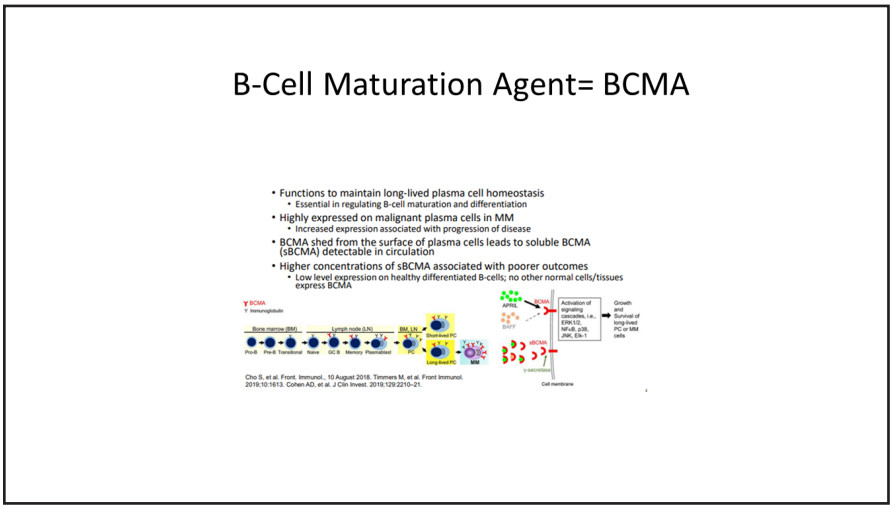
Slide 24: IMPROVING CLL THERAPY WITH CAR T-CELLS

However, it is important to know that because they express a very similar surface protein to all the lymphomas, CAR T-cell therapy currently appears very promising for patients with relapsed/refractory CLL, and we believe the complete and durable remission of CLL is possible for patients who are treated with CAR T-cells. However, many of these are still in clinical trials and still under investigation, so this is not yet FDA approved for CLL. I'm sure it's coming soon, but is not here yet.



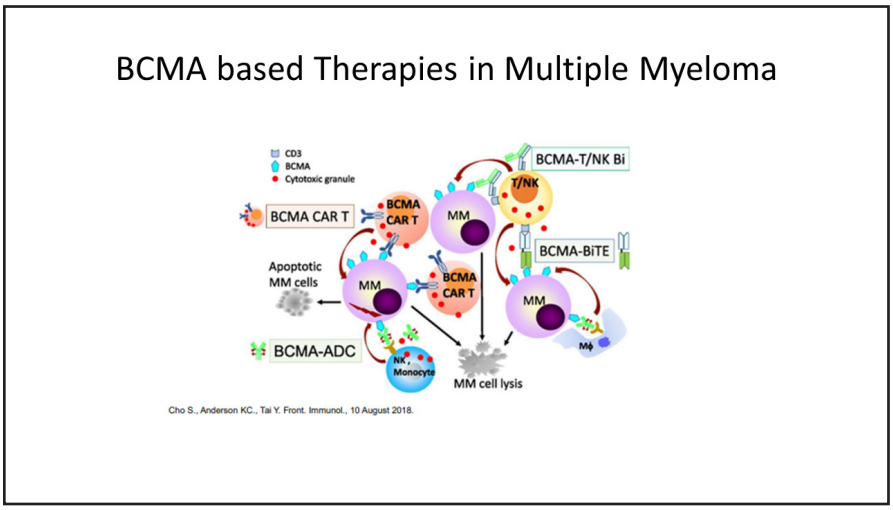
Slide 25: CAR T-CELL THERAPY IN MULTIPLE MYELOMA (MM)

Finally, CAR T-cells have recently been FDA approved for the treatment of multiple myeloma.



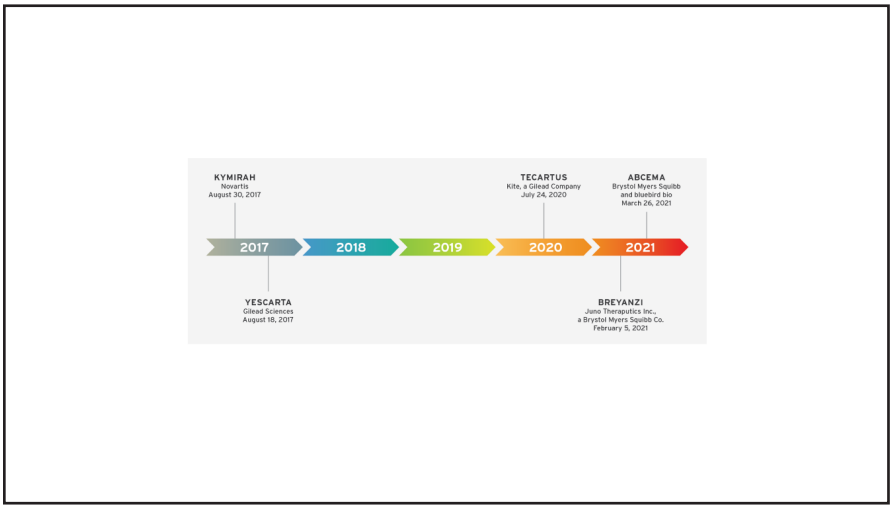
Slide 26: B-CELL MATURATION AGENT = BCMA

Here the target is completely different than in ALL and in diffuse large B cell lymphoma. Here the target for both of the FDA approved agents is something called BCMA, B cell maturation agent. That target is an important target for multiple myeloma cells because it functions to maintain the plasma cell homeostasis, and it is very important in regulating B cell maturation and differentiation. Like I told you in the beginning of the talk, the important thing about a CAR T target is it has to be highly expressed on the malignant cell, and in fact BCMA is highly expressed on malignant plasma cells in multiple myeloma, and the more BCMA you have it appears that increased expression is also associated with progression of disease. It can be found in the circulation because it's shed from the surface of plasma cells, and high concentrations of BCMA, can be associated with poorer outcomes. So similar to the CD19, BCMA is very important for the survival of multiple myeloma cells and makes an excellent target for the treatment of multiple myeloma.



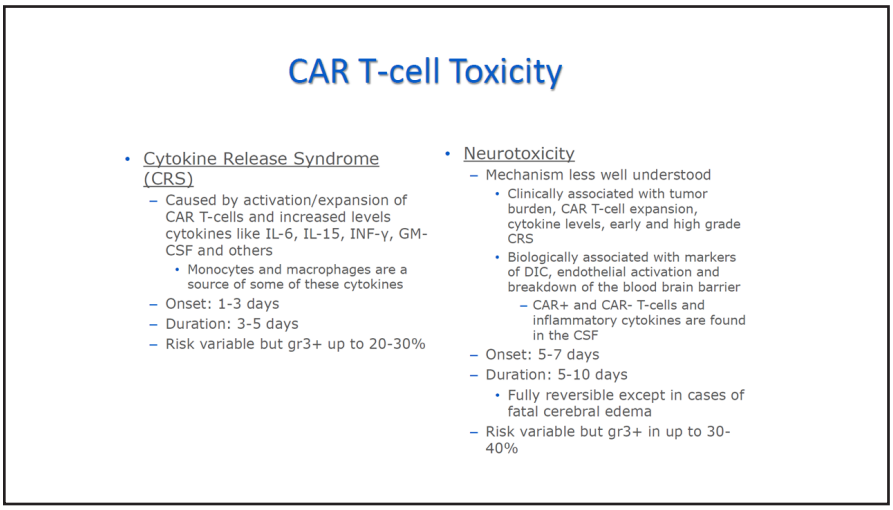
Slide 27: BCMA-BASED THERAPIES IN MULTIPLE MYELOMA

This is a cartoon showing you how there are many BCMA-based therapies in multiple myeloma. Currently there are 2 BCMA CAR T-cells that are approved for treatment in patients with relapsed/refractory multiple myeloma. We will not talk about NK (natural killer) cells or BiTE (bispecific T-cell engager) therapies or ADCC (antibody-dependent cellular cytotoxicity), but those are other immunotherapies that are also targeted against the BCMA protein in multiple myeloma.



Slide 28: UNTITLED

So just to give you a sense of the timeline, Novartis started trials and was approved for use in childhood ALL in August of 2017. Shortly thereafter, Yescarta did clinical trials and was approved for the treatment of diffuse large B cell lymphoma. Clinical trials went on from 2017 through 2020 in all of these diseases, and eventually Tecartus was approved as therapy for adult ALL. The 2 agents for multiple myeloma were approved in 2021. And so, this gives you kind of a sense of how many agents we have and the timeline of the approval.

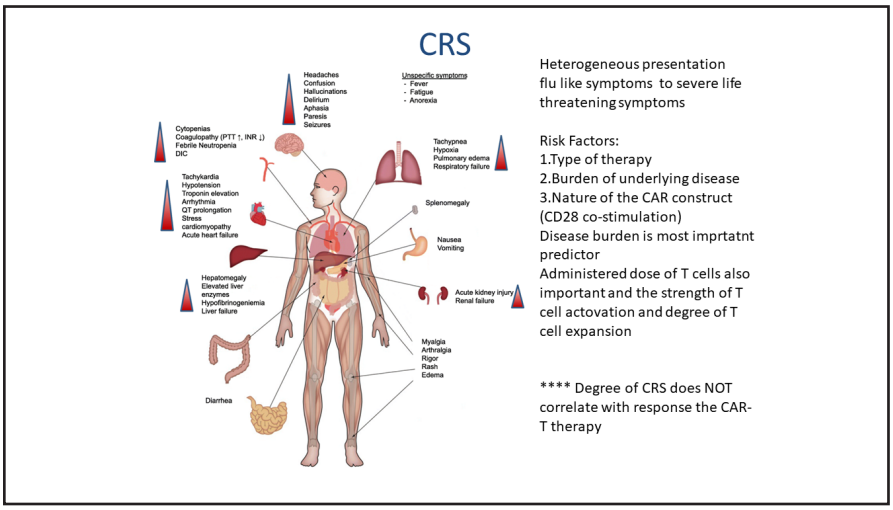


Slide 29: CAR T-CELL TOXICITY

Okay, so we all now understand that CAR T-cells are effective and FDA approved for multiple different diseases, but they are not without their toxicity. You may have heard that there are 2 major toxicities we have to take into account when using CAR T-cells. The first is something called cytokine release syndrome (CRS). This is caused by the activation of the CAR T-cells and the production of increased levels of certain cytokines. Those are called IL-6, IL-15, interferon gamma, GM-CSF (granulocyte-macrophage colony-stimulating factor), and others. These are coming from monocytes and macrophages which are in the circulating blood. This is a very, very similar process to what happens when you get an infection. When you get an infection you can get fever, you can get rapid heart rate, you can get flushing, you can get rash, and that is because of the inflammatory milieu in which your immune system is fighting an infection. When you're giving CAR T-cells to patients who have active malignancy and the CAR T-cells begin to work, one of the side effects can be this cytokine release syndrome, in which the patient really feels like they have a really terrible flu. Usually they don't have a runny nose, but they'll have a very prominent inflammatory response. In most cases the onset is within the first couple of days of receiving the therapy, although the truth is that depending on the different products and the different disease state of the patient, the onset can be anywhere from 1 to 3 days or sometimes even a little bit later.

If a patient develops cytokine release syndrome, the duration can last anywhere from 3 to 5 days or only maybe 1 day. And the risk is variable, but if you take all products together probably it's about a 20 to 30% chance of getting cytokine release syndrome in patients who develop CAR T-cells.

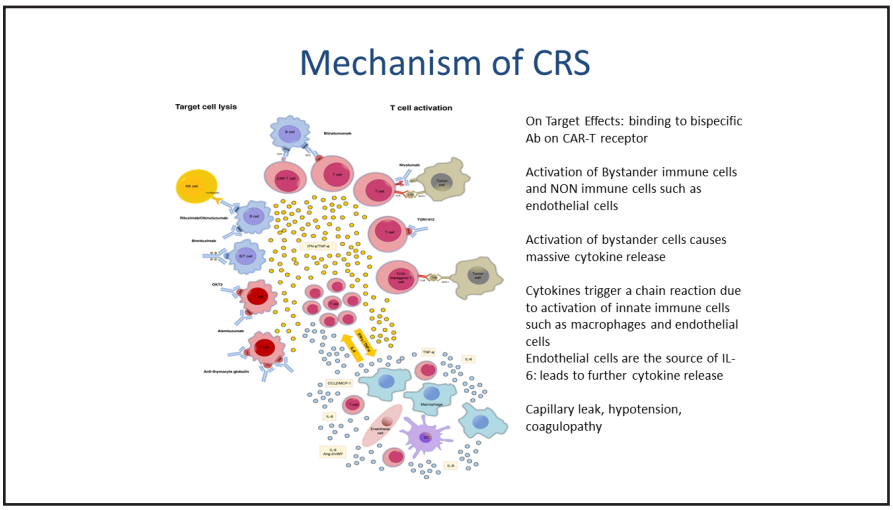
The other major toxicity that we worry about is something called neurotoxicity. Here we don't really understand what the mechanism is, but we do know that it's associated with a very high tumor burden with the CAR T-cell expansion, much like in cytokine release syndrome, and probably is associated with certain inflammatory markers. Usually this happens after CRS happens, several days later, and it is considered fully reversible. Depending on the product that is used, the risk can be up to as high as 30 to 40%.



Slide 30: CRS

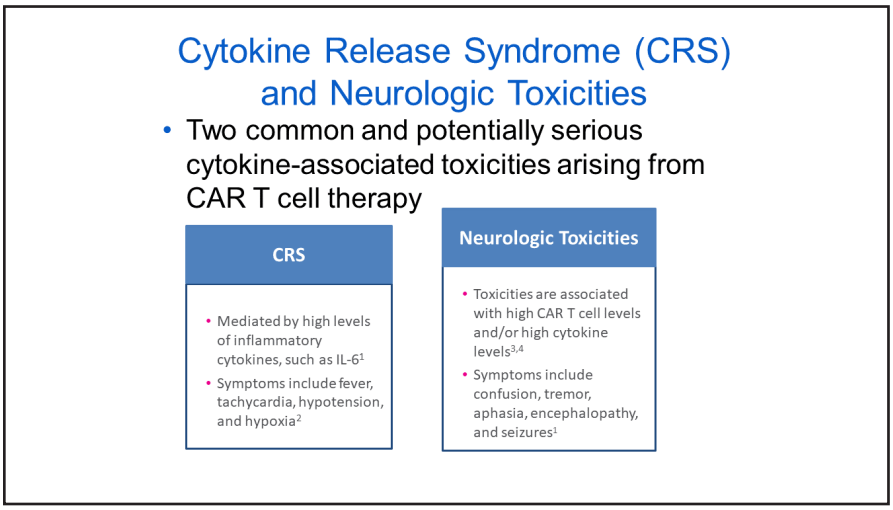
Here you see a cartoon of all the different organ systems that can be affected by cytokine release syndrome. As I said, it's a heterogeneous presentation, it can appear in many different ways from anywhere, from something as mild as flu-like symptoms to severe life-threatening symptoms. The risk factors for getting CRS are the type of therapy that you're getting, in other words, which different kinds of CAR construct you're getting, how much tumor you have before you get the CAR T-cells, and we believe perhaps have to do with the dose of the T cells that are being given and the strength of the T cell activation.

What's very important to remember and a lot of patients worry about this, is whether the degree of CRS correlates with how well the CAR T-cells work. And I'm here to tell you that there is no correlation. The correlation is only between how much tumor there is and the number of cells infused and how effective the costimulatory molecules of those cells. Just because you don't get CRS when you get CAR T-cells does not mean that you're not going to have a complete response to the CAR T-cells.



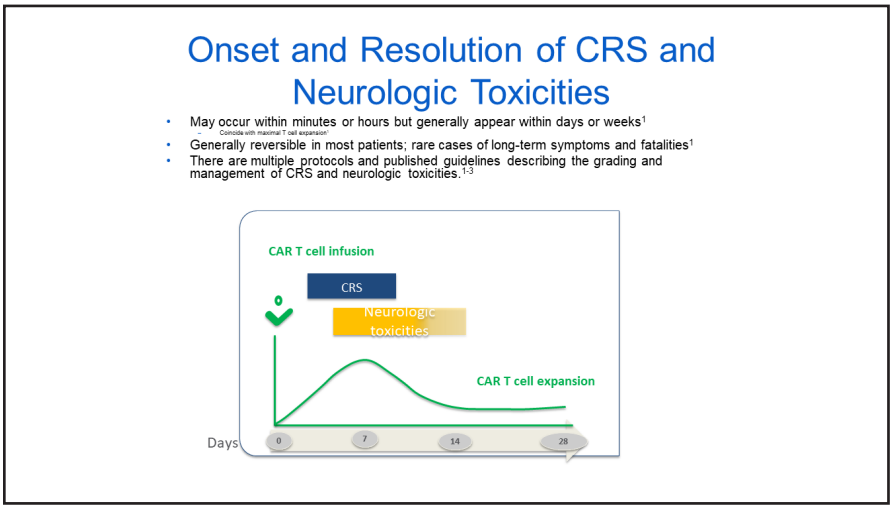
Slide 31: MECHANISM OF CRS

This is on a sort of smaller and cellular level, what we believe happens. Basically there are the on target effects, which is where the CAR T-cell receptor binds the antibody on the tumor cell, but then what happens is that there's activation of other immune cells and non-immune cells through this inflammatory process. This causes activation of bystander cells and then release of the cytokines in a chain reaction, which causes the cytokine release syndrome.



Slide 32: CYTOKINE RELEASE SYNDROME (CRS) AND NEUROLOGIC TOXICITIES

As I said, there are 2 common and potentially serious toxicities that come from the use of CAR T-cells. What happens is that CRS is mediated by high levels of inflammatory cytokines, one of the most important ones is the cytokine called IL-6. There are symptoms, like I said, that include things like fever, tachycardia, hypotension, maybe low oxygen. The neurologic toxicities that are associated with high CAR T-cell levels may include things like confusion, tremor, we use the word aphasia, which means inability to speak, encephalopathy, which is confusion, and sometimes also patients are at risk for developing seizures.

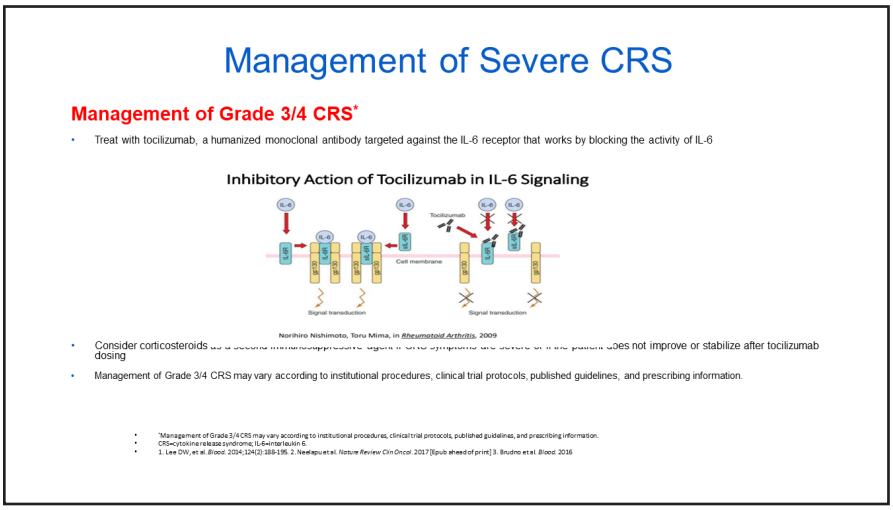


Slide 33: ONSET AND RESOLUTION OF CRS AND NEUROLOGIC TOXICITIES

This is a timeline which shows you what the sort of common timeline is of CRS and neurotoxicity. And this is one of the reasons that we monitor patients in the hospital for about 2 weeks after we give them CAR T-cell therapy. It's really so that we can manage these 2 toxicities. It really has very little to do with fighting the tumor itself.

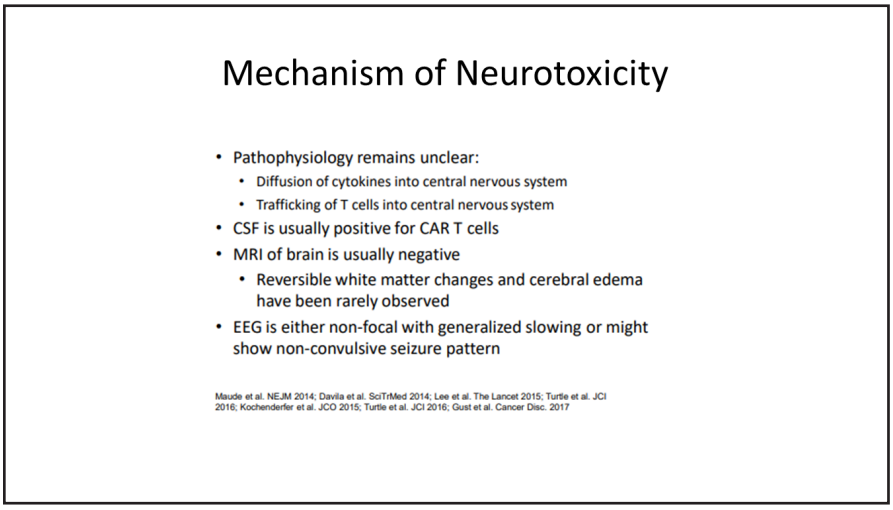
CRS can happen within minutes to hours, but usually takes a couple of days. The neurologic toxicities are reversible in what I have seen for almost all patients. Although there may be some long-term effects, which we're really only learning about now. In the early days of clinical trials some patients actually died of neurologic toxicity, but I haven't seen that in many, many years, now that we've gotten much better at managing these.

And there are multiple different protocols and guidelines which continuously are under revision to kind of describe the grading and the management of both cytokine release syndrome and neurologic toxicity.



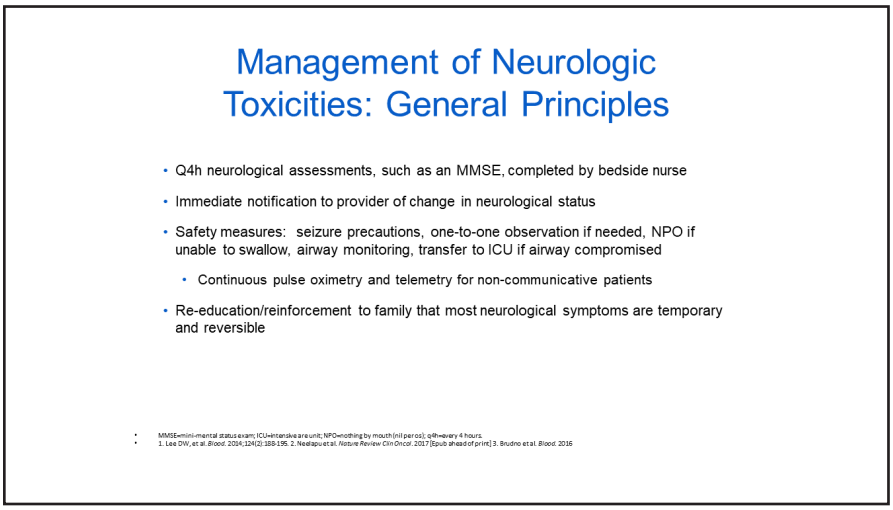
Slide 34: MANAGEMENT OF SEVERE CRS

The management of severe cytokine release syndrome is that first we treat with a drug called tocilizumab (Actemra®), which is also a monoclonal antibody, targeted against the IL-6 – IL-6 receptor, so that it blocks the activity of IL-6, which is the most prominent cytokine that is released during the time of cytokine release syndrome. We also can give steroids safely after the use of IL-6, if the patient doesn't respond to tocilizumab alone. There are many different institutional procedures, but in general those are the 2 drugs that we use most commonly for severe CRS.



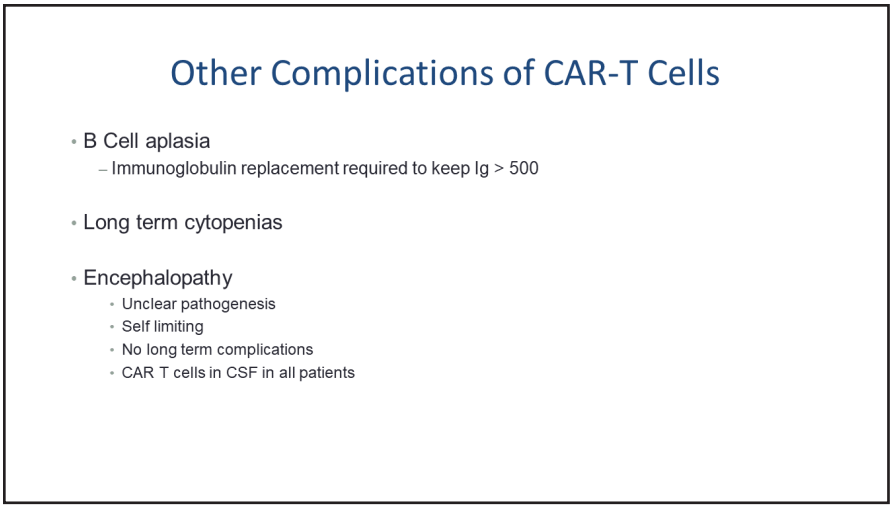
Slide 35: MECHANISM OF NEUROTOXICITY

The same thing happens with neurotoxicity. We don't understand why patients develop it, but we believe that probably there are these cytokines that are circulating into the blood also diffuse somehow into the central nervous system. There probably also are some of these CAR T-cells that exist in the spinal fluid around the brain. When you take out the spinal fluid and look at it under the microscope you can find the CAR T-cells in the spinal fluid. If you do an MRI of the brain of a patient with neurotoxicity, usually don't see anything significant. And you can do what's called an EEG (electroencephalogram), looking for seizures, but usually doesn't also show much in the way of information.



Slide 36: MANAGEMENT OF NEUROLOGIC TOXICITIES: GENERAL PRINCIPLES

However, we do treat patients very aggressively who are either at risk for neurologic toxicities or begin to develop them. We check the patients every 4 hours with neurologic assessments if we have any suspicion that that's happening. We immediately ask the nurses to notify the physicians, and we take a lot of safety measures. So we give seizure precautions to the patients so that they don't develop seizures. We observe them, usually with putting a nurse into the room with one-to-one. We make sure that they're not eating at the time when they develop some confusion so that they don't have the risk of choking. We monitor their airway. And if they really are not well, we will transfer them to the ICU so that they're monitored very carefully. And while it's very scary for family members to see patients have neurologic toxicity, we have to continuously reassure people that it is reversible.

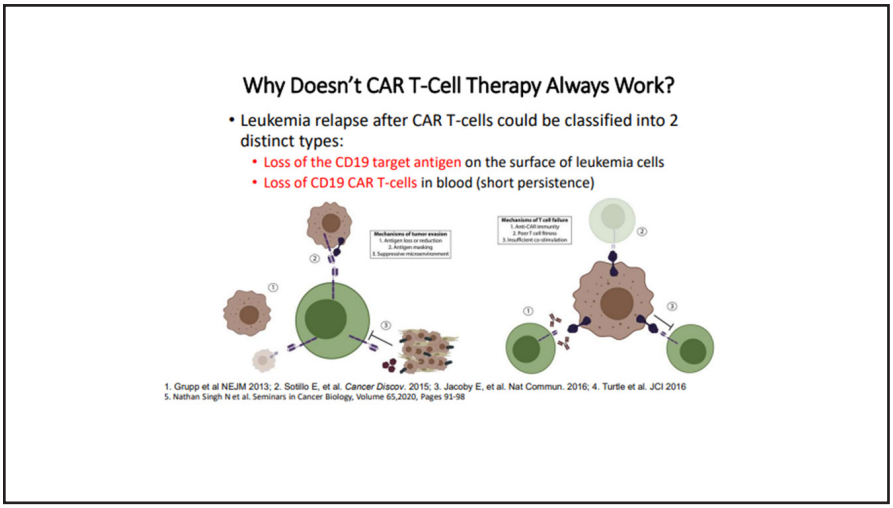


Slide 37: OTHER COMPLICATIONS OF CAR-T CELLS

In the long-term, patients also have other complications of CAR T-cells. One of the most common ones is what we call B cell aplasia. In other words, in the process of killing the B cell tumor, whether it's the ALL or the various different diffuse large B cell lymphomas or other lymphomas, some B cells stop producing immunoglobulins. And so for some months after the infusion of CAR T-cells, patients have what we call B cell aplasia, and therefore they need to have replacement with immunoglobulins. We monitor them very carefully after CAR T-cell infusion and replace the immunoglobulins with a drug called IVIG (intravenous immune globulin) for as many months as it takes.

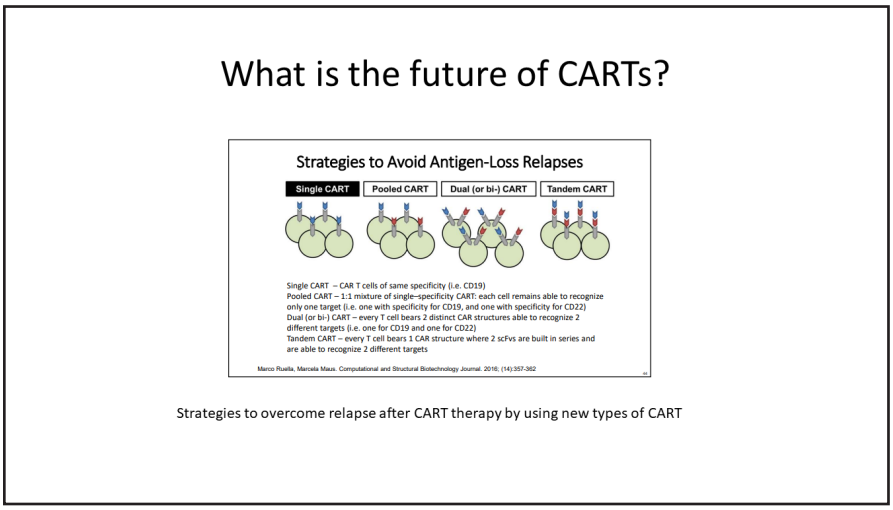
There's also now emerging much literature about long-term cytopenias. In other words, patients who get CAR T-cells maybe for months after receiving CAR T-cells can have very low blood counts, low white blood cell counts, low platelets, and may need a lot of support with things like Neupogen® or platelet transfusion or red blood cell transfusion after the use of CAR T-cells. This is something that we're still trying very hard to understand and we don't know what causes these long-term cytopenias. And the treatment for it is not easy. It's mostly supportive and very often it will go away, but in some cases for some patients this is a problem that lasts for years.

Finally, encephalopathy (abnormal brain function) is another long-term complication, which we don't understand why it happens, but it's probably related to the patient having had neurologic toxicity during the use of CAR T-cells. It's usually self-limiting in the sense that it goes away by itself and doesn't have any long-term complications but can be quite disturbing to the patients after CAR T-cell use.



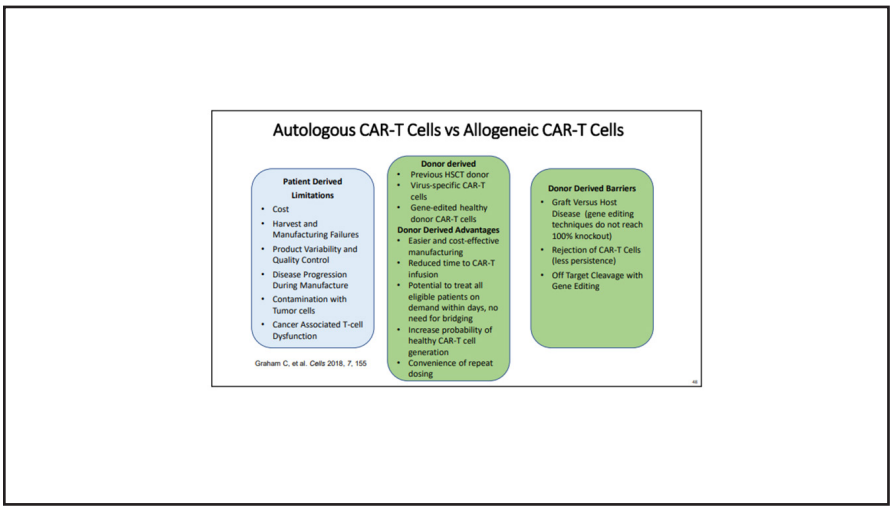
Slide 38: WHY DOESN'T CAR T-CELL THERAPY ALWAYS WORK?

Okay, we have to address the fact that CAR T-cells also don't always work. Some patients have relapsed after CAR T-cells and that is what we're understanding now is probably classified into 2 distinct reasons, either the CD19 target antigen goes away from the leukemia or lymphoma cells and therefore when you give the CAR T-cells they don't have anything to attack. Or, the CD19 CAR T-cells don't persist and live a long time in the blood. These are 2 theories as to why it doesn't always work and what to do about this is obviously something to think about in terms of what other therapies we should be developing if patients have relapsed after CAR T-cell.



Slide 39: WHAT IS THE FUTURE OF CARTS?

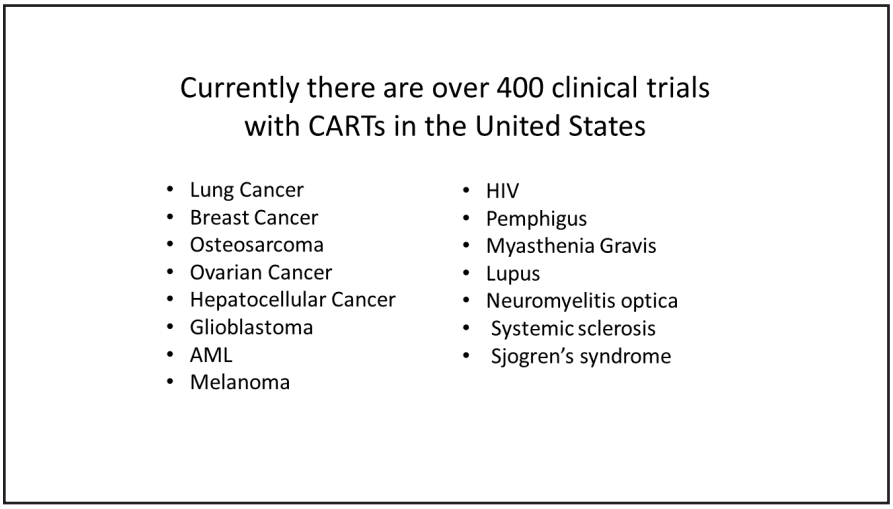
And so, what's the future of CAR T-cells because now we have a large armamentarium, but there are many more diseases. First we would like to develop some strategies to avoid antigen loss and to avoid relapse for those patients who get CAR T-cells but are at risk for it to relapse later. There are many different new strategies that are being developed. There are single CAR T-cells, there's a way of infusing pooled CAR T-cells, dual or bispecific CAR T-cells where there are different targets, tandem use, in other words, giving one and then giving a different one. All of these are strategies that are being developed and are in clinical trials to try to improve the efficacy of these CAR T-cells.



Slide 40: AUTOLOGOUS CAR-T CELLS VS ALLOGENEIC CAR-T CELLS

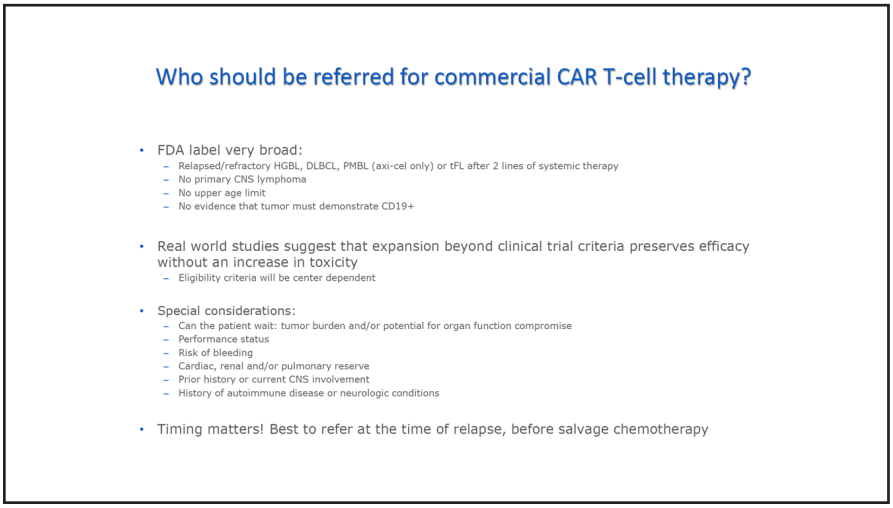
Finally, another strategy that is being developed is something called allogeneic CAR T-cells. That is what we would call an off-the-shelf product. One of the problems with autologous CAR T-cells is that it is based on the patients and the limitations for the patients. First you have to collect the patient's cells, then you have to wait for the manufacturing, and then you have to reinfuse them. The kind of downside of that is that there's this long period of time where if patients have a disease that is growing rapidly, sometimes they can't make it to get a CAR T-cell or their T cells because they've gotten so much chemotherapy, are not going to make excellent CAR T-cells. If you use off-the-shelf products from donors, healthy donors, you can use these T cells, infuse them with the same virus that you would for the patient and gene edit them, and essentially they are like a product, like a drug that you get off the shelf. However,

these have not been FDA approved yet and one of the reasons is that they take some time to perfect, and that they have some of their own risks, notably for those of you who are familiar with allogeneic stem cell transplant, there's still some risk of graft-versus-host disease that may happen. And in addition, because they are not the patient's own cells, there's also the risk of the patient rejecting these cells since they don't belong to them. So, these are currently in clinical trials and we don't really have data yet on how well they work and I'm sure that there will be many iterations for the use of allogeneic CAR T-cells in the future.



Slide 41: CURRENTLY THERE ARE OVER 400 CLINICAL TRIALS WITH CARTS IN THE UNITED STATES

In addition, currently there are over 400 clinical trials with CAR T-cells in the United States, just to give you a sense of how exciting this new technology is. Currently they're being tested in lung cancer, breast cancer, osteosarcomas, ovarian cancer, hepatocellular cancer, glioblastoma, AML (acute myeloid leukemia), and melanoma. They're also being tested in non-malignant diseases because, as it turns out, a lot of these targets are also important in viral diseases and in autoimmune diseases. Pemphigus, we have a clinical trial open here for that, myasthenia gravis, lupus. There was a very interesting publication in the *New England Journal* about treating lupus patients with CAR T-cells, systemic sclerosis, and Sjögren's syndrome. And so their uses are expanding significantly.

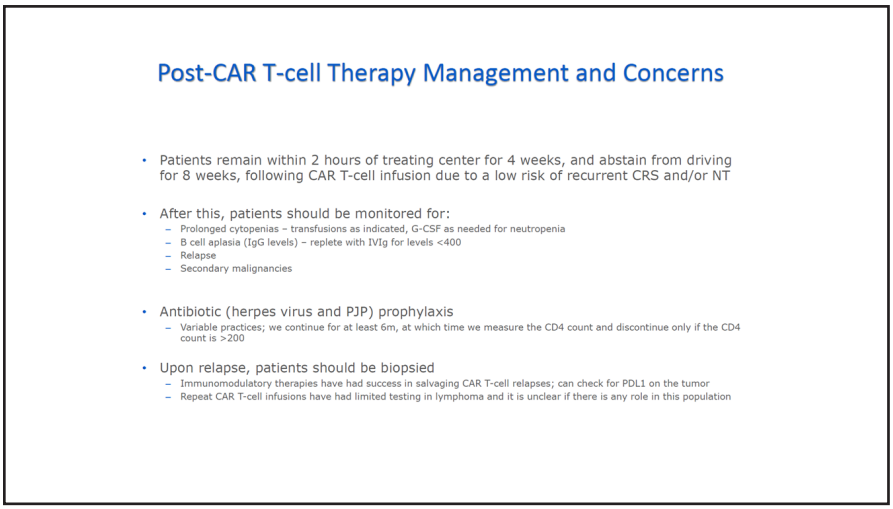


Slide 42: WHO SHOULD BE REFERRED FOR COMMERCIAL CAR T-CELL THERAPY?

So, who are the kind of patients that should be referred for commercial CAR T-cells? Like I said, the FDA label can be quite broad for relapsed/refractory non-Hodgkin's lymphoma, primary mediastinal B cell lymphomas that fail after 2 lines of therapy. Obviously for certain multiple myelomas where they relapse after 4 lines of therapy or 5 lines of therapy. At the moment we don't have any upper age limit as to who should or should not be referred for commercial CAR T-cells and for the CD19-directed therapies, there's no real need to stain those tumors to make sure that they express CD19 because we know that this will work in a lot of the lymphomas and leukemias, and so we don't routinely stain them.

The real-world studies suggest that there is excellent efficacy outside of the kinds of criteria that were used in clinical trials to get the FDA label and there are some special considerations that we need to think about when we first evaluate patients for CAR T-cells. Can the patient wait the period of time of manufacturing that it takes? What kind of good shape are they in and will they be able to tolerate getting something like cytokine release syndrome or neurotoxicity? What are their risks of bleeding, how good is their heart function, their kidney function, their lung function? Do they have prior involvement with CNS (central nervous system)? In other words, do they have a history of tumor in their brain, and is that going to increase their risk of getting neurotoxicity? And, do they have other history of autoimmune disease or neurologic conditions that may increase their risk of cytokine release syndrome and neurotoxicity?

From the point of view of somebody like myself, who's seen a lot of patients for CAR T-cells, timing matters. It's best to refer patients early on so that we can organize ourselves and decide if it's a good option for them before patients go on to get many different types of therapies that may make it very difficult for us to either collect their T cells or that they're so sick that we have to work really, really quickly to try to make the cells work.



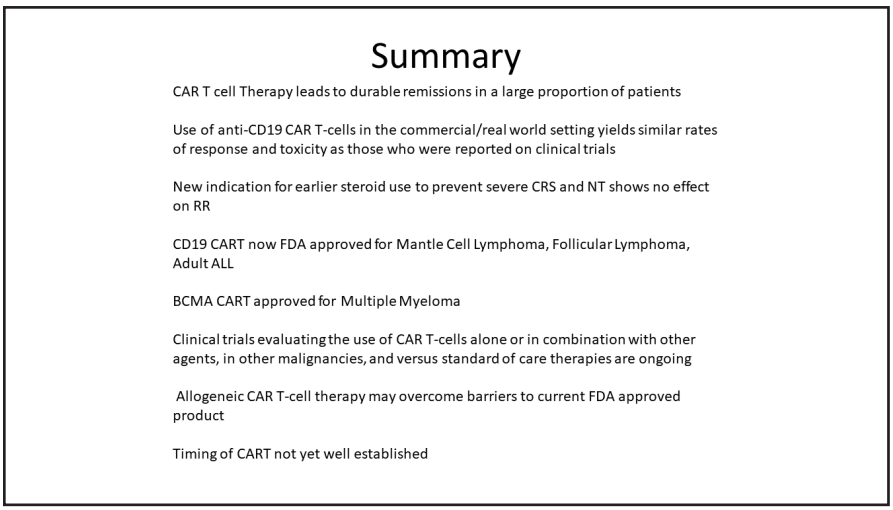
Slide 43: POST-CAR T-CELL THERAPY MANAGEMENT AND CONCERNS

Finally, we have a bunch of post-CAR T-cell therapy concerns. Right now we're asking patients to stay within 2 hours of the treating center for the first couple of weeks and not to drive because of the risk of delayed CRS and delayed neurotoxicity, so that we can monitor the patients pretty carefully. We monitor them for low blood counts for these prolonged cytopenias. We monitor them for B cell aplasia by measuring the IgG (immunoglobulin G) levels and give IVIG for patients who have an IgG level of less than 400. Obviously, we also have to monitor the patients for relapse. I don't have slides about this specifically, but sometimes when a patient gets a PET scan after CAR T-cell and it lights up, that doesn't actually mean that the patient is relapsing. The PET scan sometimes lights up because of how active the inflammatory response is with the CAR T-cell against the tumor itself. And so, it's very important to monitor for these things and to biopsy, if appropriate, to make sure that you're not assuming that the patient is relapsing, when in

fact they're not.

Finally, we should monitor patients for what we call secondary malignancies because we don't know yet what the very long-term effects of CAR T-cell are and whether they increase a patient's risk for getting other tumors.
We currently give antibiotic prophylaxis (measures to prevent or protect from disease) for many patients who've received CAR T-cells because of the effect that it has on the immune system. So we give prophylaxis against herpes virus and we monitor the CD4 count to make sure that the patients are not at risk for certain additional infections, such as PCP pneumonia.

As I said, if we believe that the patient relapses, we should biopsy them. We still don't have a lot of data on whether giving repeat CAR T-cells a second time is effective for patients who relapse after the first one. But those things are under investigation at the moment.

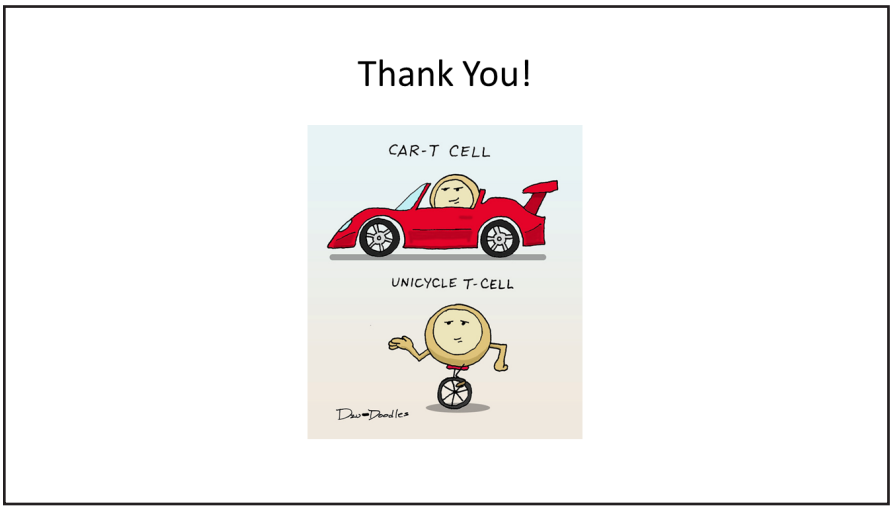


Slide 44: SUMMARY

So in summary, what I've told you today in the last 40 minutes is that CAR T-cell therapy can lead to durable remissions in a very large proportion of patients. The use of anti-CD19 CAR T-cell therapy, both in the commercial and real-world setting, yield similar rates of response and toxicities as those that were reported on clinical trials. There are new indications for steroid use to prevent CRS and neurotoxicity with no effect on response rates in patients, and so we've gotten very good at managing CRS and neurotoxicity by adding a lot of these drugs earlier with no effect on how effective these therapies are for patients.

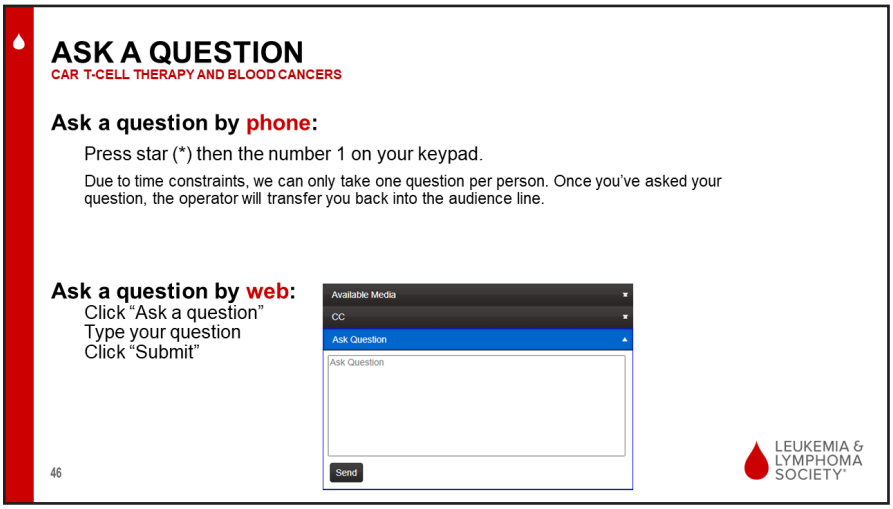
CD19 CAR T-cells are now also FDA approved for mantle cell lymphoma, follicular lymphoma, and adult ALL. BCMA CAR T-cells are approved for multiple myeloma. We have clinical trials all over the country evaluating the use of CAR T-cells alone or in combination with other agents or in other malignancies, and various standard-of-care therapies are ongoing.

Allogeneic CAR T-cells may overcome barriers to some of the current FDA approved products, but that is still under investigation. And the timing of CAR T-cells in different tumors is still not well established and is really something which is a subject of much research in the oncologic community.



Slide 45: THANK YOU!

So thank you all for attending the talk. I am here and excited to answer any of the questions that you may have.



Slide 46: ASK A QUESTION

Ms. Figueroa-Rivera:

Thank you so much for all of this information, Dr. Osman. And as you said, it's now time for the question and answer portion of our program.

Ms. Figueroa-Rivera:

Thank you. And we'll take the first question from our web audience. Dr. Osman, you touched on this and Lorraine is asking, at what point in treatment do you ask your doctor about CAR T-cell therapy? I know that especially since CAR T-cell therapy right now is not approved for first-line therapy and some of our new folks to their diagnosis may not know what first-line therapy is. But when do you start that discussion with your doctor?

Dr. Osman:

I guess, look, you always ask your doctor anything or you should be able to ask them anything. At the moment there is no CAR T-cell that is approved for any disease in first-line therapy. First-line therapy meaning the moment at which

you're diagnosed with whatever cancer it is that you have. It's always fine to ask your doctor is there a CAR T-cell for me for this disease, and when would be the right time to think about it. And, if your doctor doesn't know then they can refer you to a CAR T-cell center. So that's a very general answer to what I think is a very general question. But, it's always worth talking about if you think that it's a possibility. There are a lot of diseases for which CAR T-cells are not an option just yet.

Ms. Figueroa-Rivera:

Sure. And I know that there's a lot of blood cancers and a lot of folks on the line that have different types of blood cancers like Waldenström's macroglobulinemia, some more rare types of lymphomas. For folks with other types of diagnoses that are blood cancers, how should they look to see if CAR T is an option for them? Are they in clinical trials at this point?

Dr. Osman:

So the best thing to do is to go on clinicaltrials.gov if you have access, I mean, it's a public website, and if you go on clinicaltrials.gov you can type in your disease and you can type in CAR T-cells and see if there's an open clinical trial that is enrolling patients with your disease using CAR T-cells. It's not necessarily the best first thing to use just because it's out there for any particular disease, but your physician should know, at least if they don't have a clinical trial open at their center, where there may be one or where there may be a CAR T-cell center that they can refer you to where they can talk about that with you.

Ms. Figueroa-Rivera:

Definitely. And I will also give you the contact information for our Clinical Trial Support Center where our Nurse Navigators can actually assist folks in finding a clinical trial or if a clinical trial is appropriate for them.

Operator, can we take the next question from our telephone audience, please?

Operator:

Certainly. This question comes from George.

George:

Yes, thank you so much. Thank you, Dr. Osman, I appreciate your presentation. I have had LLC (Note: George may be referring to chronic lymphocytic leukemia/small lymphocytic lymphoma, a slow-growing lymphoma) for the past 3½ years, for a series of other health issues, I couldn't go to the chemotherapy. So my doctor prescribed 3 years ago Venclexta® (venetoclax). It is for treatment and does a beautiful job, however, it doesn't eliminate the LLC. Is there anything in the horizon or something that would be available sometime soon?

Dr. Osman:

So I think I'm understanding that you're talking about small lymphocytic lymphoma and that is a particular type, I think, what I'm understanding from the question, is a particular type of low-grade lymphoma which currently we don't have an FDA approved CAR T-cell for that. And so in short, the answer is that if there are clinical trials for this. I would encourage you to go onto clinicaltrials.gov and see if there is a CAR T-cell for that. For the low-grade lymphomas, if they have transformation to a more aggressive type of lymphoma, like diffuse large B cell lymphoma, then we have CAR T-cells available for those.

Ms. Figueroa-Rivera:

Thank you. And our next question Doctor is from Terry. Terry is asking, are there any underlying or preexisting conditions that would automatically disqualify a patient from receiving CAR T-cell therapy?

Dr. Osman:

Are there conditions that automatically would disqualify a patient from receiving CAR T-cell therapy? The only thing that would automatically disqualify the patient is if they didn't have the disease for which the therapy was FDA approved. Otherwise, I think it's really up to the physician to decide if the patient is in good enough shape to get the CAR T-cell therapy. We don't give CAR T-cell therapy to patients who have active infections because this is a therapy which depresses the immune system, so if you have a very big pneumonia or big active infection, we wait for the infection to improve before we do that. But otherwise, it's on a case-by-case basis that the physician will evaluate you and see if you're in good enough shape to receive CAR T-cell.

Ms. Figueroa-Rivera:

Sure, and along that line, especially now in COVID-19 times, Michael is asking does CAR T-cell therapy leave you permanently compromised?

Dr. Osman:

No, it doesn't leave you permanently compromised. However, again this is different for different patients, for some patients their B cells eventually do recover and they don't need to continue getting IVIG. In the case of the children who were treated for ALL, they have a kind of much longer B cell aplasia and they need to get IVIG we think probably for their lifetime.

Also, if the patient develops these long-term cytopenias and the white blood cell count is not adequate, that can become a more long-term immune problem to manage. We don't believe at the moment that these are permanent, we re-vaccinate our patients, at some point their CD4 counts do tend to recover, but within any group of patients there's always a possibility that some of the immune system will not recover as quickly.

Ms. Figueroa-Rivera:

Sure. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. The next question comes from Gary.

Gary:

I have multiple myeloma and I wasn't able to comprehend. I wanted to do the one that uses my own cells and I wanted to make sure…

Dr. Osman:

That's the only one we have at the moment.

Gary:

You do have one for multiple myeloma?

Dr. Osman:

There are 2 FDA approved products for multiple myeloma.

Gary:

Okay, that's what I thought I heard. I wanted to make sure they were both using your own cells and not the cells from other people.

Dr. Osman:

That's right. At the moment the 2 that are FDA approved for multiple myeloma use the patient's own cells. I spoke only very briefly about what we call allogeneic or off-the-shelf CAR T-cells. Those are in clinical trials now and we don't have FDA approval to use those in multiple myeloma. Actually or in any disease at the moment.

Gary:

Okay, great, that's what I wanted to make sure I heard. Thank you.

Dr. Osman:

Yes, you were right.

Ms. Figueroa-Rivera:

Thank you for the question. And our next question comes from Joy. Joy is asking, I'm having a hard time finding a caregiver. Is there a possibility that someone could have CAR T without a caregiver?

Dr. Osman:

Oh, you mean a caregiver, someone to take care of you at home?

Ms. Figueroa-Rivera:

Yes.

Dr. Osman:

Yes, of course. We usually like the patients to have somebody, but it doesn't have to be a family member. It can be a neighbor, it can be a friend. And if it really becomes impossible, then I would urge you to speak with your care team, with your physician, your nurse, nurse practitioner, and with a social worker at the CAR T center to see what kind of care can be set up for you. I don't think it's an absolute no-no.

Ms. Figueroa-Rivera:

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

Operator:

Thank you. The next question comes from James.

James:

I'm a multiple myeloma survivor and my question is, what's the longest CAR T survival that the doctor is aware of for myeloma?

Dr. Osman:

By survival you mean without myeloma, without relapse? Or just alive?

James:

Once they've had the CAR T, how long has the CAR T kept them in remission?

Dr. Osman:

I don't have an answer for that. There are patients that run all the different types of therapy who relapse very soon

after CAR T and there are patients who have remission for many years afterwards, which is exactly the same as it is for transplant or any of the other therapies.

Ms. Figueroa-Rivera:

Thank you so much for the question. Our next question Dr. Osman is from Joe. Joe is asking, what are the options if the first stem cell collection doesn't provide enough cells to move forward?

Dr. Osman:

Oh, you mean the T cell collection?

Ms. Figueroa-Rivera:

Yes.

Dr. Osman:

Yes, that does happen for some patients, and in that case usually the company will contact us and let us know that the collection was inadequate. We try to make sure that that doesn't happen by making sure that the patient has adequate lymphocyte count at the time that we are collecting them. But despite that, even when the lymphocyte count is adequate, sometimes the company will call us and tell us that they had an inadequate collection for manufacturing cells. It's a rare occurrence and over time has become a more rare occurrence. In the early days of CAR T-cells we did see this sometimes and in that case we try to recollect the patient. But, it is a rare occurrence.

Ms. Figueroa-Rivera:

Thank you. And Paula's asking, I would like to skip stem cell transplant and look into CAR T sooner. Is this now more feasible than previously discussed?

Dr. Osman:

So at the moment, first of all we would have to know what disease we were talking about. If we're talking about lymphoma and diffuse large B cell lymphoma, there was a very important study called ZUMA-7 that looked at patients who had relapsed lymphoma or what we call refractory lymphoma, lymphoma that never went away, and compared those patients in 2 groups, 1 group got CAR T-cells and the other group got the standard autologous stem cell transplant. And as a result of that study, we can now give CAR T-cells to patients in the first relapse or who have refractory disease with diffuse large B cell lymphoma. However, the caveat there is that the patients have to relapse within the first year or have refractory disease that happens within the first year. The data for patients who relapse after the first year is not so clear as to whether CAR T-cells are good for them in that particular category. So if you are in that category, then I would say CAR T-cells may be appropriate for you. If you're in any other category, that's a conversation you need to have with your physician about whether transplant is good for you or not good for you. And honestly, we don't know, we know some things, but, we're really still early on in the CAR T world and so whether it will replace transplant in general is not clear just yet.

Ms. Figueroa-Rivera:

Thank you. And our next question, Carla's asking are there other therapies that when taken before CAR T-cell diminishes its effectiveness or are there other therapies that have diminished effectiveness after CAR T that we know about?

Dr. Osman:

That is an excellent question. And that's why in my summary I wrote that timing is still not well understood. So in other words, we have a lot of drugs in clinical trials and recently FDA approved that may or may not influence the

effectiveness of our CAR T-cells. One very simple one that we know about, for example, is a chemotherapy called bendamustine (Treanda®), which can cause a lot of bone marrow suppression and makes it very difficult for us to collect T cells after the use of bendamustine. We don't know what the relationship is between using bispecific antibodies and CAR T-cells, if you use the bispecific antibodies before CAR T-cells, after CAR T-cells, what's the right timing, when should we use them.

Other chemotherapies that are very T cell toxic may affect our ability to collect adequate T cells for the manufacture of autologous CAR T-cells and so all of those factors we look into very carefully. Currently we don't use CAR T-cells in patients who have had allogeneic stem cell transplantation except in the case of ALL. So we don't know what the effect of allogeneic transplantation is on the use of CAR T-cells in other lymphomas and in multiple myeloma. So there are some things that make CAR T-cells difficult, but all of the questions are still open, we don't know yet.

Ms. Figueroa-Rivera:

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

Dr. Osman:

Thank you. The next question comes from Clara.

Clara:

Hello. Yes, I have ALL and subtype B cell CD20. And you just continually referred to CD19. What about the CD20?

Dr. Osman:

So usually if patients have ALL that expresses CD20 it also expresses CD19. And remember that I said that we don't stain cells specifically for CD19. If you have ALL then this may be a good therapy for you to discuss with your physician.

Ms. Figueroa-Rivera:

Thank you. And, I don't know if we have an answer for this, Doctor, but Alfred is asking about the length of time CAR T-cell is effective after treatment.

Dr. Osman:

You mean after you've infused the cells?

Ms. Figueroa-Rivera:

Yes.

Dr. Osman:

So one of the wonderful things about CAR T-cells is that they're what we call a living therapy, a living drug. And so we know that CAR T-cells persist in the body for a very, very long time. Perhaps even as long as years, which probably is what causes some of the long-term toxicities, such as the long-term cytopenias. In patients who relapse, we sometimes go back and look and that's why I showed that slide as to whether the CAR T-cells are gone or whether the target, the CD19, is no longer on the tumor cells, so that even though the CAR T-cells may be there, they may not be able to recognize it. But we believe that the CAR T-cells persist for a very long time, not the same length in all patients, but as I said, because it's kind of thought of as a living therapy, they're there in your body and perhaps even surveilling and making sure that the cancer doesn't come back. Not the case for everyone, but they do persist for a very long period of time.

Ms. Figueroa-Rivera:

Thank you. And Nora is asking about the recovery period, the duration, side effects, is it similar to transplant?

Dr. Osman:

So, the recovery is much shorter than for transplant because you haven't gotten very aggressive chemotherapy. And so, most of the time patients who are in the hospital for CAR T-cells don't have the same side effects as patients who are getting autologous stem cell transplant. They don't get the level of mucositis, mouth sores, they don't get diarrhea, even if they do get CRS and get fever, they tend not to get neutropenic fevers in the same way that transplant patients get them. They don't have the same problems with loss of appetite and fatigue and weight loss and weakness that patients who go through autologous stem cell transplant do. However, patients who go through autologous stem cell transplant, once their counts recover, they recover fully and they don't deal with the long-term cytopenias that some of the patients with CAR T-cells do. Most patients feel physically quite well after CAR T-cells, maybe not perfect, but not as exhausted and their recovery is not as long as those who get autologous stem cell transplant. But, we still don't understand very well the long-term effects of the cytopenias. So for patients who develop cytopenias, I don't know if the right word there is recovery, but they have to continuously be under monitoring and that can be annoying for patients who get CAR T-cell.

Ms. Figueroa-Rivera:

Thank you. And Doris is asking, how many patients develop anemia and low blood cell counts after CAR T-cell treatment?

Dr. Osman:

A significant number, I would say probably in the 30 to 40% range. How long it lasts, the low blood counts, is variable between patients. Some patients, it lasts for them for a very long period of time and for some patients it's just a couple of months or weeks. And some patients never get it.

Ms. Figueroa-Rivera:

Okay. Thank you. And we'll take our next question from our telephone audience, please.

Operator:

Thank you. The next question comes from Karen.

Karen:

Hi and thank you. My son was diagnosed with diffuse large B cell and underlying follicular. He had the R-CHOP and it failed. He had radiation treatment. He had auto. All of which failed. So he did have CAR T in 2021. Now one nodule in his neck completely resolved, but the other one remained. They did give him some radiation and then they started him on Keytruda® (pembrolizumab). The Keytruda shrunk the nodule, that in conjunction with the radiation treatment to his neck, it was just in his neck. The abdomen had resolved and pelvis area, all the nodules had resolved. My question is, he did not have the Yescarta, which I see in your slides is effective for both B cell, diffuse large B cell, and follicular. He had Kymriah.

Dr. Osman:

Which one did he have?

Karen:

He had Kymriah, he didn't have the Yescarta, as I see in your slide was for both. My question is, how do we know

that it's still effective in his system? Is there a blood test? How do we know that the T cells are still working? Is there a specific blood test?

Dr. Osman:

No, there isn't a blood test. There are not approved tests to look and see if CAR T-cells are still in the system or not. They can do certain other tests to see what his T cell components are in his blood. But the fact that he relapsed after the CAR T-cell probably tells you that it wasn't fully effective in terms of getting rid of it and that his response is probably to the pembrolizumab and not anymore to the CAR T-cell.

Ms. Figueroa-Rivera:

Thank you for the question. Now if somebody relapses after CAR T-cell, can they get CAR T-cell again or do physicians look more to transplant?

Dr. Osman:

So we don't currently give a second type of CAR T-cell if you've relapsed after the first type. The follow-up, in other words, giving a second CAR T-cell after the first one is in clinical trials, like I was telling you about these tandem CAR T-cells or ones that are targeted against different antigens on the same type of tumor, so those we'll hear more about in upcoming meetings, but that's currently not something that we do as a standard of care.

For certain diseases transplant is an option after CAR T-cells, both are options if a patient had autologous stem cell transplant and then they got CAR T-cells, depending on the disease and depending on whether they can find a donor, etcetera. An allogeneic stem cell transplant is an option for certain lymphomas and actually allogeneic transplantation works quite well for follicular lymphoma. And so, if your patient is young and has a good donor and has relapsed after CAR T-cell and he's a good candidate for allogeneic transplantation, that is something to think about.

And so, yes, the short answer is yes, it's possible to do transplant after CAR T-cell if it wasn't already done.

Ms. Figueroa-Rivera:

Thank you. And we did have a lot of questions coming in, in regards to, do folks need to have a transplant prior to being eligible for CAR T-cell therapy?

Dr. Osman:

No, the FDA labels for all the different CAR T-cell therapies don't specify transplant. They specify lines of systemic therapy. So for example, for diffuse large B cell lymphoma, adults with relapsed/refractory diffuse large B cell lymphoma, after 2 or more lines of therapy are eligible. If the diffuse large B cell lymphoma arose from follicular lymphoma, primary mediastinal, etcetera. Currently for the anti-BCMA CAR T-cells in multiple myeloma, like I said, have to be more than 4 lines of therapy, but transplant is not one of the lines that is required.

Ms. Figueroa-Rivera:

Jason is also asking about neuropathy, is that a potential side effect from CAR T-cell therapy?

Dr. Osman:

That's another one I haven't seen. Not the kind of neuropathy that we think about with like numbness in fingers and toes. Like I said, there are patients who get neurotoxicity, some patients can get some encephalopathy after CAR T-cells. And certainly there's been some literature about longer term neurologic effects, Parkinson's-like syndrome after some of the myeloma-related CAR T-cells. But specifically, neuropathy in the fingers and toes like you get from chemotherapy, I have not seen that as a specific side effect of CAR T-cells, but if you got neurotoxic chemotherapy, you might feel your neuropathy a little bit worse afterwards.

The chemotherapies that we use for CAR T-cells are not known for neuropathy. In other words, the fludarabine and cytoxan are not very neurotoxic agents, not like some of the other drugs that we use that cause a lot of neuropathy in patients.

Ms. Figueroa-Rivera:

The next question is from Jeff. Jeff is asking, any experience regarding CAR T impact on pleural effusion?

Dr. Osman:

I guess it would depend on whether the pleural effusion was full of tumor cells or was the pleural effusion because of pneumonia, heart failure, or just low oncotic pressure that causes fluid to accumulate in the lung. So in all the other settings that the pleural effusion is not related to the cancer, I don't think the CAR T-cell would have any effect. On the other hand, if what the pleural effusion is, is a sign that there are a lot of tumor cells, then perhaps the pleural effusion will get better if you get a response from the CAR T-cell. I hope that answers the question.

Ms. Figueroa-Rivera:

Yes, thank you. And Tim is asking, are there any vitamins recommended or not recommended while receiving CAR T-cell therapy?

Dr. Osman:

There are no specific vitamins that are recommended and then in terms of using medications or supplements while getting CAR T-cell therapy, I think that that would be something you'd have to speak about with your physician in terms of what supplements you were thinking of taking and how that interacts with any of your other medications and any of the other chemotherapies that you may be receiving.

Ms. Figueroa-Rivera:

Thank you. And our next question, Deborah's asking when coming out of remission is there an advantage to going into CAR T before exhausting another treatment first?

Dr. Osman:

So I guess again that depends on the kind of cancer that we're speaking about. If it's coming out of remission for diffuse large B cell lymphoma within the first 12 months of treatment, then there appears to be an advantage to using CAR T-cells. Again if it's any of the other cancer types, then it depends on how many lines of therapy you've gotten beforehand. And then when it comes to multiple myeloma, again you would have to have had a relapse after 4 lines of therapy or participate in a clinical trial in which the CAR T-cells are given earlier. So it really depends on the disease and which coming out of remission we're talking about, after how many lines of therapy.

Ms. Figueroa-Rivera:

Thank you. And Michael is asking why CAR T works better on blood cancers than on solid tumor cancers?

Dr. Osman:

I don't know that we can say that it works better, I think that the clinical trials right now are looking actually at how CAR T-cell works in solid tumors. I can tell you that we've had extraordinarily good results in a clinical trial here, looking at CAR T-cells for prostate cancer. The issue with the solid tumors is finding the right antigen for the CAR T-cells to attack. But once we've identified the antigen, then it's a question of testing those CAR T-cells in those cancers, and I'm not sure that it works better in blood malignancies than in solid tumors. Time will tell.

Ms. Figueroa-Rivera:

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

Operator:

Thank you. The next question comes from James.

James:

Yes, I was curious about, I have MDS now and I'm wondering what the probability is that to become AML (acute myeloid leukemia) and whether this CAR treatment has any possibility with that?

Dr. Osman:

So MDS is a complex disease that has many different types. The risk of MDS becoming AML has a lot to do with what the cytogenetic abnormalities of your MDS are and what percentage of blast cells you have in the bone marrow. So without knowing any of those things it's very hard to know what is the risk of it turning into AML.

In terms of CAR T-cells for MDS or AML, there are clinical trials using CAR T-cells for AML. I'm not aware of clinical trials for MDS, partially because the tumor antigen is not very clear in MDS, it's quite a heterogenous disease. But again, those are only in clinical trials now and there aren't really CAR T-cells that are FDA approved for the use in either of those 2 diseases

Ms. Figueroa-Rivera:

Thank you. And Keith is asking, CAR T intervention early in disease, perhaps during watchful waiting with the goal of nipping the disease in the bud, perhaps CAR T could be more successful in achieving full remission with this approach?

Dr. Osman:

It's a possibility. We're not currently doing that. And remember, while it sounds like a great idea, it's not clear what the long-term effects of CAR T-cells are. So only once we understand the use of these cells in more advanced disease will we be able to move it into an earlier stage. You don't want to give something that potentially causes toxicity if you're just in the watchful waiting phase and you're not at high risk of developing overt disease, then you might get side effects from something and therapy you may not have been needed. So that's always a tricky situation to be in.

Ms. Figueroa-Rivera:

Yes, and thank you for the question. We'll take the next question from our telephone audience, please.

Operator:

Thank you. The next question comes from Vicki.

Vicki:

Hi. I have both CLL (chronic lymphocytic leukemia) and CML (chronic myeloid leukemia) and I was wondering would I be a candidate when you have both kinds of leukemia?

Dr. Osman:

So CML is not a disease for which we have CAR T-cells right now and CLL is in clinical trials. I don't know in clinical trials whether the existence of CML would exclude you from participating in a clinical trial for CLL. That would be dependent on how that trial was written, but I imagine in most clinical trials, having another malignancy excludes the patient from clinical trials. If it becomes FDA approved, then it's up to your doctor to decide. Just like in the early clinical trials, we excluded all patients who had HIV (human immunodeficiency virus). But I can tell you that we've used

CAR T-cells in patients with HIV with no problem. So it's a question of how the trials are written and how they want to gather their data.

Ms. Figueroa-Rivera:

Thank you. And a lot of participants are asking about cost and if insurance companies, Medicare and other insurances, do they cover CAR T-cell therapy?

Dr. Osman:

Yes, most insurance companies do cover CAR T-cell therapy, that's a project for the referral center. In other words, any patient who's referred to us for CAR T-cell therapy, we go through the procedure of making sure that we don't do anything for patients where their insurance will not pay for it. Most insurance, most commercial insurance, Medicare and so on will pay for CAR T-cell if it is under the FDA label.

Ms. Figueroa-Rivera:

Thank you. And Joanna is asking, is CAR T an option as it pertains to a person with kidney damage or being on dialysis?

Dr. Osman:

Yes. We have treated patients on dialysis with CAR T-cell.

Ms. Figueroa-Rivera:

That's good to know, thank you. And we'll take the next question from our telephone audience, please.

Operator:

Certainly. The next question comes from Russell.

Russell:

Hello, thank you very much for a very informative presentation, first off. Second, you've answered this question a little bit. I'm young, I'm healthy, I'm tired of getting beat up on chemo and some of these other drugs. Any trials looking at using this earlier and combining it with other treatments or drugs to get an earlier remission? I know that I'm a recurring revenue for drug companies, but I really need to look out for my health.

Dr. Osman:

For which disease?

Russell:

Multiple myeloma.

Dr. Osman:

Yes, there are many clinical trials that are looking at using CAR T-cells early, post-first transplant or earlier in the disease. As I said earlier, I would recommend that you go on clinicaltrials.gov and see which clinical trials are open for multiple myeloma and then see if you fit any of the descriptions and then contact the centers that are participating in those clinical trials to see if, given your particular status, whether you'd be eligible to participate in any of those.

Ms. Figueroa-Rivera:

Thank you for the question. And Richard is asking, what are your thoughts about next generation CAR Ts and the new bispecifics? How are you all thinking about how they may be incorporated into patient care as well as the future?

Dr. Osman:

Well, we're all excited about them. We have one bispecific that was FDA approved for the treatment of multiple myeloma. We don't yet know what the timing and sequencing should be using those, and the next generation CAR Ts similarly we don't know what the sequencing should be, but that's why they are all still in clinical trials until we figure that out.

In terms of the bispecifics, we had been using them after CAR T but for patients who either were not eligible for CAR T some of them were using bispecifics before and now there's a question of what should be the sequencing. I think this is a big conversation among the myeloma physicians that has yet to be determined.

Ms. Figueroa-Rivera:

Thank you. And Kitty is asking if there is a certain blood count that's required to do CAR T-cell therapy?

Dr. Osman:

No, but in order to collect the T cells, you need to have a minimum lymphocyte count in order to be able to collect the T cells to make the CAR T-cells. As I said, sometimes you have manufacturing problems when you don't have enough lymphocytes, and so we look at that very carefully.

Ms. Figueroa-Rivera:

Thank you. And Jason as well as others are asking post-treatment, when are they able to go about their normal lives, life events, possibly getting a tattoo?

Dr. Osman:

I don't think there should be a problem with getting a tattoo if the platelet count is okay and the white blood cell count is pretty good. And most people go about their normal lives pretty much after CAR T-cell, without much fanfare. I mean we do monitor the patients pretty carefully, and we give them some prophylactic antibiotics and medications, but most patients go back to their pretty much normal lives.

Ms. Figueroa-Rivera:

That's good to know. And our last question today, what are you most excited about in regards to CAR T-cell therapy and its progression? You've showed over the years how we have progressed, not just with the procedure, but also with treating the side effects for CAR T-cell therapy.

Dr. Osman:

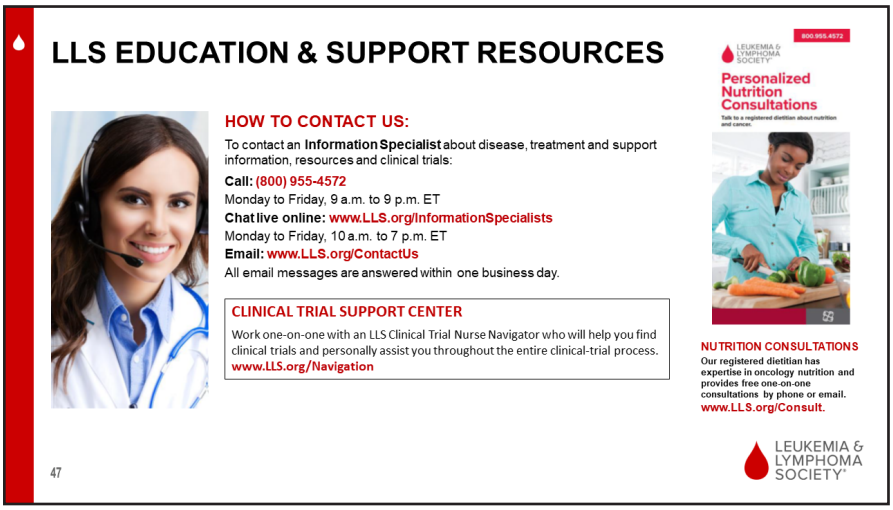
Yeah, I'm very excited. First of all for the possibility of using it for multiple different diseases, not just cancers, but as I said, also autoimmune diseases and diseases like HIV. I'm excited for the new generation of CAR T-cells and the potential off-the-shelf CAR T-cells that we might be able to use without having to collect the patient's first. And certainly for using them earlier on in diseases, so patients don't have to wait to relapse so many times before they're able to get a therapy that is potentially life-saving and curable.

Ms. Figueroa-Rivera:

Well, thank you so much, Dr. Osman, for volunteering your time today, providing so much information and providing so much hope for our blood cancer patients. Thank you.

Dr. Osman:

Okay, thank you all for inviting me.



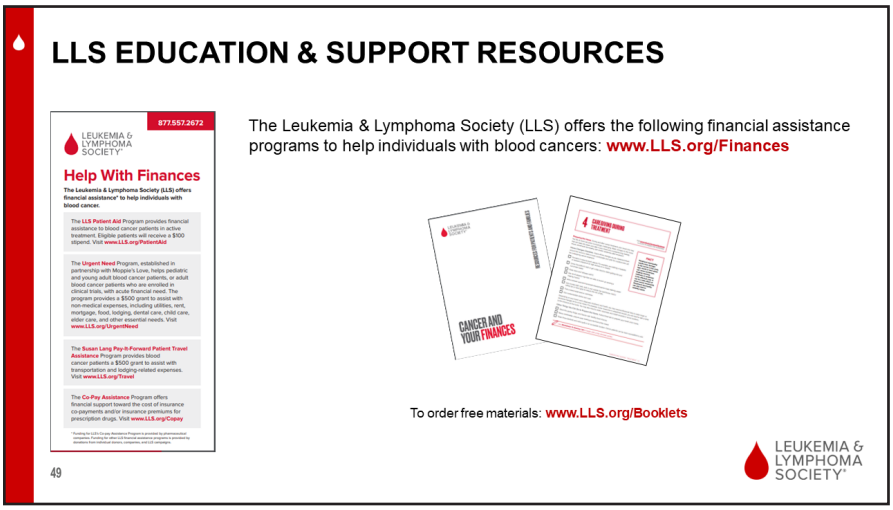
Slide 47: LLS EDUCATION & SUPPORT RESOURCES

Ms. Figueroa-Rivera:

Thanks. And if we were not able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or you could reach us by email at LLS.org/ContactUs.

Slide 48: LLS EDUCATION & SUPPORT RESOURCES

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. You may also reach out to one of our Clinical Trial Nurse Navigators in our Clinical Trial Support Center by visiting LLS.org/Navigation or call an Information Specialist for assistance to see if there are any clinical trials that are appropriate for you.



Slide 49: LLS EDUCATION & SUPPORT RESOURCES

Again, we'd like to acknowledge and thank Allogene Therapeutics; Bristol Myers Squibb; CRISPR Therapeutics; Janssen Oncology and Legend Biotech; Kite, a Gilead Company; and Novartis Oncology for their support of this program.

Slide 50: THANK YOU

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