Slide 1: CONSIDERING CAR T-CELL THERAPY: A HOPEFUL TREATMENT FOR BLOOD CANCERS

Operator:

Welcome to *Considering CAR T-Cell Therapy: A Hopeful Treatment for Blood Cancers* telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you, Lizette. Please begin.

Slide 2: WELCOMING REMARKS

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I'd like to welcome all of you. LLS is the largest nonprofit dedicated to creating a world without blood cancers. Since 1949, we've invested more than $1.8 billion in groundbreaking research, pioneering many of today's most innovative approaches. Researchers at The Leukemia & Lymphoma Society were some of the first to recognize and champion the use of a patient's immune system to attack their blood cancer, and our research support to develop new immunotherapies continues to this day.

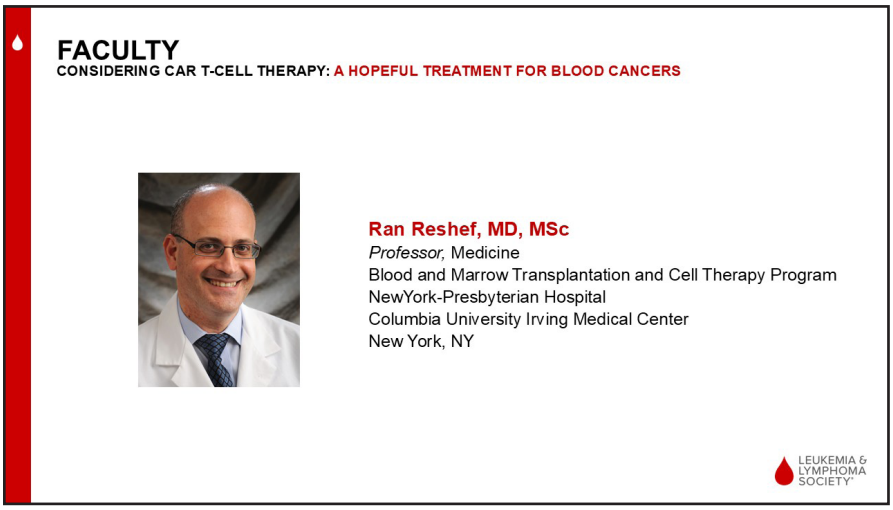
LLS was also among the earliest financial supporters of CAR T-cell therapy research, beginning in the 1990s and continuing to support the development of next-generation CAR T-cell therapies. LLS provided grants to many of the first people to recognize the importance of harnessing the immune system to attack blood cancer. And, 30 years later,

our support continues to fuel the latest research into new immunotherapies.

This promising therapy has been able to impact so many patients and their families in such positive ways. We continue our commitment to searching for cures. In the present, we strive to be there for you every step of the way. Thank you so much for joining us today on this program and we hope to assist you as much as we can through treatment and survivorship.

Support for this program is provided by Bristol Myers Squibb, Johnson & Johnson, and Legend Biotech, and Kite, a Gilead company.

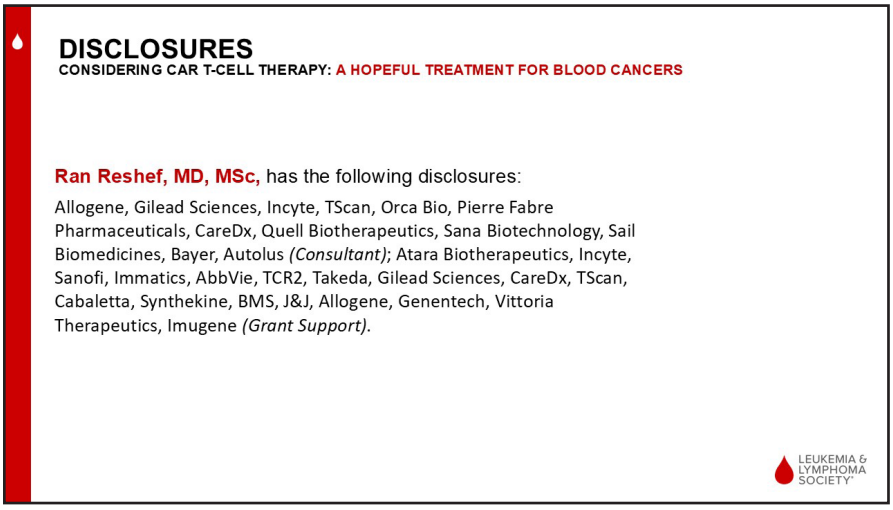
It's now my pleasure to introduce Dr. Ran Reshef, Professor of Medicine at Columbia University Irving Medical Center in New York, NY. Dr. Reshef, I'm privileged to turn the program over to you.



Slide 3: FACULTY

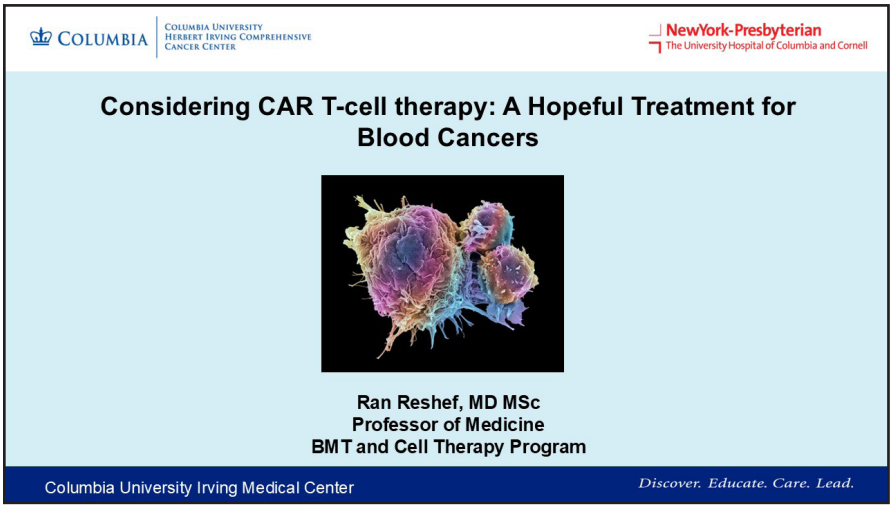
Dr. Ran Reshef:

Thank you so much. I hope everyone can hear me okay. Thanks for the introduction and thank you so much for the opportunity. If there's one organization that I never say no to, it's The Leukemia & Lymphoma Society. I think your mission is so important and you're doing it so well and not just providing education but other things like financial support, research support, in fact, LLS has been a participant in the development of some of the CAR T-cell therapies we use today. I'm really privileged to be able to spend an hour or an hour and a half with so many participants to discuss something that is really close to my heart and is in the center of my work, both my clinical work and research work.



Slide 4: DISCLOSURES

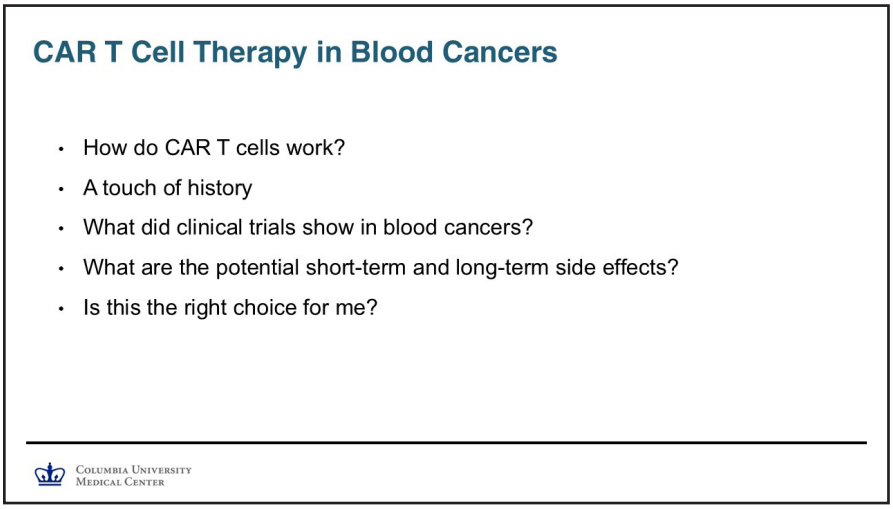
This is just a list of my disclosures. We at Columbia are working very closely with many CAR T manufacturers and other commercial entities that develop new medications in cell therapy. This is just a list of these collaborators.



Slide 5: Considering CAR T-cell therapy: A Hopeful Treatment for Blood Cancers

I like the title of this talk, “A Hopeful Treatment for Blood Cancers.” I would add to that perhaps the fact that we know today that CAR (chimeric antigen receptor) T-cell therapy is a curative approach in a number of blood cancers.

In fact, it’s gratifying to watch it evolve over time and to see it now being used even outside blood cancers, which is not something we’re going to discuss today. There are several types of cancers outside the blood system that can now be treated with certain types of cell therapies.



Slide 6: CAR T Cell Therapy in Blood Cancers

What are our goals today? As the director of the CAR T program at Columbia, I will focus this on CAR T cells. There are some other types of cell therapies that we might be able to touch on very quickly, but our main focus will be this new type of medications called CAR T cells.

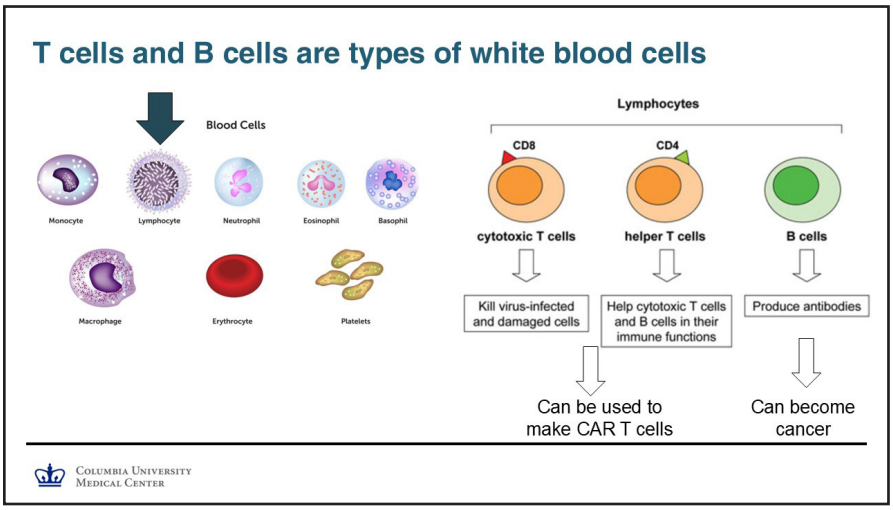
I'm going to try to explain how they work. It's a completely novel and very different type of medicine in cancer therapy, so it requires a little bit of a basic understanding of how the immune system works in the body and how we can use our own immune system to fight cancer. I find the history of this quite fascinating, and I hope you will too. I'm going to spend just a little bit of time describing the history of how CAR T cells were developed and in what type of patients they were shown to work for the first time.

We're going to review some of the clinical trial data that supported the approval of CAR T cells and are the reasons why we have them available today to administer to patients outside clinical trials as FDA-approved medications. I can already tell you that maybe compared to 10 years ago, it would be impossible to review all of the clinical trial data for all of the diseases where we now use CAR T cells.

I'm going to use a couple of examples and show you very briefly what the outcomes are expected in certain other diseases. This will not be completely comprehensive. Obviously, it's also not going to be pertaining to individual patients but talking about it more globally in terms of how we use these therapies today. There's no therapy in cancer or in any other field in medicine that has zero side effects. I'm going to dedicate some time to discussing the side-effect profile and also how much we've evolved over 15 years to know how to identify and manage these side effects, mostly preventing many of them nowadays.

I'm going to spend a little bit of time at the end. This will become a good segue for the Q&A section and trying to understand who should really be getting CAR T cells. Is this the right choice for individual patients?

I'm going to use that as an opportunity to tell you a little bit how I think about it, not necessarily give you an exhaustive list of who should get CAR T cells and who shouldn't but give you the guiding principles of the way I think about this as a physician.



Slide 7: T cells and B cells are types of white blood cells

We'll start by describing a little bit of how CAR T cells really work. That does require understanding a little bit of the terminology we use about types of cells we have in our blood system.

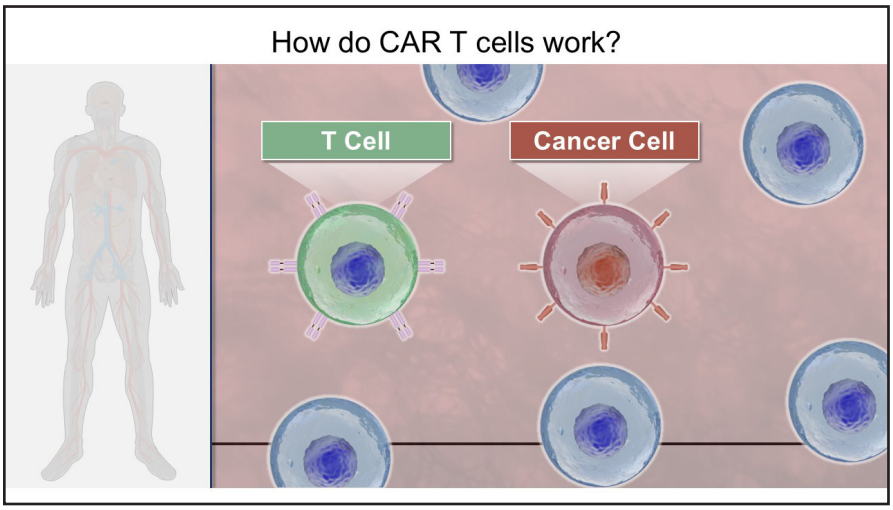
CAR T cells are a type of immune therapy in which we use our own immune system or in this case, the patient's own immune system to fight their cancer. We've known for decades that the immune system can eliminate and kill cancer cells. It just doesn't always do it very efficiently. We can use our own immune cells and enhance them or help them identify the cancer cells better, which is exactly what we're doing with CAR T cells.

When you look at your blood counts, when you get a blood count down at the physician, you're going to see all of these blood types listed there. The way we identify them is under the microscope. Today, we obviously have machines that can count them, but we're going to focus on the lymphocytes, which are the part of the immune system. Maybe one of the most important parts of the immune system. These are the ones that can recognize bacteria and viruses. What many people don't know is that lymphocytes are also capable of identifying abnormal cells in the body, cells that are mutating and are on their way to becoming a cancer. We can definitely use them.

When we talk about lymphocytes, there are several types of lymphocytes. We're going to focus on these 2 primary types. One of them is the B cell, which normally is part of our immune system, is designed to produce antibodies, antibodies against the flu, against bacteria, against COVID, against other viruses. We have another type of lymphocytes called T cells that can directly engage with an abnormal cell or with a virus or bacteria and kill them in what I would call a face-to-face battle as opposed to the B cells that would produce antibodies that would get anywhere in our body and can kill abnormal cells or bacteria that way. What's critical for our discussion is that B cells are one of the most common cells that end up turning into cancer.

When we talk about non-Hodgkin lymphoma, when we talk about certain types of acute leukemia and even myeloma, these are all diseases that originate from a B cell that became ill, became mutated, started behaving abnormally, and ultimately started multiplying until it created a tumor. The cancers we're going to be talking about are mostly B-cell cancers. What we're doing with CAR T cells is basically taking healthy T cells and genetically modifying them, educating them to identify cancer cells, which is basically what CAR T cells do.

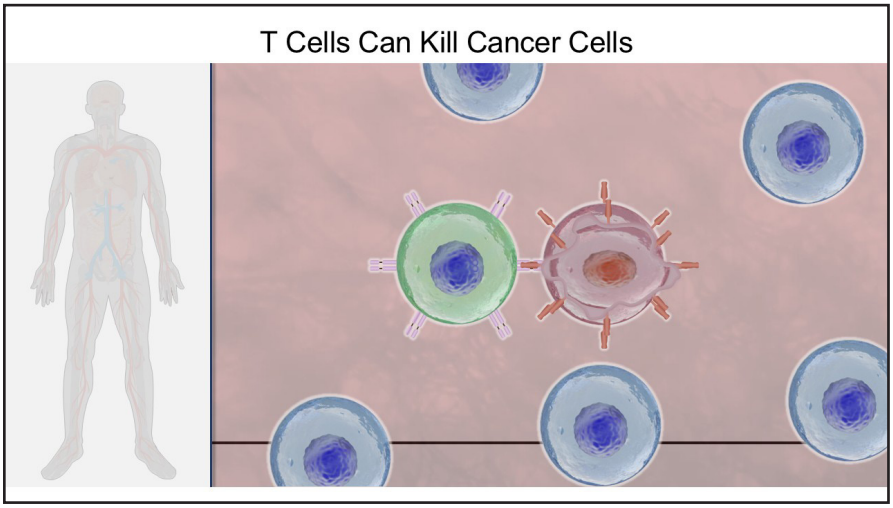
This is the extent of what I'm going to teach about basic immunology since we're not going to turn this into a college-level immunology course. We're going to keep it at this level.



Slide 8: How do CAR T cells work?

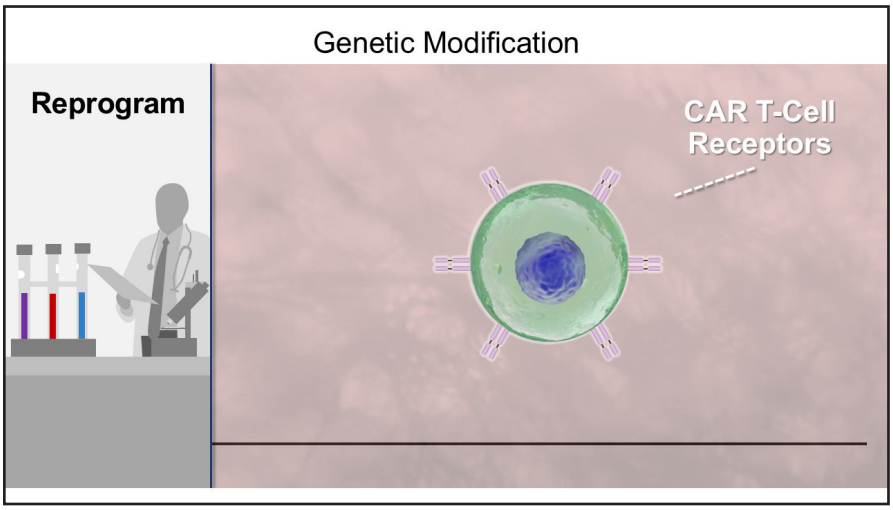
How do CAR T cells really work? We do know that T cells are already designed and are able to kill abnormal cells in our body. When we have a cell in our body that is becoming abnormal, we have T cells that are capable of identifying it and frequently able to eradicate it.

Sometimes it works. Sometimes this cancer cell slips through the cracks, starts multiplying, becomes many cancer cells, becomes a tumor. At that point, our immune system is likely going to be unable to eradicate it. This is basically what happens when someone gets diagnosed with cancer.



Slide 9: T Cells Can Kill Cance Cells

We know that T cells can engage in our body and kill cancer cells. Just not always in a very efficient way.



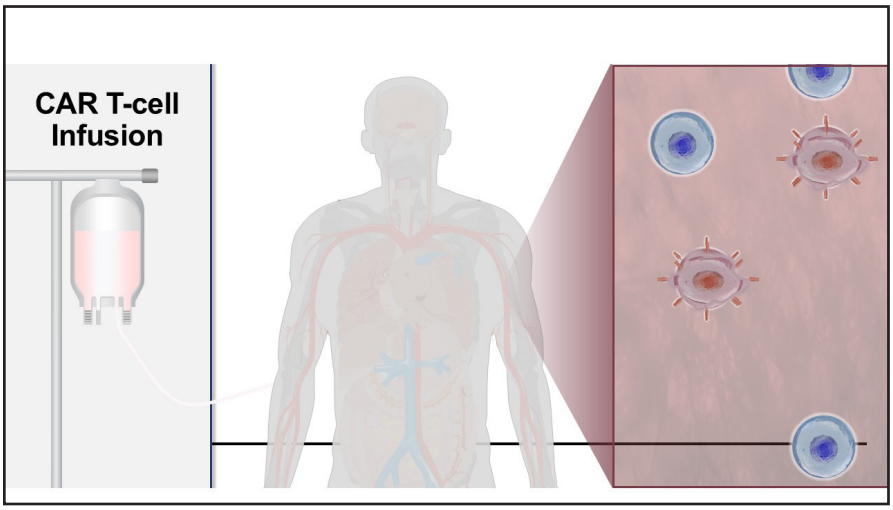
Slide 10: Genetic Modification

We're going to use that. We're going to take T cells from the body that already have this inherent killing mechanism. We're going to use genetic modification with methods that are now several decades in development. We're going to manipulate the DNA of the cell, which sounds a little bit like science fiction, but it's a reality today in almost any type of research lab.

This genetic modification would force these T cells to express something on their surface called the CAR. The CAR is a chimeric antigen receptor. It's an artificial receptor that allows these T cells now to recognize a certain marker, a certain object that they were not designed to recognize in the first place. It's an artificial manipulation of our existing T cells. Another word I like to use to describe it is listed here on the left. We reprogram our T cells to do this.

Slide 11: Expansion

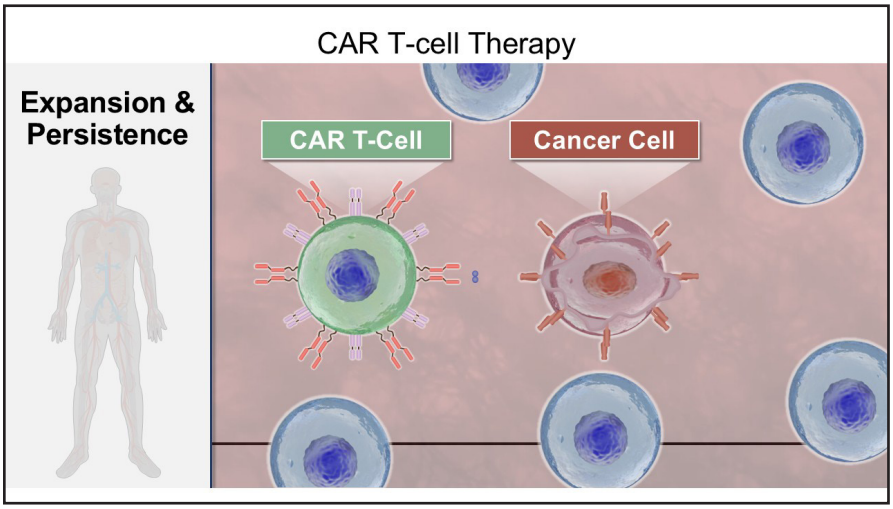
Now, we can do that in one cell, but then we can do this in hundreds and thousands of cells. Nowadays, we also have methods to generate, let's say, several thousands of these cells. Then in the culture dish in the lab, we can encourage them to multiply. This is called the expansion phase. From a single CAR T cell or a few CAR T cells, we can generate millions and millions or hundreds of millions of CAR T cells. All of them are going to be identical in the way they would recognize a cancer cell once they're put back in the body.



Slide 12: CAR T-cell Infusion

We would take these expanded CAR T cells, put them in a bag, connect that bag to a patient that looks not very different from a unit of blood or unit of platelets if anyone has ever had a transfusion. It gets infused into the body just the same way we infuse medications, antibodies like rituximab or chemotherapies. It's a bag that gets connected to a vein and infuses the CAR T cells into the body.

Once these CAR T cells get into the body, what they're capable of doing because we genetically modified them, is to identify cancer cells one after the other and kill them. By doing that, the CAR T cell itself remains unharmed. It would basically move from one cancer cell to the next. We have these amazing cases where a patient with sometimes very large lymph nodes and large masses of cancer can be completely eliminated. Pounds and pounds of tumors can be eradicated by just a few hundreds of millions of CAR T cells that we've infused. This is the basic principle.

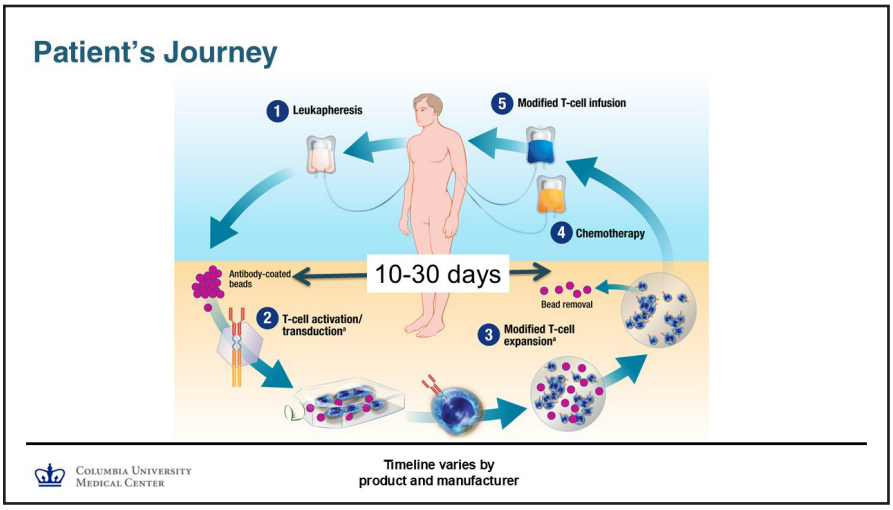


Slide 13: Expansion & Persistence

The other thing that's important to understand is that while we grew these CAR T cells in the test tube, they would actually continue to grow in the body because, at the point where they go back into the body, they are living cells just the same way we collected them from the body as living cells, they remain alive, which means that if they encounter the cancer cell that they're supposed to target, they will get this incentive and trigger to multiply in the patient just the same way our immune system responds to a flu illness or COVID or any other type of infection. This is exactly what

our immune system naturally does. We use that by allowing these CAR T cells to expand. If we would give someone a hundred million T cells and we look in their body 7 or 10 days later, they may have several billions of CAR T cells at that point because these T cells grew and multiplied.

Another thing that's going to happen is persistence. Just the same way when we recover from an infection, we have a group of immune cells that persist in the body and would recognize and remember the infection that we had. That's the reason why we don't really get chickenpox more than once in a lifetime, or if we can get a vaccine against chickenpox, we may never have that disease. The reason is that once you have it once, your immune system will develop a memory. That memory is embedded in this persistence of CAR T cells just the same way a healthy normal T cell against COVID will persist. In the case of COVID, it may not completely prevent the next infection because COVID itself can come back as a different version, but the general principle is that we have immunologic memory against things that we're exposed to. This persistence may help keep patients in remission long-term. You can see here, we have a CAR T cell that's killing a tumor cell and then basically stays in the body sometimes for very lengthy periods of time.



Slide 14: Patient's Journey

Now, I'll explain to you what happens on the biologic side, what happens in the body. What does this really look like for the patient? What is the journey that the patient needs to go through to get CAR T-cell therapy? It starts in this first phase that's called here leukapheresis. What is leukapheresis? When we make CAR T cells, we make them from each individual patient's own T cells. We don't take them from someone else, although there are some methods in development that may enable us to do that in the future.

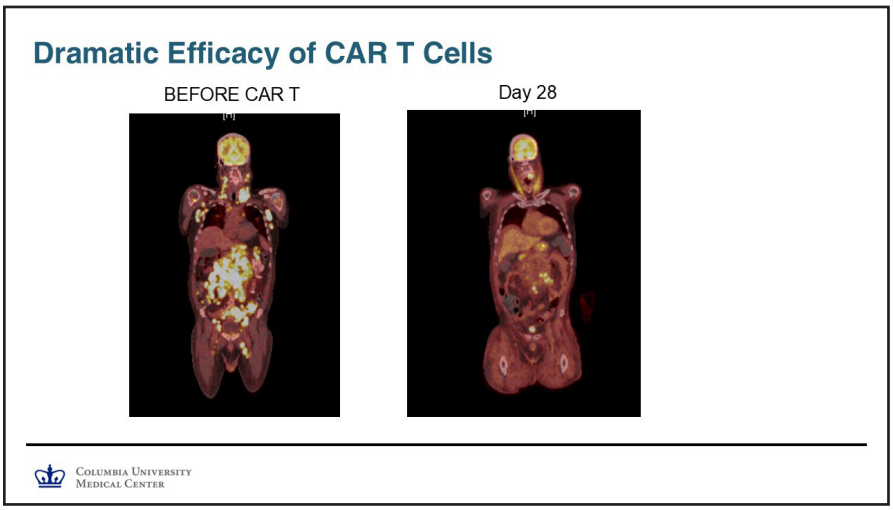
We start with what we call autologous T cells. These are the patient's own T cells. We need to collect from the patient a certain number of them. Because the number we need is fairly high, then just a simple blood draw is not going to be sufficient. The way to collect enough T cells from the blood is to get connected to a machine that's called the leukapheresis machine. You get connected to it for 4 or 5 hours. It circulates the blood through the machine, returns most of it to the patient, and collects some of these lymphocytes, some of these T cells. For those patients who may have had the experience of undergoing a bone marrow transplant, it's a little bit of a similar process to collecting stem cells, although it's actually a lot simpler. When we collect stem cells, we need to stimulate the body with injections. We need to collect usually over several days.

None of that needs to happen when we just collect normal T cells. There's no preparation. There's no mobilization. We just need to connect the patient to a machine once for one day. It's an outpatient procedure. Patient goes home. The bag goes into the manufacturing process, which is everything that's listed here at the bottom, which I described briefly earlier, the genetic modification and the expansion phase.

When the cells are ready, and this may take anywhere between 10 and 30 days depending on the type of CAR T and the type of manufacturing process, we get the bag back. At that point before infusing the bag, infusing the CAR T cells, we do use a little bit of chemotherapy. This is low-dose chemotherapy that is generally, I wouldn't say harmless, but has very low side-effect profile, doesn't cause a tremendous amount of GI (gastrointestinal) issues.

Many patients would not even lose their hair as a result of this. The idea behind this chemotherapy is not to treat the cancer but to make room for the CAR T cells to expand because this is essential for their activity in the body. They need to get infused and then expand in the body and get activated so they can search the tumor cells and kill them. Chemotherapy is part of the process almost universally when we talk about cell therapies.

Then needless to say, but maybe I should say this, some people may not know this, this is designed to be a one-time treatment. Unlike many types of chemotherapies or other immune therapies that you need to get cycle after cycle after cycle, sometimes for lengthy periods of time, CAR T cells are truly designed as a one-time treatment that would be able to eradicate cancer completely.



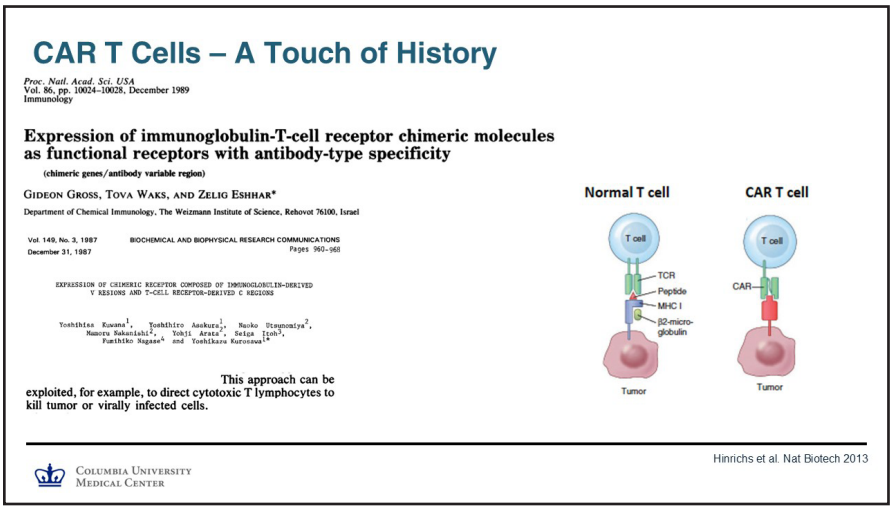
Slide 15: Dramatic Efficacy of CAR T Cells

This is, in fact, what we see frequently. Frequently, we can see a patient who comes in with a tremendous amount of cancer, sometimes because it just happened to be a very aggressive cancer or sometimes because the patient already failed previous lines of therapy and the cancer just grew out of control. For those of you who have never seen PET (positron emission tomography) scans before, this is what a PET scan looks like. You could see vaguely the shape of the body.

You could see the areas that lit up very brightly are the ones that have high glucose uptake, high sugar uptake. That means there's a very active cell there. That's usually an indication for cancer cells. You can also see some areas in the body that have high glucose uptake normally. The brain always lights up very brightly on a PET scan. It doesn't mean it has cancer. This is a normal brain.

Everywhere else that lights up very bright here in the belly, in the armpits, in the neck, all of these are tumor cells. This is right before administering a single infusion of CAR T cells and this is 4 weeks later. You could see how dramatic the response is that I would say 98% of these bright spots are completely gone and a couple of them are left behind. This is an important lesson to understand about CAR T cells.

While the infusion is only once, their activity might take a little bit of time to get the maximum result. When someone has still a few bright spots on day 28 after CAR T, that doesn't mean the treatment has failed. It means that in many of these patients, the CAR T cells are still working. We need to repeat the imaging several weeks after that, a month or 2 to see what happened to these spots. In many cases, they will just disappear.

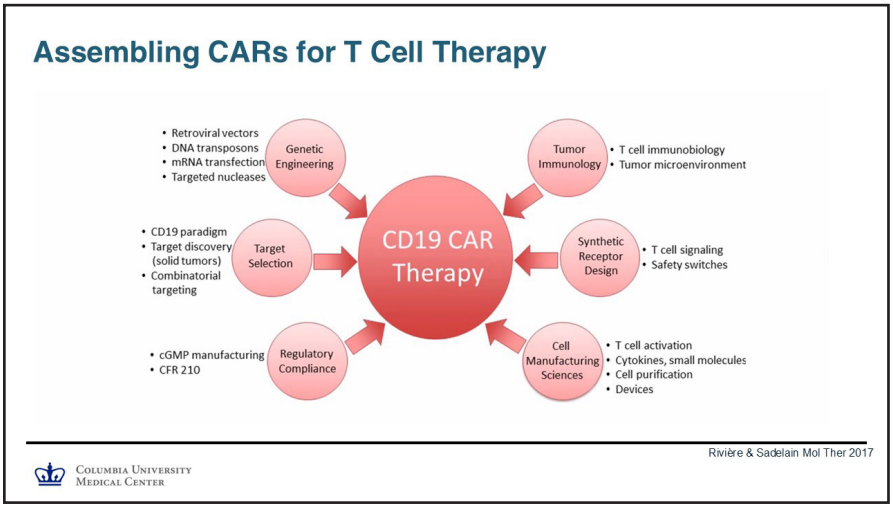


Slide 16: CAR T Cells – A Touch of History

A touch of history. The whole idea of genetic modification is a few decades old. The first couple of groups that managed to do this, that managed to genetically modify lymphocytes to make them recognize a new target that they were not designed to recognize to begin with, is one group in the Weizmann Institute and another group from Japan in the late ‘80s with molecular techniques that were very, very basic back then.

What I like about showing this is this one sentence from one of these papers that says that this approach can be exploited to direct T cells to kill tumor. Even in the 1980s, people had the vision that by genetic modification of T cells, we might be able to kill cancer cells. The way this works is that as I alluded to earlier, T cells do have a mechanism to identify tumor cells, but it’s a very complicated mechanism. Very frequently, the tumor will find way around it and will not be sensitive to killing by a normal T cell.

What the CAR T cell does is basically simplify that mechanism and really build an artificial receptor that would always identify the tumor cells fairly easily.



Slide 17: Assembling CARs for T Cell Therapy

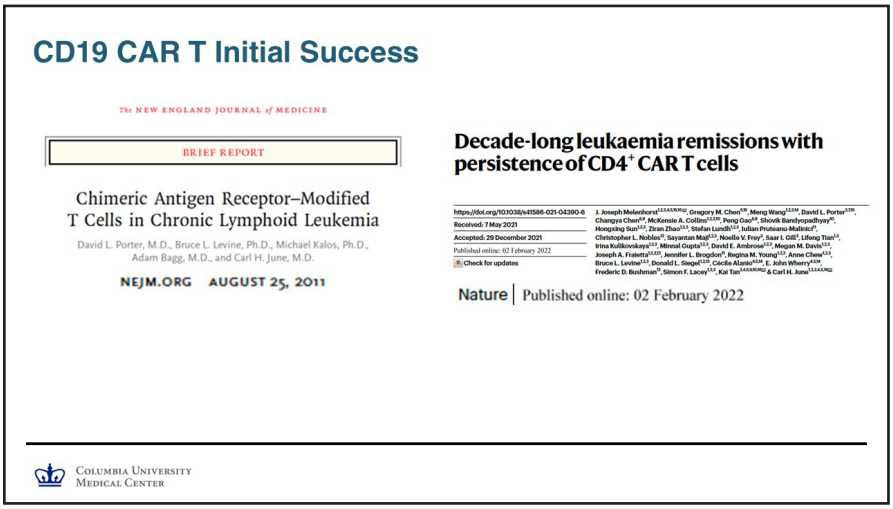
This is in the late ‘80s and we’re now in 2025. Why did it take such a long time? I’m not going to review this slide in detail,

but you could see that there's been a lot of developments that had to happen over the course of almost 3 decades to bring CAR T cells ultimately to patients, a very, very complicated process.

Slide 18: CD19 CAR T Initial Success in CLL

It ends in a happy ending or maybe a happy beginning for a new generation of therapies. I was fortunate enough to be at the University of Pennsylvania as a junior faculty member in August 2010 when the team there infused the first CAR T patient who was a patient with chronic lymphocytic leukemia (CLL) who went into remission after having had every other possible therapy for CLL that was available back then. You could see his picture 7 years later in remission.

We know from this cohort of patients, this first batch of patients that volunteered to go on a clinical trial in 2010, this is what shows us today that this can be a curative strategy in diseases that were previously considered incurable. CLL, even today, most of the time we would say, "This disease is manageable but not necessarily curable." We know based on the fact that there are patients who are 15 years out of their CAR T infusion and are still in remission that this is probably a curable disease with CAR T cells. Not in everyone, but in some patients, it would work so well that these patients will be cured.

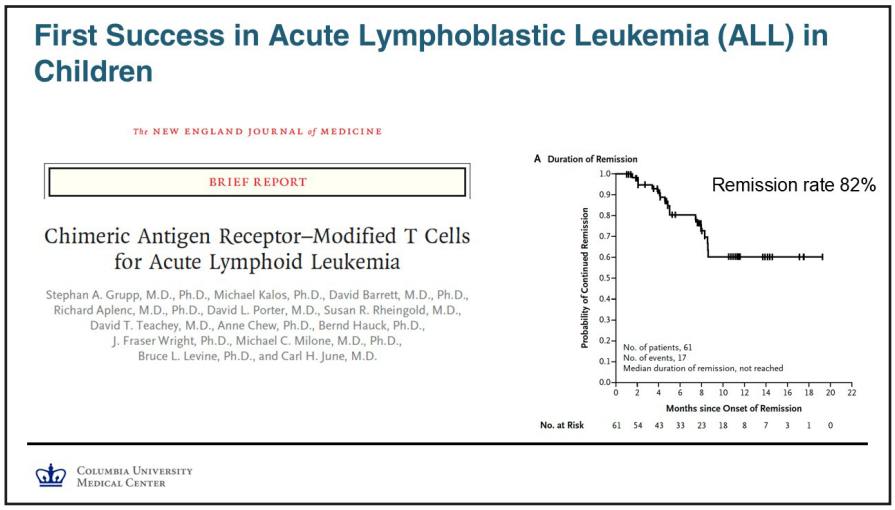


Slide 19: CD19 CAR T Initial Success

This led to a whole bunch of very famous central research papers. We know now that as a result of the first brave volunteers initially in 2010, we know from research that we did on their blood samples that these T cells can persist for at least a decade. That is what supports these longstanding remissions.

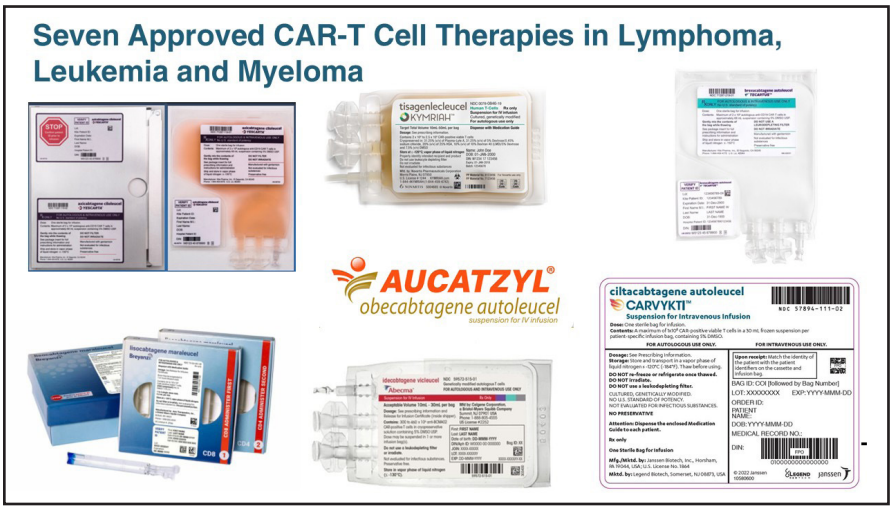
Slide 20: First Success in ALL – Emily Whitehead

Then another inspiring story that happened just the following year is a story that many people might be familiar with because she became pretty famous. That's Emily Whitehead, a cute little kid who had unfortunately acute leukemia (ALL) that has not responded well to any standard therapy back then. Her parents volunteered to be the first patient with acute leukemia in the pediatric side to get CAR T cells. Huge payoff. She was in remission within 4 weeks after that one-time infusion. This is actually outdated since she's now more than 12 years cancer-free and continues to post these lovely photos on her Facebook page. She's a college student at Penn. She remained close to the place that really saved her life.



Slide 21: First Success in Acute Lymphoblastic Leukemia (ALL) in Children

This has become an inspiring story for many other patients and led to this very important publication a year later, where the first cohort of patients of kids with acute leukemia were treated. This taught us that this works in 4 out of 5 patients beautifully in putting them into remission. Not only did it put patients in remission, but about two-thirds of the patients who achieve the remission will remain in remission without any further therapy long-term. There are now many patients like Emily who are more than 10 years out.



Slide 22: Seven Approved CAR-T Cell Therapies in Lymphoma, Leukemia and Myeloma

Fast forward from 2010, 2011 to 2025, we now have CAR T therapies that are not just delivered on clinical trials. We have 7 different CAR T-cell therapies that have gone through all of the work of clinical trials with hundreds of patients treated and have made it through FDA approval. This is what it looks like. It's built basically just a bag that contains several hundreds of millions of genetically modified T cells.

They all have a name on them because each one of these bags was made from an individual patient, which explains a little bit why this is such a complicated strategy that requires really a lot of work and developing it took many years, but it's so gratifying to see how widely applicable this is now.

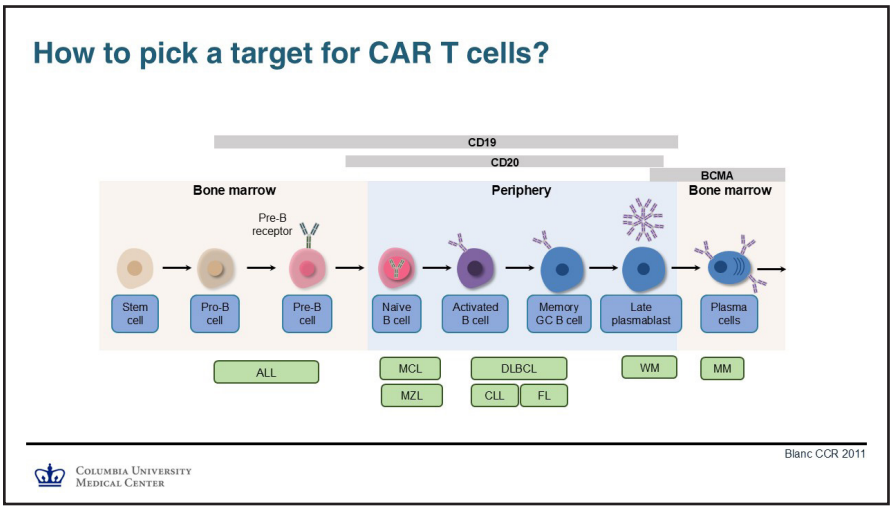
Approved Cellular Therapies in Blood Cancers

Target	Indication	Line	
CD19	Large B-cell Lymphoma	2nd	**Yescarta - Axicabtagene ciloleucel** **Breyanzi - Lisocabtagene maraleucel** Kymriah – Tisagenlecleucel (3rd line only)
	B-cell Acute Lymphoblastic Leukemia	3rd / Refr. 2nd 2nd	Kymriah - (Age≤25) Tecartus - Brexucabtagene autoleucel Aucatzyl – Obecabtagene autoleucel
	Follicular Lymphoma	3rd	Yescarta, Breyanzi, Kymriah
	Mantle Cell Lymphoma	2nd	Tecartus, Breyanzi (3rd line only)
	Chronic Lymphocytic Leukemia	3rd	Breyanzi
BCMA	Myeloma	**3rd** **2nd**	**Abecma - Idecabtagene vicleucel** **Carvykti - Ciltacabtagene autoleucel**

Columbia University Medical Center

Slide 23: Approved Cellular Therapies in Blood Cancers

Here, you can see, there's the list of diseases that we now have CAR T cells for. Diffuse large B-cell lymphoma (DLBCL) is the one that has been the number one indication just because it's a very common disease. It's a common type of non-Hodgkin lymphoma (NHL). It's an aggressive disease. I'm going to spend some time talking about that. You can see many other types of B-cell diseases. More frequently, myeloma is another disease where this is evolving so quickly. We're treating myeloma patients almost weekly. We have patients getting CAR T cells for this disease.



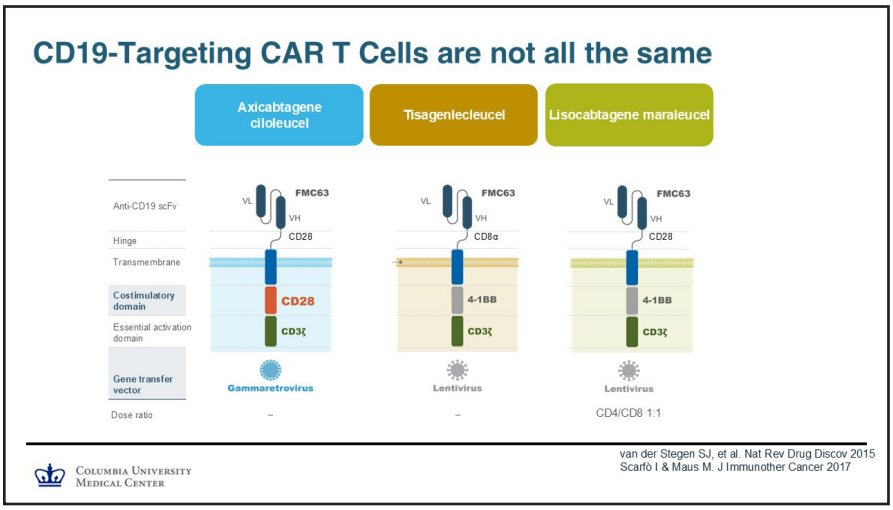
Slide 24: How to pick a target for CAR T cells?

How do we really design CAR T cells? How do we know it's going to target diffuse large B-cell lymphoma versus myeloma? The secret is that the CAR really needs to be designed against the specific marker. We have cells in our body that carry on their surface certain proteins, certain markers that we can design a CAR to identify. The first CAR T-cell therapies were all targeting a protein called CD19.

You can see here why CD19 was chosen as one of the first antigens. You can see that it covers a very broad range of diseases that come from B cells. Here, this is acute leukemia that is highly relevant for children but can also happen in adults through mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), diffuse large B-cell lymphoma (DLBCL), CLL. All of those can be targeted with CD19.

We only needed to make basically one CAR T and already be able to cover a very broad range of diseases. When it gets to myeloma, it gets a little bit more tricky because even though myeloma is a B-cell malignancy, these are B cells that have converted into plasma cells during their maturation. They no longer express CD19, but they do express other markers. The CAR T that were developed for myeloma are a different CAR. They target B-cell maturation antigen (BCMA) That's the way the CAR can find these malignant cells in the body.

Now, we're working with a much broader range of antigens and a much broader range of CARs because we also want to develop therapies for AML (acute myeloid leukemia) and myelofibrosis and polycythemia and, of course, lung cancer and bladder cancer and prostate cancer. For each one of those diseases in clinical trials, we have a range of different markers that we're already working with.

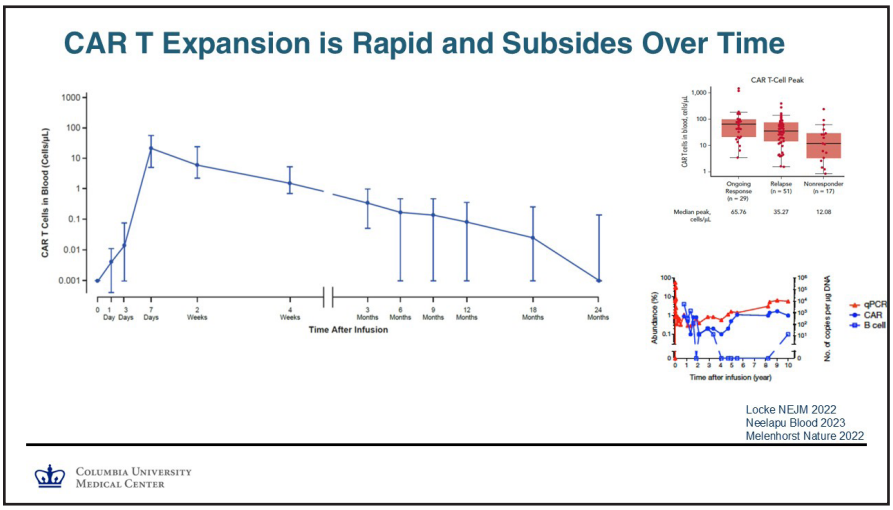


Slide 25: CD19 – Targeting CAR T Cells are not all the same

This looks like a very complicated slide. We're not going to have an exercise in how to build CAR T cells in your own kitchen. The purpose here is really to show you that we have multiple CAR T cells even against the same antigen. They're not all created equal. You might come and ask, "If they all target CD19 and you just showed us that CD19 is on all B cells basically and can be used in any B-cell cancer, why do we need 3 of them?" We actually have 5 of them. I'm only showing 3 on this slide.

Well, that's like asking, "Why do we have different types of cars on the road?" One person might get a BMW and another person might get a Honda. They still serve the same function of getting us from point A to point B quickly, efficiently, and safely, but they're still all very different. Someone who lives on a farm will not buy the same type of car as someone who lives in Florida and can get them convertible to drive to the beach. Someone who needs to drive in the snow like I did this morning here in New York, then definitely needs a different type of car.

CAR T cells also have these subtle differences between them in their structure, in the way they're manufactured, in how quickly they're manufactured, and in what diseases they were really tested. This is also the reason why you don't just order CAR T cells on Amazon. You need to go to a specializing doctor, in a specialist center to discuss: What is the CAR T cell that is the most appropriate one for my disease?



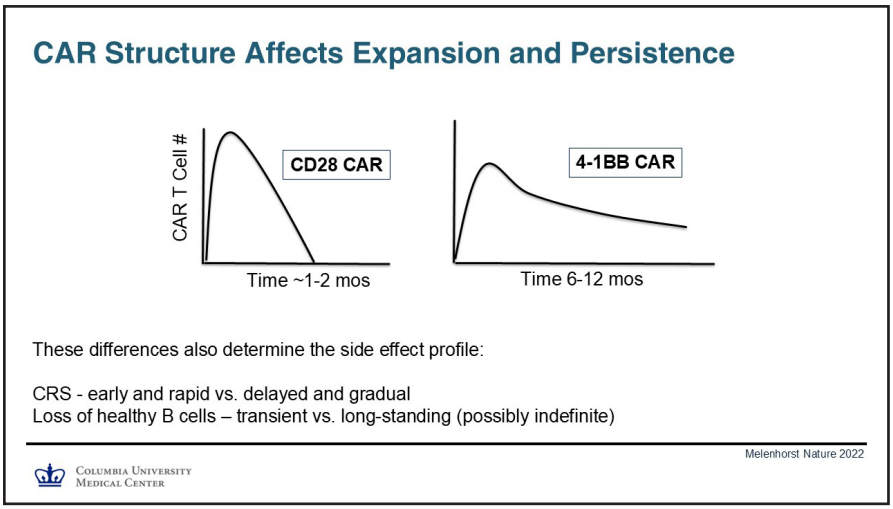
Slide 26: CAR T Expansion is Rapid and Subsides Over Time

What happens to the CAR T cells when they go in the body? As I alluded to earlier, we give a certain number of T cells. They actually expand in the body to hundreds and millions and billions of cells. We can measure that. You could see here on this axis; you could see the time after the infusion. Day zero is the day of infusion. You could see here the level of CAR T cells that we can measure in the blood. You could see that the expansion phase is very rapid.

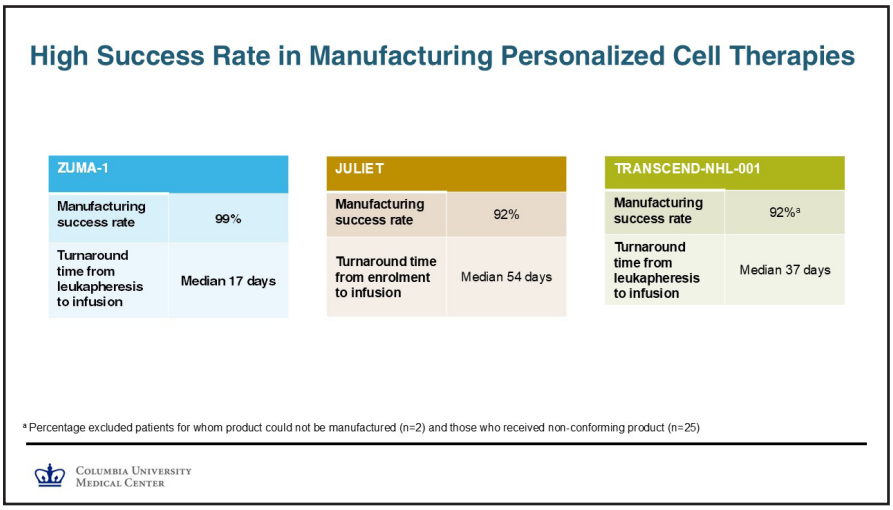
By day 7 or day 10, somewhere around this, the CAR T cells will expand to a degree that you can even detect them on a simple blood count. The regular blood counts that you use at your PCP (primary care physician) would generally not be able to detect them. If we use more sophisticated techniques and we look at all the T cells in the blood, we could see that sometimes on day 7, 20% or 50% or 70% of all of the T cells are actually CAR T cells. This is how wild their expansion is.

Then it subsides over time. It does not subside all the way to zero because in many patients, we can still find CAR T cells in the blood or in the tissues even a year or 2 after the infusion. As I showed you earlier in some patients, even at much later time points. We know that this expansion is important. In those patients who don't have any expansion, for whatever reason, we don't even always know why. The chances of response to CAR T depends significantly on the ability of these cells to expand.

You can see here when you look at the CAR T expansion in patients who achieve a durable response versus non-responders, the non-responders, it might be because their cells did not expand well. We're doing a lot of research work to try and understand why there's a small portion of patients who don't have good expansion of CAR T cells and working on methods to resolve that as a problem. As I showed you earlier, in some patients, you could follow this plot for 10 years. You will still be able to identify some CAR T cells even at such a late time point.

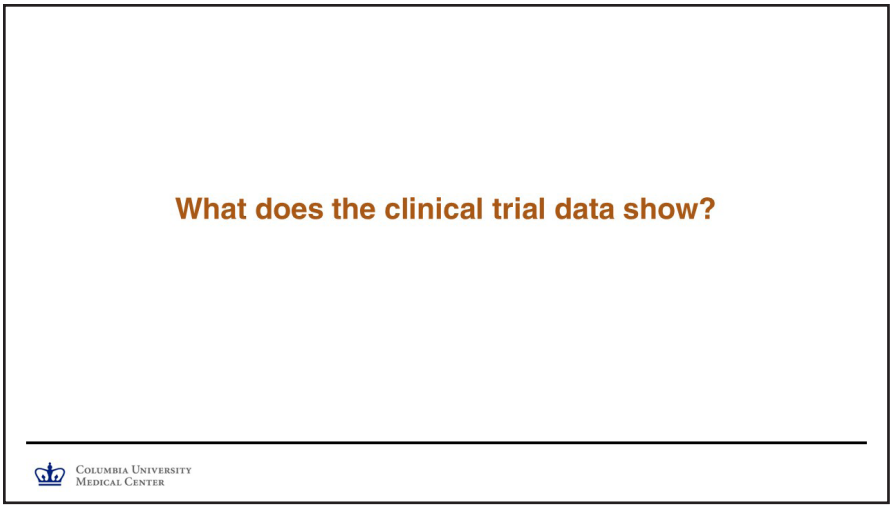


Slide 27: CAR Structure Affects Expansion and Persistence



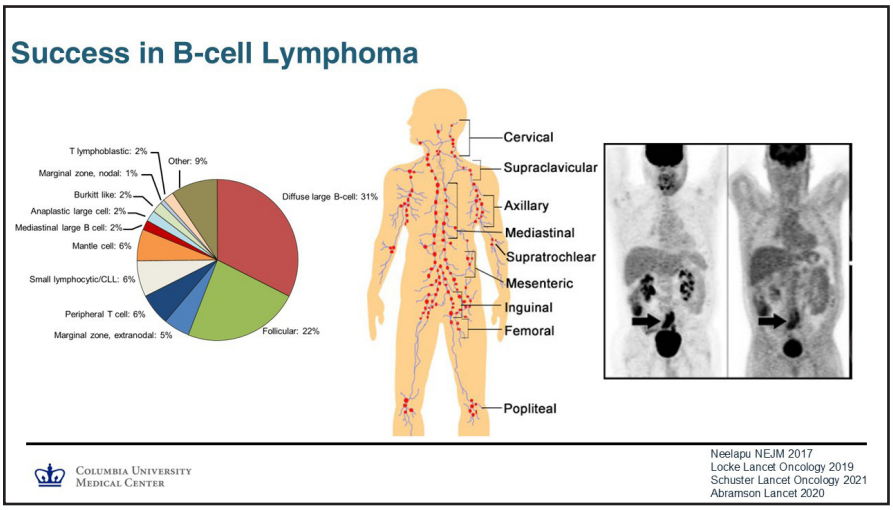
Slide 28: High Success Rate in Manufacturing Personalized Cell Therapies

I'm going to skip a couple of slides just because I want to leave enough room for discussion, but all of these slides are posted. I think you should be able to have access to them.



Slide 29: What does the clinical trial data show?

Let's talk a little bit about the clinical trial data and how it supported the approval of CAR T cells.

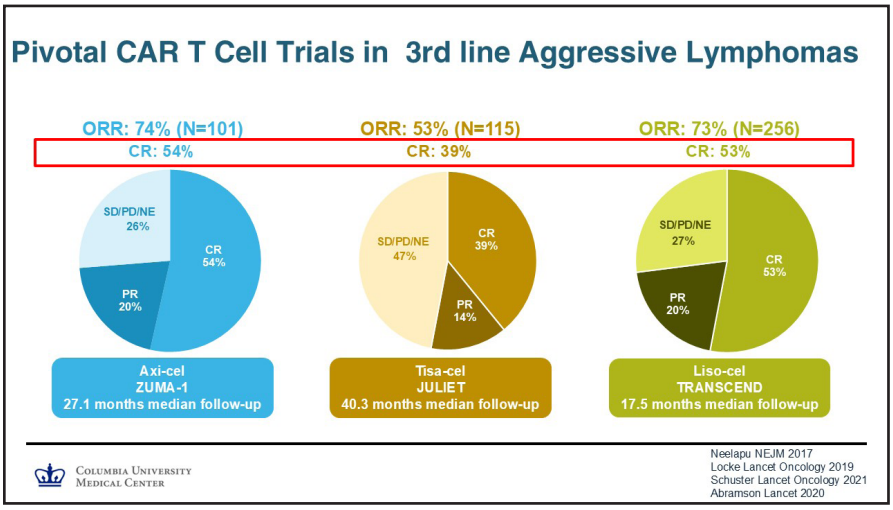


Slide 30: Success in B-cell Lymphoma

Most of the work has been done in B-cell malignancies as I mentioned. Maybe the one that's most important is a disease called diffuse large B-cell lymphoma (DLBCL) and it's important for 2 reasons.

Number one, it's the number one most common disease within the B-cell lymphomas. Number 2, it is a fairly aggressive disease, and it is curable. Many patients are actually cured of diffuse large B-cell lymphoma even with a standard therapy like R -CHOP or some other chemotherapy regimens, but some patients are not. We need better therapies to help them and give them a curative option even if the first-line therapy did not work.

B-cell lymphomas can happen in various places in the body, usually arising from lymph nodes, which as you can see here, can be present in various places in the body. This is what a PET scan would look like. Again, showing high uptake or high brightness. This is now in black and white, so the colors are reversed. The black areas are the ones that actually have lymphoma in them, except for the bladder and the kidneys, which actually have their own brightness naturally.



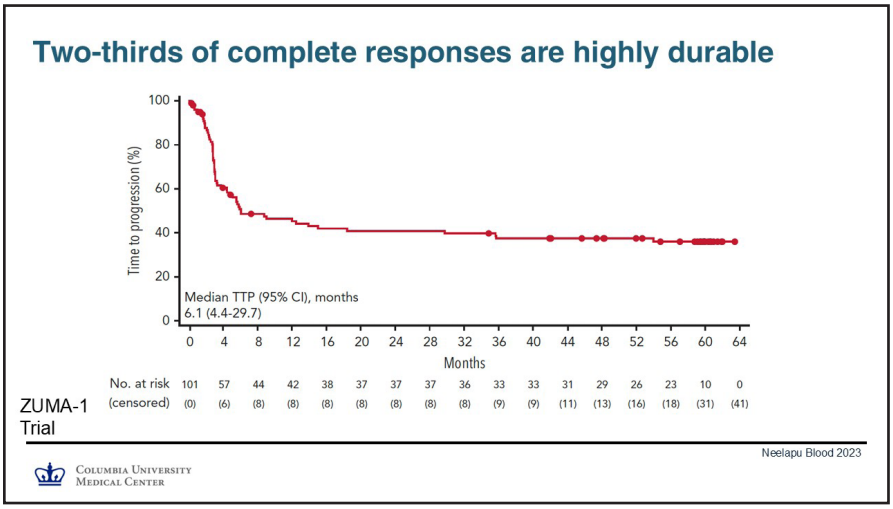
Slide 31: Relapsed/Refractory MCL

There have been a number of clinical trials that were done in this aggressive type of lymphoma and other aggressive types of lymphomas. We started by studying patients who failed a number of therapies, so not patients initially

diagnosed. You can see in patients who are at least in their third line of therapy, these were the first clinical trials published in 2017, 2019. You could see that the overall complete remission rate, which is really the number I'm looking for because you have to achieve a complete resolution of the cancer with CAR T cells for that to be effective on the long run.

More than 50 % of patients achieve that despite the fact that some of these patients have had very refractory, very resistant disease. You could see that the numbers are not completely the same across all different products, which, again, is a good example for this level of diversity that we have among these products. These are also not identical clinical trials. These are not necessarily comparable.

Again, another reason to go see a specialist in this field is to ask them, "Well, which of these trials would I have been a good fit? What does that mean? Which CAR T cell now should I be getting for my disease?"

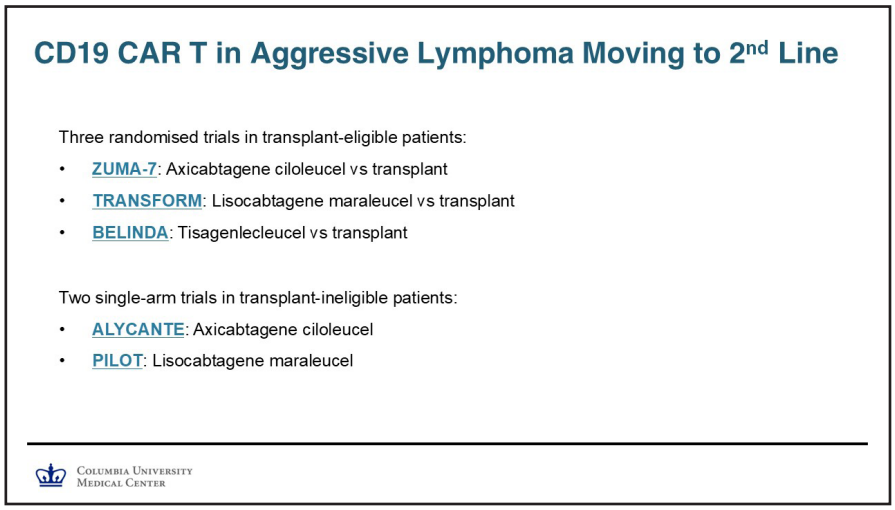


Slide 32: Two-thirds of complete responses are highly durable

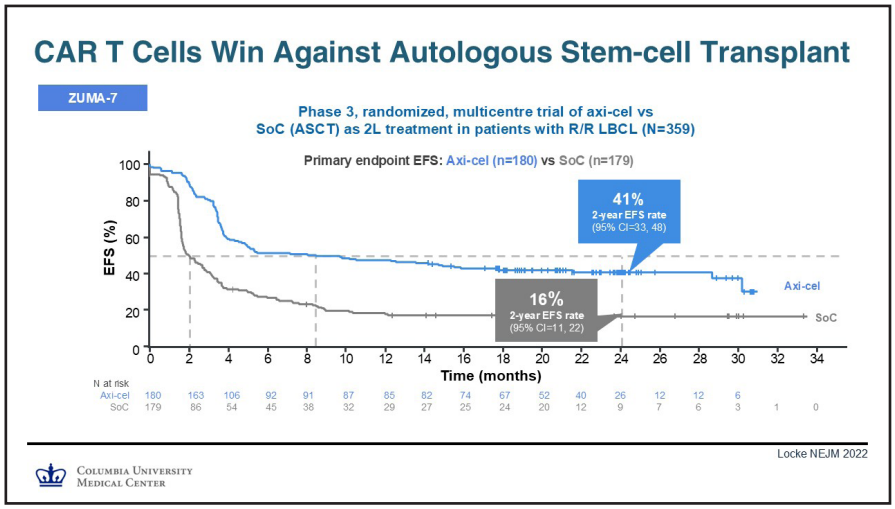
What we've also learned through this clinical trial data is that if you do achieve a complete remission, about 2 to 3 of those patients will just remain in a durable remission long term.

Because some of these studies were done and completed in 2017 or 2018, we now have more than 5 years of follow-up on these patients. We can tell, you can see on this plot, this is time from the infusion, and this is the percentage of people who remained in a durable response. You can see that if you don't respond well, you will know that by about the 1-year milestone. If you've crossed the 1-year milestone and your disease is in remission, this flattens out.

Your chances of the disease coming back after the first year are actually very low. This is true in aggressive lymphomas, but also true in some other diseases. I'm going to show you some of these plots in a second.



Slide 33: CD19 CAR T in Aggressive Lymphoma Moving to 2nd Line



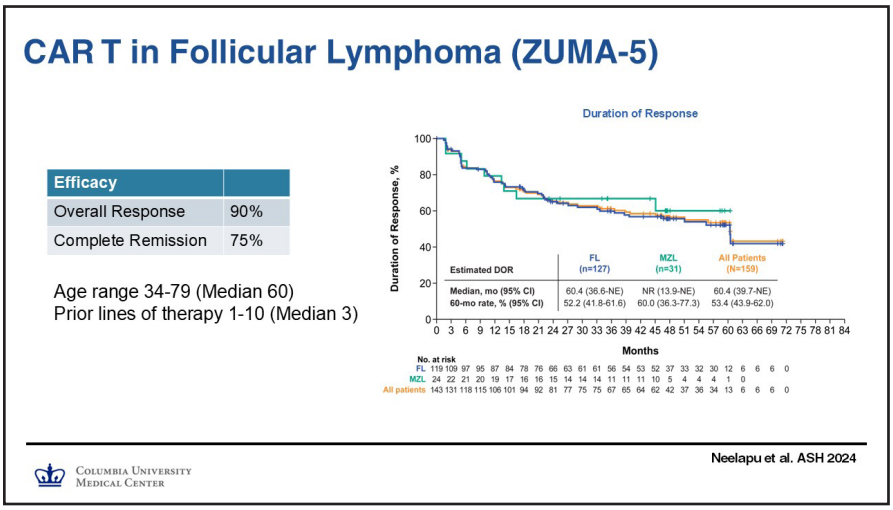
Slide 34: CAR T Cells Win Against Autologous Stem-cell Transplant

What happened after the approval in this third-line setting is that we very quickly were aiming to move this to an earlier line. In an earlier line, we already had some therapies that were working quite well.

Primarily, we were doing a lot of bone marrow transplants in patients with diffuse large B-cell lymphoma and other types of aggressive lymphomas. That was the standard of care. What we had to do to prove that CAR T cells work is actually do what we call a randomized trial. Take 360 patients and split them one-to-one by computer. We didn't decide who gets what. It was basically by a draw made by a computer.

In which case, half of the patients got CAR T and half of the patients proceeded with what was considered standard at that time, which was a bone marrow transplant. Then we compared which patients did better. At the end of the study, it was very, very clear that again, we were able to put about two-thirds of the patients in remission with CAR T and about less than 20% in a durable remission with a bone marrow transplant.

The success of CAR T was clearly better than a bone marrow transplant. After the results of these studies came out, pretty much overnight, we stopped doing bone marrow transplants. Any patient who came to us who had already had one line of therapy for an aggressive lymphoma, we started giving CAR T. That remains today for the past 4 years, basically, the standard of care for second-line treatment in diffuse large B-cell lymphoma.

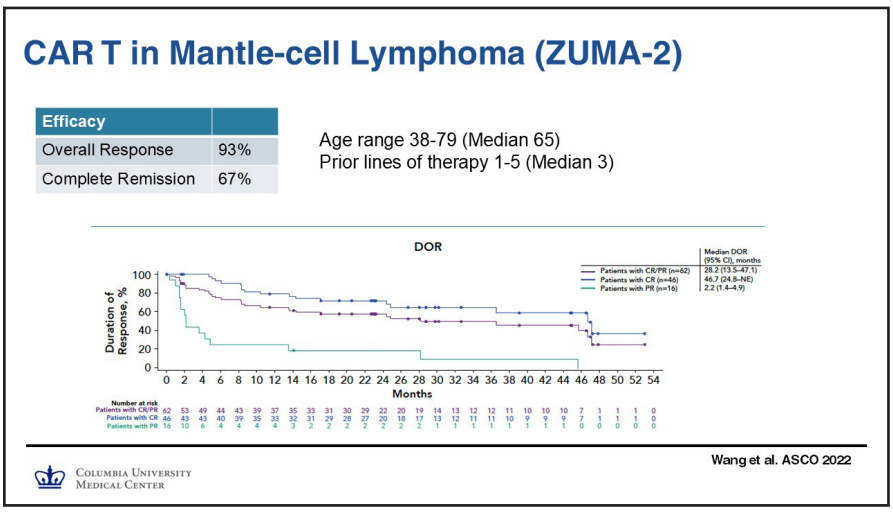


Slide 35: CAR T in Follicular Lymphoma (ZUMA-5)

We've also given now CAR T cells in a bunch of other diseases. I'm not going to have time to review each and every one of them, but I'm just going to show you some examples of how well it works in other diseases. This is follicular lymphoma (FL). I'm not going to show you each and every product because there are 3 different products approved for follicular lymphoma. I'm showing you an example here for one type of CAR T that was able to generate a response in 90% of the patients.

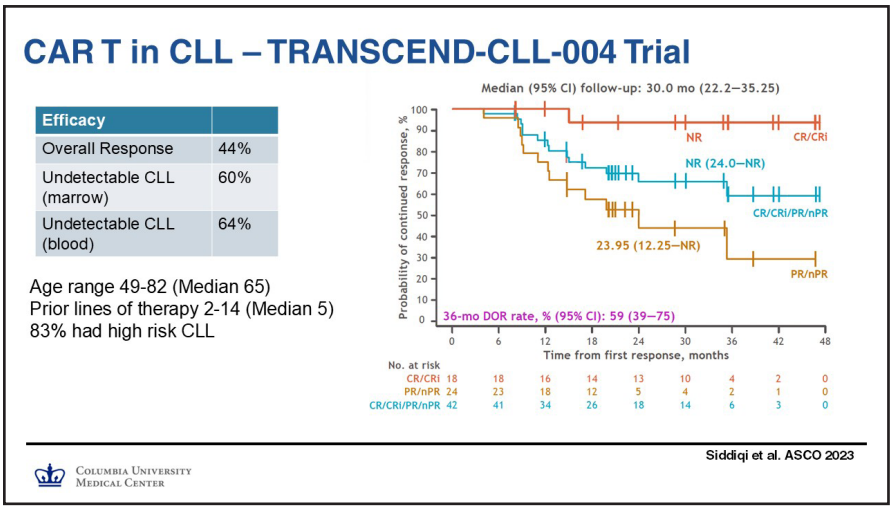
Then 3 out of 4 patients had a complete remission. Patients up to age 79 were treated. Patients with up to 10 prior lines of therapy were treated on this trial. You could see again here that these responses are very durable. Here again, we have up to 5 years of follow-up data, which shows that more than half of the patients who had an initial response are still in remission 5 years later without receiving any therapy.

They went back to work, went back to school, went back to taking care of their children, grandchildren and having fun with them, and mainly stopped all therapies. Their immune system was able to recover. They were able to remove any side effects that they've had from prior therapies and were leading a normal life. I have patients who are CEOs of companies, kindergarten teachers, people who do farming work in upstate New York and other types of places more distant from the city. Definitely, these are people who are able to go back to normal life several months after getting CAR T.



Slide 36: CAR T in Mantle-cell Lymphoma (ZUMA-2)

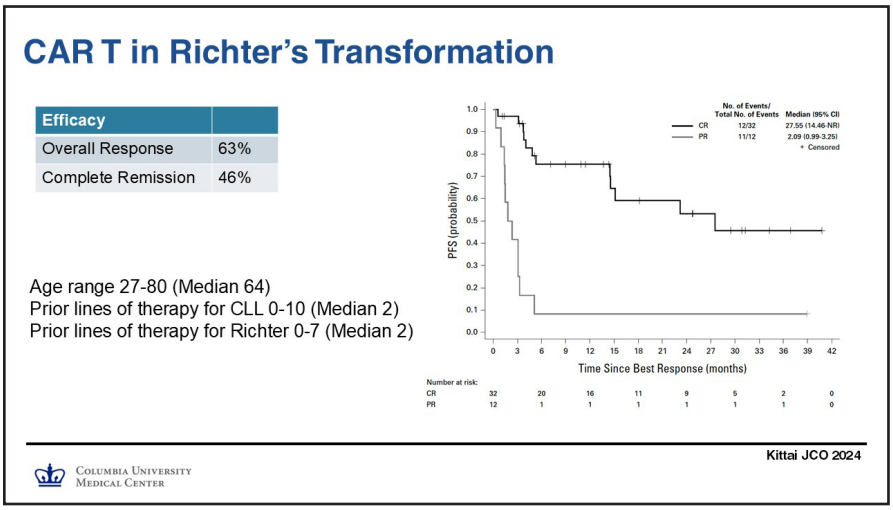
In mantle cell lymphoma, also major success. This is a pretty challenging disease to treat. Thankfully, it's not particularly common, but we see complete remissions in 2 out of 3 patients. You could see a similar pattern. About two-thirds of these remission patients will remain in remission on the long run. It's quite possible that they will never have a recurrence of their disease.



Slide 37: CAR T in CLL – TRANSCEND-CLL-004 Trial

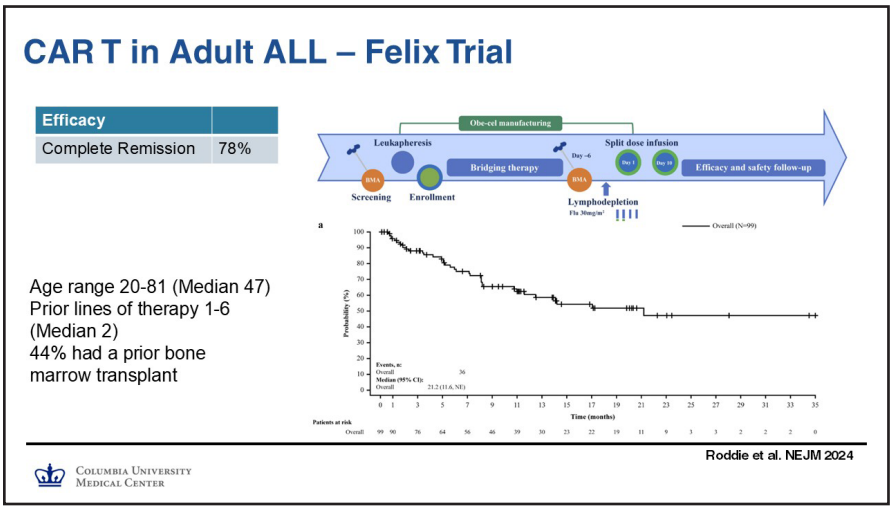
A more recent product that was approved is the first CAR T in CLL (chronic lymphocytic leukemia). Despite the fact that the first patients we treated at Penn 15 years ago were CLL patients, that was set aside a little bit because there are some challenges in manufacturing CAR T in CLL. CLL has also seen a huge amount of development of other therapies throughout these years, but we circled back to studying CAR T in CLL. Thankfully, we now have the first CAR T approved.

We're able to generate undetectable CLL state in the marrow and in the blood in more than 60% of the patients. You could see here as time goes by, we're getting definitely more gutsy in what type of patients we treat. Up to age 82 were treated here and up to 14 prior lines of therapy and nearly all patients had high-risk disease. In CLL as well, we don't yet have 5 or 6 or 7 years of follow-up on these large clinical trials, but we know from our experience back at Penn that CLL can be cured with CAR T in at least some of the patients.



Slide 38: CAR T in Richter's Transformation

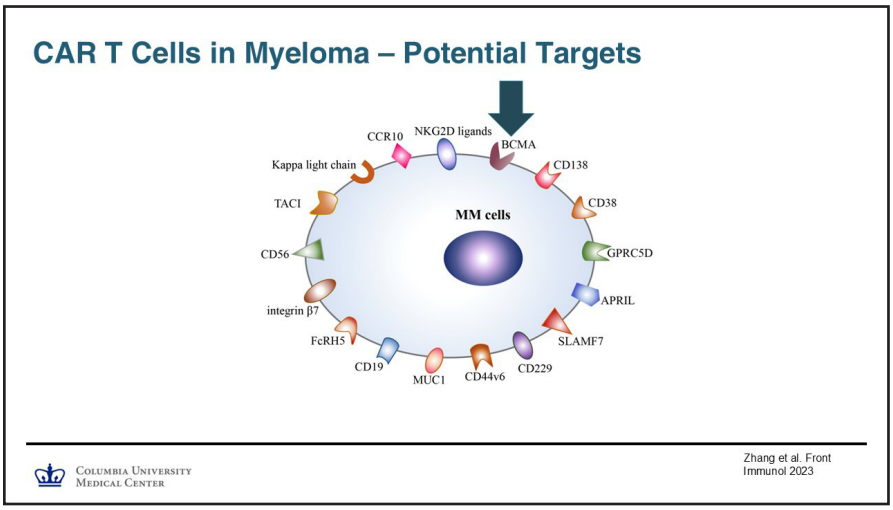
Another form of CLL, which is called Richter's transformation (RT), which is when CLL decides to become an aggressive type of lymphoma, very difficult disease to treat in some patients. We're also seeing some very favorable responses.



Slide 39: CAR T in Adult ALL – Felix Trial

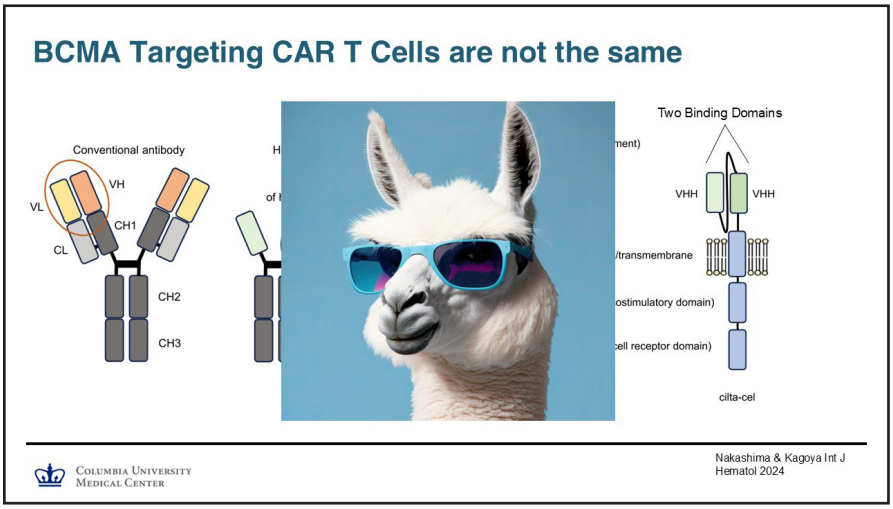
Very recently, we've had another approval of CAR T in adult acute leukemia, which is quite challenging to treat. It's a very aggressive disease in adults.

One thing that they did here was a new concept, which is to split the infusion into 2 separate infusions. The reason you do that is that sometimes you have so much leukemia in the body that throwing the CAR T on top of that will just cause a lot of side effects. If you split the dose and you give a small dose initially and a bigger dose later on, you may actually reduce the leukemia a little bit more gently and avoid a lot of the more severe side effects.



Slide 40: CAR T Cells in Myeloma – Potential Targets

Let's move on for a few minutes to talk about myeloma and then we'll spend a few minutes on side effects and move to the Q&A. Myeloma does not respond to CD19 CAR T because CD19 is not meaningfully expressed in myeloma cells, but turns out that on the surface of myeloma, there's a whole bunch of other markers you could use. The work so far has been focused on this antigen called BCMA (B-cell maturation antigen).



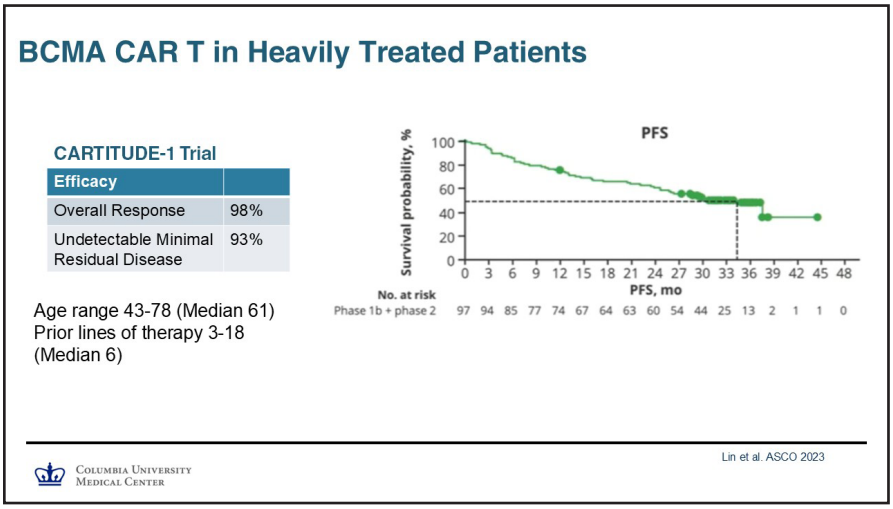
Slide 41: BCMA Targeting CAR T Cells are not the same

We have 2 products that are approved against BCMA and work really, really well. Again, why do we need 2 products? They're not identical. They have differences even in their main structure. The regular CAR T cells, and one of them is I would call it more similar to the ones we have against CD19, they rely on a certain structure that uses something called a heavy chain and a light chain. It creates this Y shape as you could see here, but we can also make antibodies that are a little bit more stable to make the CAR T cells.

That's when we use them only from heavy chains, which means that we can create 2 completely different types of CARs against BCMA. Both of them will target BCMA, but they will bind BCMA in a very different way. Very importantly, this heavy-chain CAR will have 2 binding domains. It'll be able to target and bind 2 molecules of BCMA at the same time. The anecdotal thing about this, which is again a funny anecdote, is where would we get high heavy-chain

antibodies? How did we even learn that this exists?

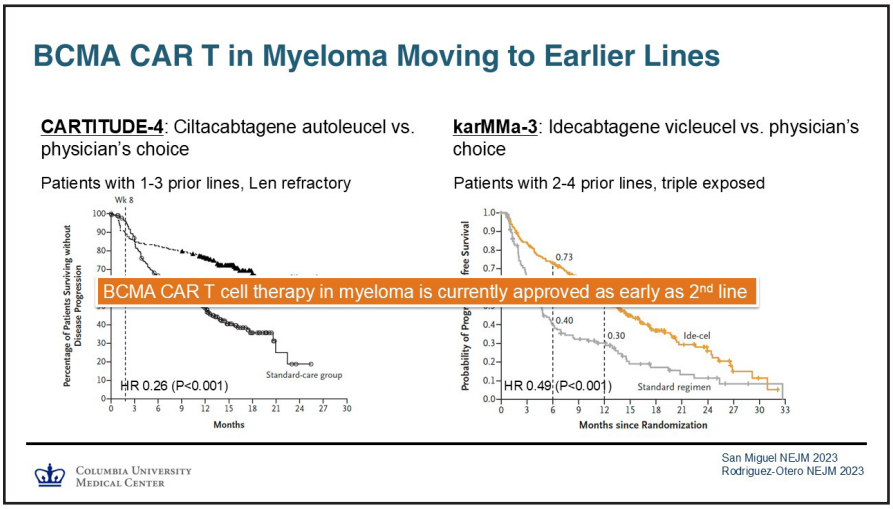
Humans don't have heavy-chain antibodies, but this is why we sometimes study other species. Turns out that llamas and camels and other desert animals have heavy-chain antibodies. The reason they have those is because they're more heat-resistant. We are just using that knowledge. We're using that biology to make, to engineer CAR T cells that use the same principle. These seem to be working better in myeloma specifically.



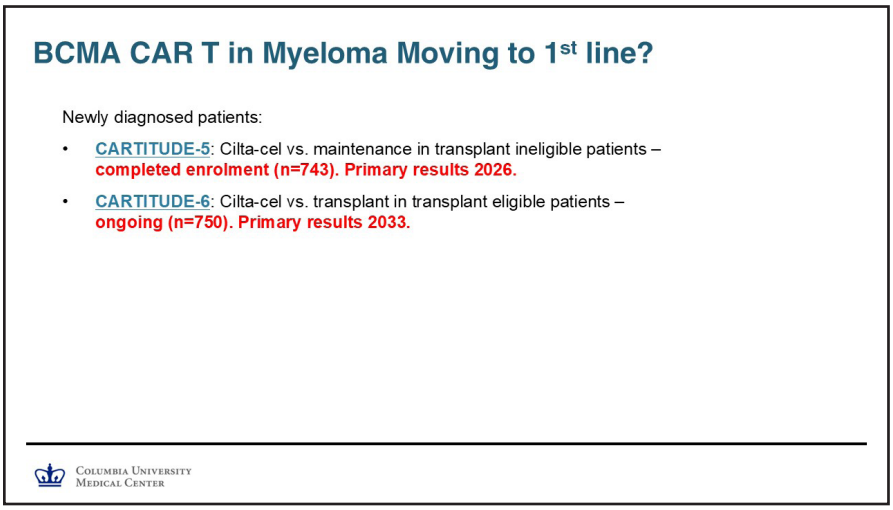
Slide 42: BCMA CAR T in Heavily Treated Patients

We could see here amazing results with CAR T in myeloma in patients up to age 78 with up to 18 prior lines of therapy achieved a response in nearly 100% of the patients.

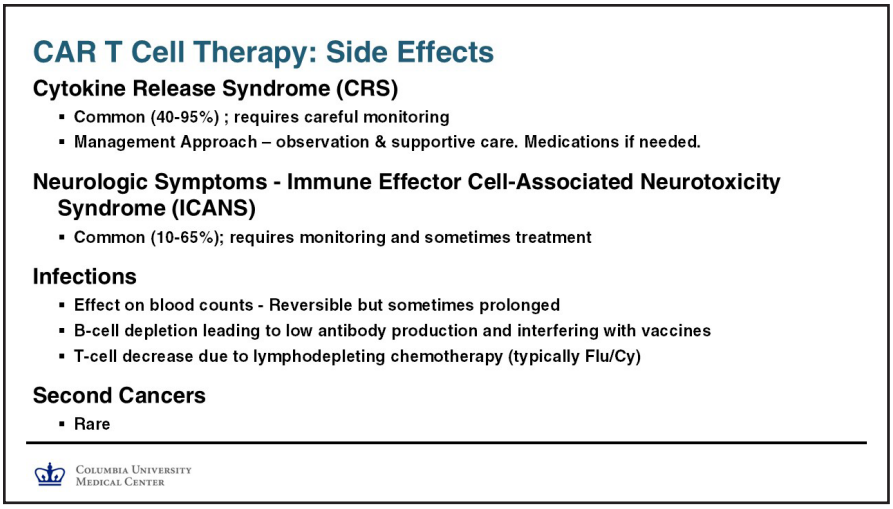
Half of those patients are still in remission 3 years later. Now, that may sound a little bit short for someone who is just diagnosed with myeloma because we can achieve remissions that are years long in newly diagnosed patients, but these are not the patients who went on these initial clinical trials. These are patients who've already had numerous lines of therapy. Their disease has already become very resistant, so to achieve an average of 3 years in remission with no other therapy on board is quite successful.



Slide 43: BCMA CAR T in Myeloma Moving to Earlier Lines



Slide 44: BCMA CAR T in Myeloma Moving to 1st line?



Slide 45: CAR T Cell Therapy: Side Effects

Let's talk about the side-effect profile a little bit. The side effects of CAR T cells have to do with the way they work. They work against cancer the same way the immune system works against a bad infection. It can induce a large amount of inflammation that can make you feel pretty sick, just the same when you feel sick when you have the flu. Instead of calling it the flu, we call it cytokine release syndrome (CRS) because it's related to certain chemicals that the CAR T make and cause us fevers and chills and rigors and muscle pain and joint pain and can sometimes make us even sicker than that.

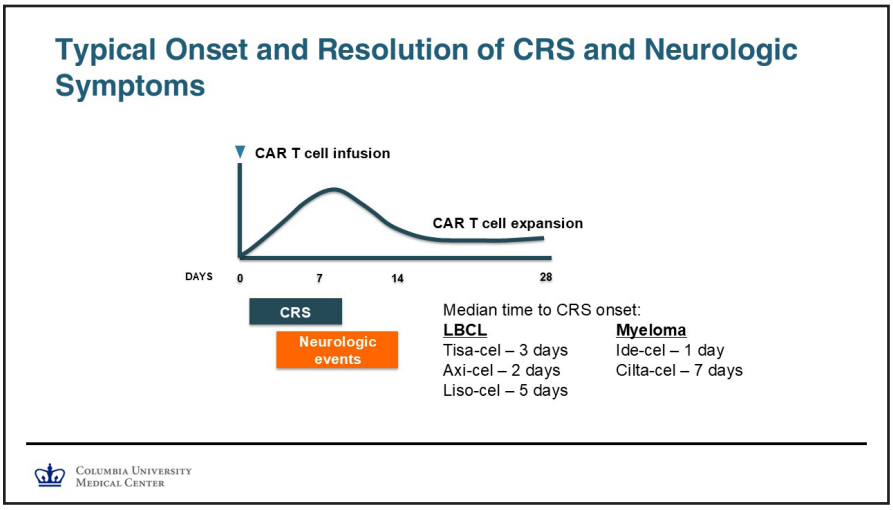
It's an almost universal side effect in some CAR T cells, a little less common in others, but this is something I tell all patients to anticipate. In most cases, it'll be just a high fever. Neurologic symptoms also have to do with this level of inflammation because CAR T cells don't distinguish between different organs in the body, and they can go into the brain just as much as they can go into any other organ. This is a strength of the CAR T cells because one of the weaknesses of chemotherapies and antibody therapies is that they don't penetrate the brain. Many cancer cells sometimes use that to their advantage and hide in the brain and can come back later because chemotherapy couldn't touch them.

The fact that CAR T cells can penetrate the brain is actually helpful, but the downside is that some patients may develop some neurologic side effect, which could be anything from a tremor or a headache all the way to having mental status changes or, even in extreme situations, seizures or swelling of the brain. Thankfully, those cases are very rare.

Infections are important to keep in mind because when we give CAR T cells, we weaken the immune system transiently. The blood counts will come down because of the chemotherapy. B cells will come down because that's part of what CAR T cells do. T cells will come down again because of the chemotherapy. Those will all recover over time, but for the first few weeks after CAR T-cell therapy, you may have a high risk for infections. You may need to be on certain medications to prevent infections.

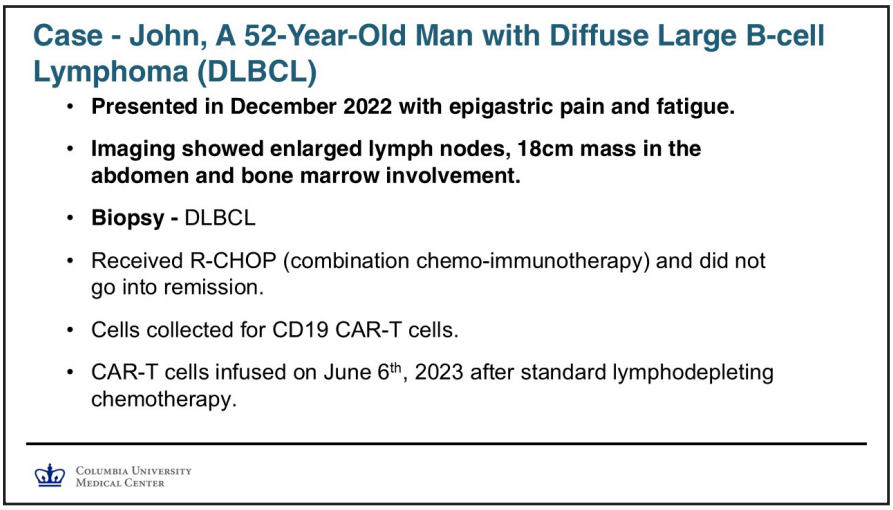
The last thing that has become a little bit of famous in the past few months is the chance of getting second cancers over time. Now, second cancers is a side effect of almost any cancer therapy. In fact, anyone who has one cancer has a slightly higher risk of getting a second cancer down the road. These are ultimately pretty rare. Having a second cancer that is derived from the CAR T cell itself because of the genetic modification is something that probably happens in 1 in 1000 cases. It's not common.

We're keeping an eye on that to try and understand why that happens and who is really at risk for that, but it's not something that to me as a physician is a barrier to getting CAR T cells because it may happen in 1 in 1000, but so many hundreds of patients will be cured of an otherwise life-threatening disease.



Slide 46: Typical Onset and Resolution of CRS and Neurologic Symptoms

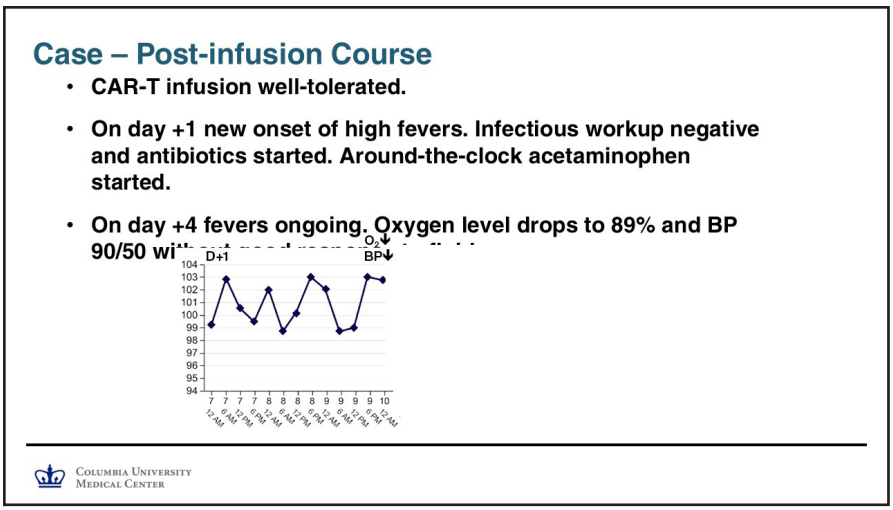
The onset and resolution of these symptoms is all within the first 14 days. It may vary from one CAR T to the other. It may vary based on what disease you're taking care of, but it ultimately happens within the first 14 days, which is when you will be under very close monitoring in the hospital or very close monitoring is an outpatient. The other side effects, such as infections may last a little longer until you really recover in the immune system, but these more, I would say, scary ones would happen during the acute monitoring phase pretty much universally.



Slide 47: Case – John, A 52-Year-Old Man with Diffuse Large B-cell Lymphoma (DLBCL)

Let's just look at a quick case of a patient. One of the patients we treated very early on in our program around-- no, I actually took a different patient for this presentation. I'm sorry. This is a more recent patient who presented with some pain in the belly and fatigue, had a very large mass in the belly and enlarged lymph nodes in some other places. The biopsy showed diffuse large B-cell lymphoma. He started with what a standard therapy called R-CHOP, which many patients who've had lymphoma are familiar with and then did not go into remission.

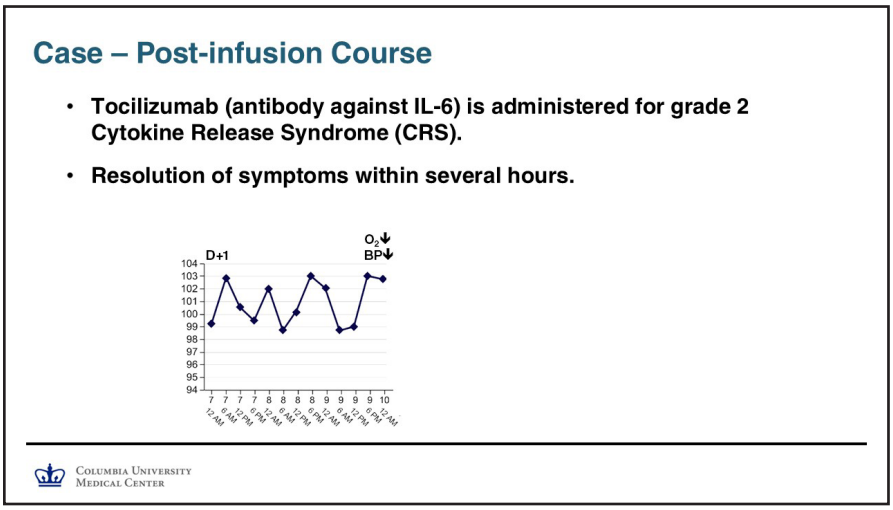
Nowadays, we don't wait for patients to fail multiple lines of therapy. We take a patient like John and immediately go for CAR T cells. We collect cells by leukapheresis and then infuse the cells with standard chemotherapy as I explained initially.



Slide 48: Case – Post-infusion Course

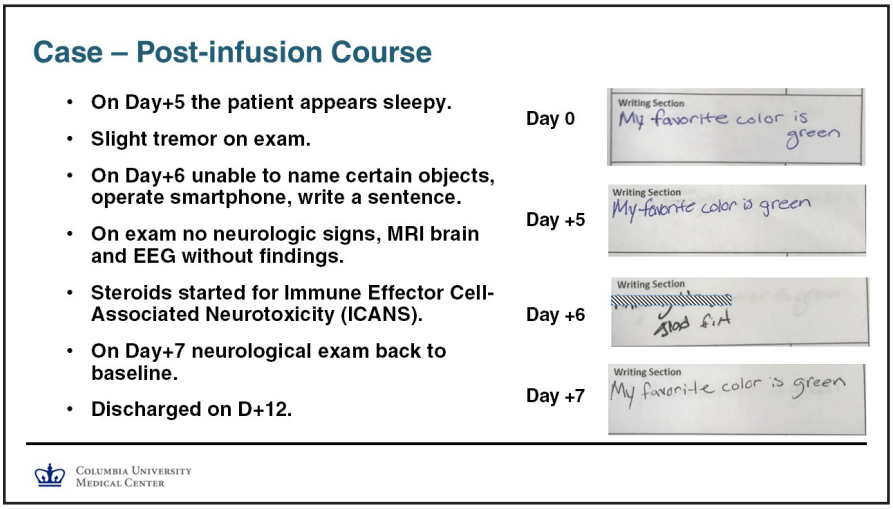
This is what happens after the infusion. In this patient specifically within 24 hours, you can see the timeframe here at the bottom, and this is a temperature curve. It's seated within 24 hours after the infusion, a temperature of 103.

You can feel pretty poorly with the temperature of 103, but you get some fluids, you get Tylenol®, and ultimately, we don't necessarily do anything about it if it's really just a fever, but at some point, John is experiencing low oxygen levels and maybe a somewhat low blood pressure. At that point, we want to pour some water on the fire and extinguish it a little bit. We give a drug called tocilizumab.



Slide 49: Case – Post-infusion Course

Tocilizumab is a drug that mitigates some of that inflammation. As you could see, it worked really well for John, and within several hours, fever has come down and he, in fact, remains pretty much afebrile for the rest of his hospital stay.



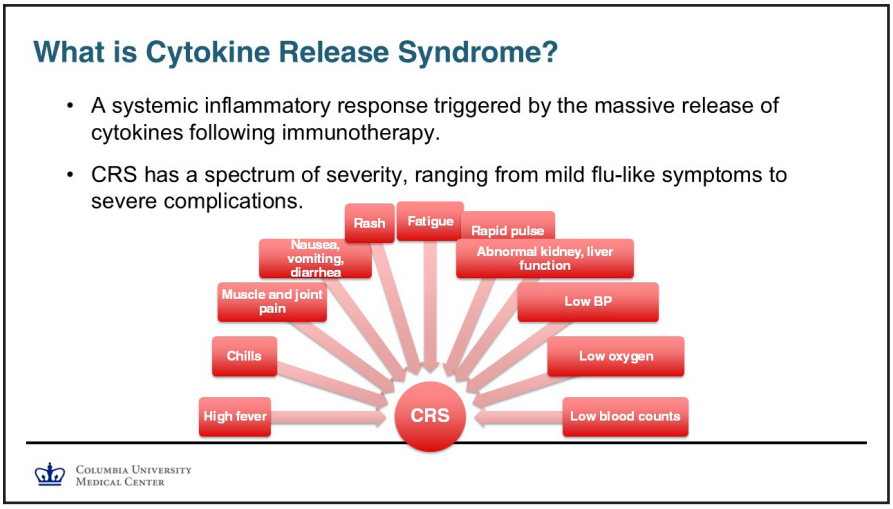
Slide 50: Case – Post-infusion Course

What happens next is an interesting evolution, but on day +5 after the infusion, he seems a bit more sleepy to his family members and has a little bit of tremor on exam when he wakes up. We have our patients undergo a very meticulous neurologic monitoring during the hospital stay. For example, we ask them to write a sentence 2 or 3 times a day on a piece of paper. We ask them to pick their own sentence. It's pretty funny what type of sentences people choose to write.

You could see on day +5 that the patient has a little bit of tremor that you would even notice just by their handwriting. Then this continues to evolve. Then the next day the patient is awake, communicates but is unable to name certain objects, can't operate their smartphone, can't write a sentence. At this point, the patient is asked to write a sentence, and instead, he writes his name, which is why I blocked it here, but write something that is very different and illegible.

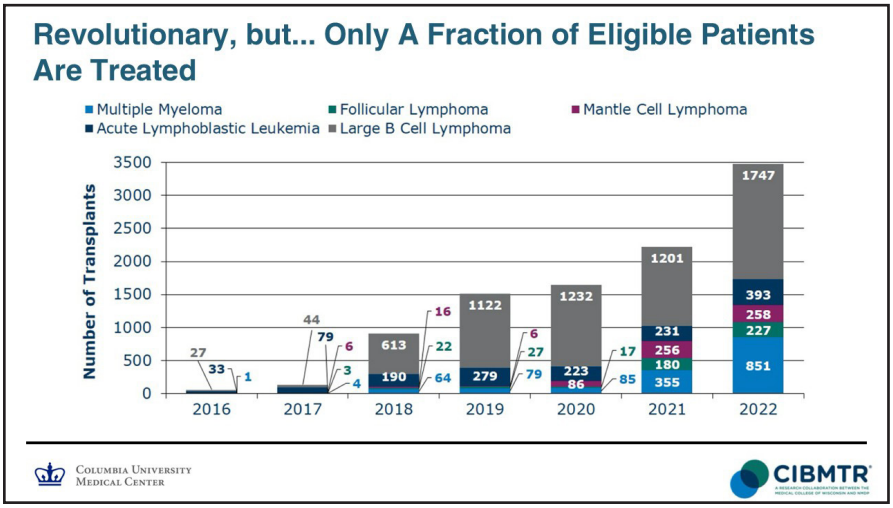
At this point, again, this is a good enough reason to try and mitigate some of the inflammation. We give this patient

steroids. We send the patient to an MRI of the brain; we get an EEG just to make sure there's nothing else going on. This is called immune effector cell-associated neurotoxicity (ICANS). You can see the response to steroids is very fast in this case, and by the following day, the patient is completely intact, doesn't have a very good recollection of what happened before the previous day, but has a perfect handwriting, can remember how to name things, and knows exactly what's going on. This patient goes home on day +12 and is completely intact, has no residual neurologic issues.

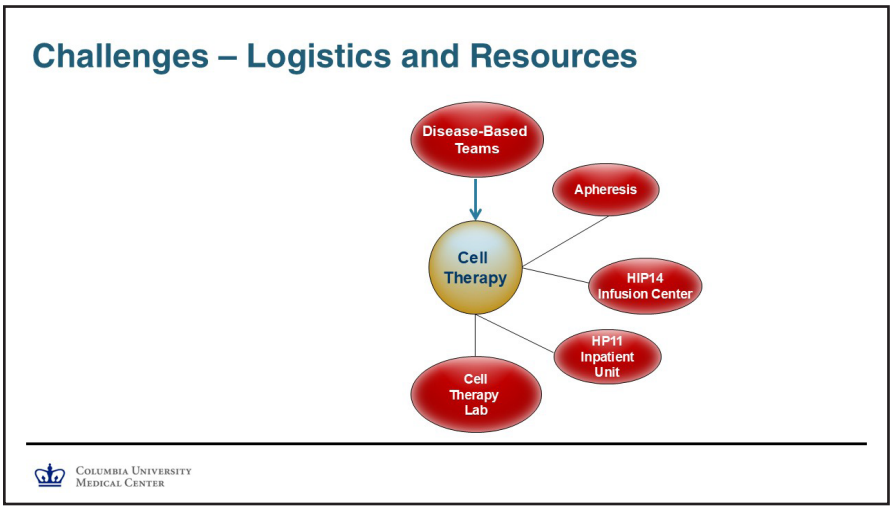


Slide 51: What is Cytokine Release Syndrome?

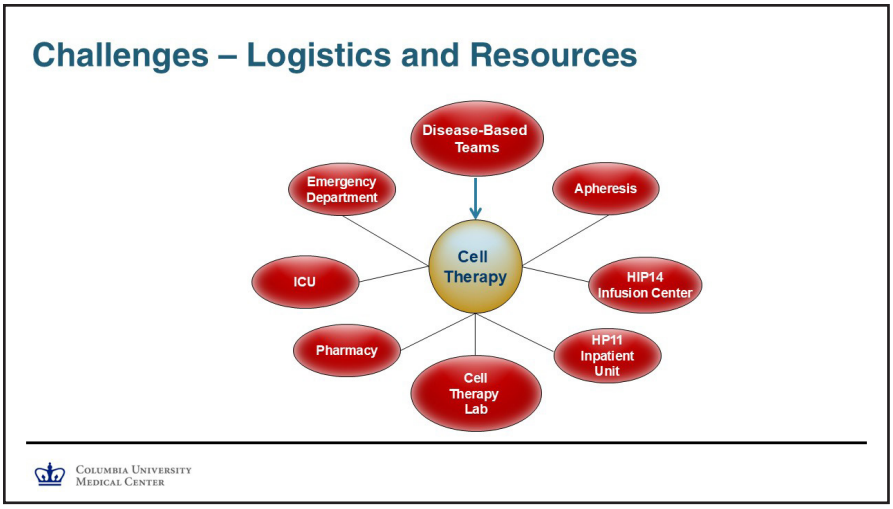
This is kind of a typical syndrome, and you could see here some other symptoms that may happen, and we choose to intervene based on how severe they are. If it's someone who only has a fever for a couple of days, we might just give Tylenol®. You don't need to intervene. You just can allow the inflammation to happen because it will subside on its own at some point, but in cases where some more significant symptoms happen, we pull the trigger very quickly on some of these medications that we have and that we can use to help medicate this.



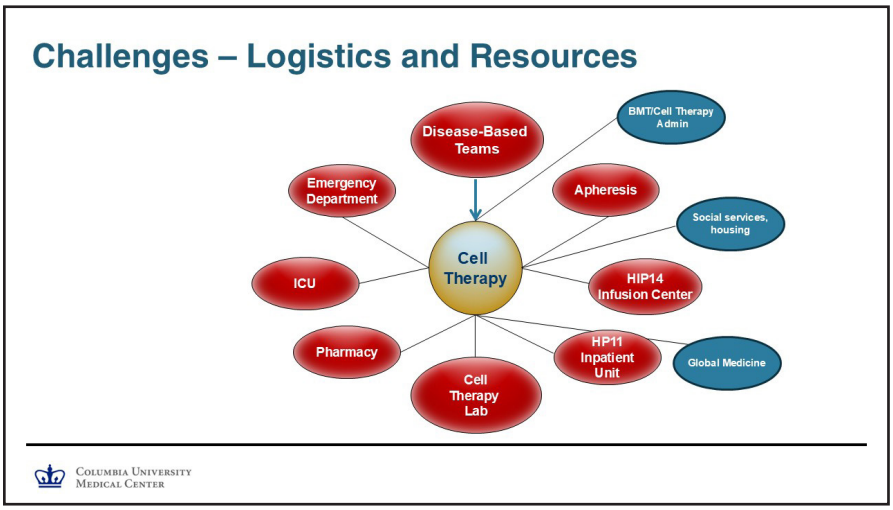
Slide 52: Revolutionary, but... Only a Fraction of Eligible Patients are Treated



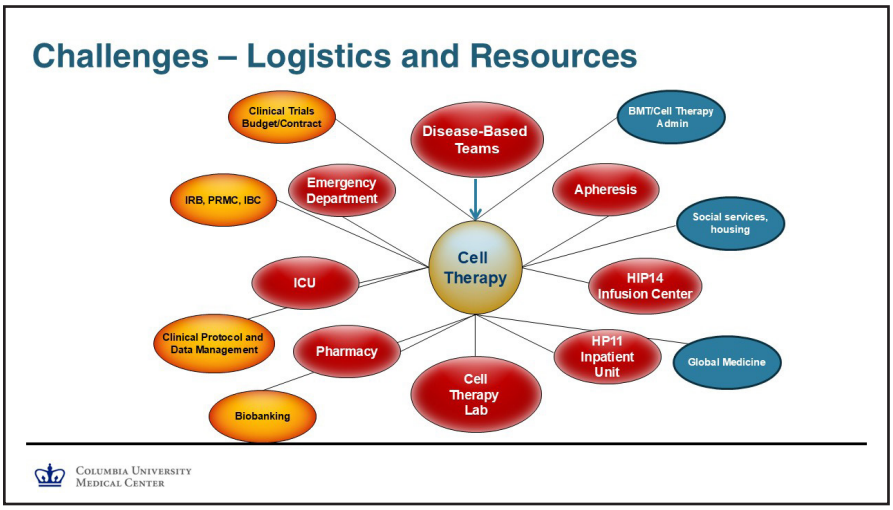
Slide 53: Challenges – Logistics and Resources



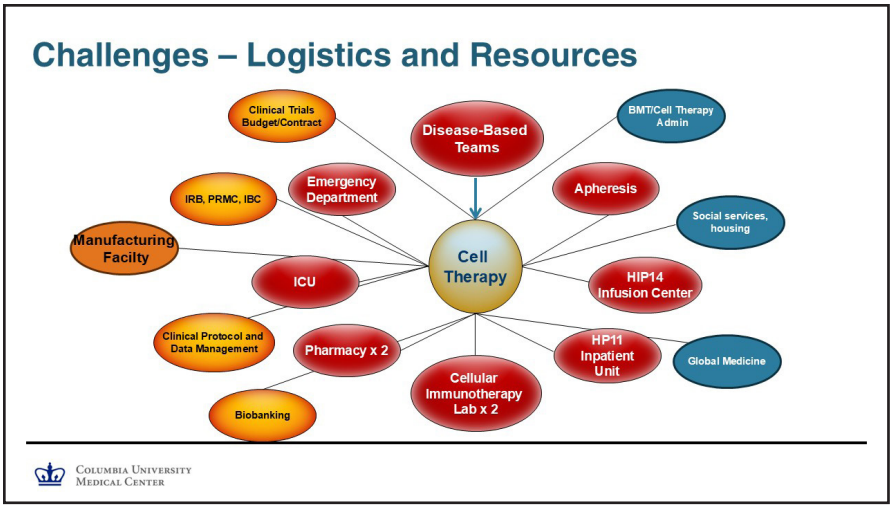
Slide 54: Challenges – Logistics and Resources



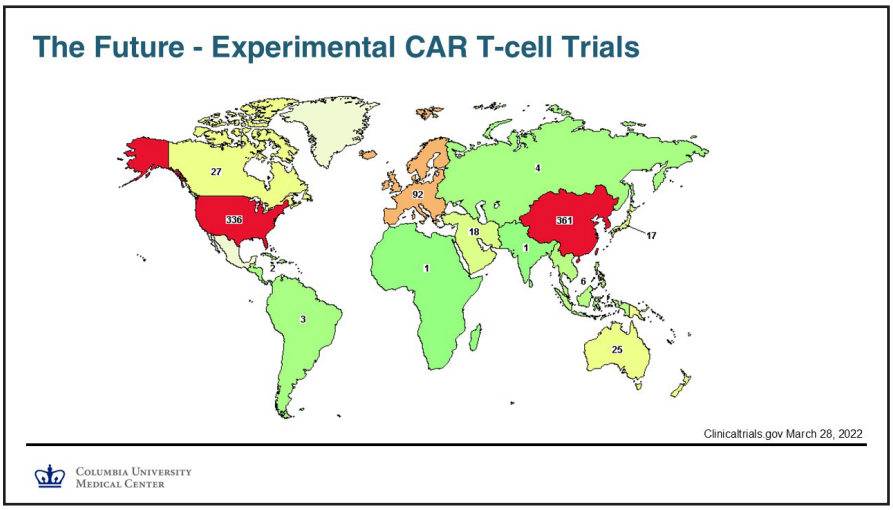
Slide 55: Challenges – Logistics and Resources



Slide 56: Challenges – Logistics and Resources



Slide 57: Challenges – Logistics and Resources

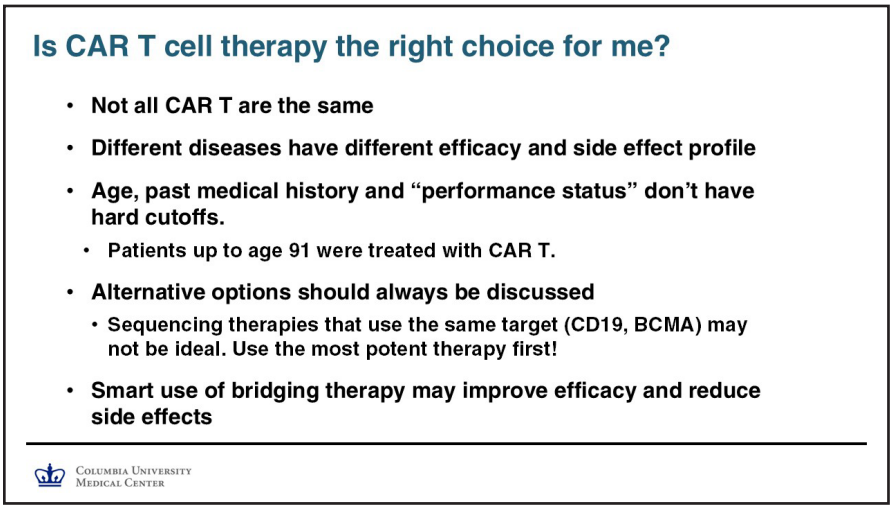


Slide 58: The Future – Experimental CAR T-cell Trials

I've shown you some of the side effect profile. I'm not going to discuss each and every one of them. Anyone who wants to know more can definitely feel free to ask questions. I walked you through some of the evolution of CAR T cells. I would want to circle back to the fact that this all started with very extensive clinical trial work. You can't give CAR T cells to the masses of people who have lymphoma or leukemia without testing them first in clinical trials.

Some of the people who were the pioneers and the volunteers to go on these clinical trials first were the lucky ones who ended up getting these therapies sometimes years before they became commercially available. Even for the diseases where we have clinical trials right now where, even in diseases where we have approved products at this point, we are still doing clinical trials to try and improve upon the current outcomes that we have, either to make the CAR T cell safer or to make them work even better so they don't just work in 70% of the patients, we want them to work in 80%, 90%, or maybe even 100% of the patients.

There's an enormous number of clinical trials available. Thankfully, in our area of the world, in the US, there's really hundreds of clinical trials with CAR T that are always worth at least exploring and listening to these options.



Slide 59: Is CAR T cell therapy the right choice for me?

Is CAR T-cell therapy the right choice for me? What are the things that I really look for? First of all, to remind you one important message I try to communicate. CAR T cells are not all created equal. They might be appropriate for one patient but not a different patient. Even if you have the same disease as a different patient, you specifically might have a significant feature or significant underlying health condition that make CAR T cells better for you.

The manufacturing process for CAR T cells may be different. Some patients may have more trouble in the manufacturing phase. These are all things that are happening in the background. They're not under your control, but this is where going to an expert center is important, and there are today more than 120, maybe 150 centers in the US that specialize in giving CAR T cells.

Different diseases have different efficacy and side effect profiles. If you read on a Facebook® group or in a support group or listen to someone who tells you that they have, they've had a certain type of experience with CAR T that may not apply to the experience that you might have, because you might have a different disease, or a different burden of disease, or a different underlying health condition.

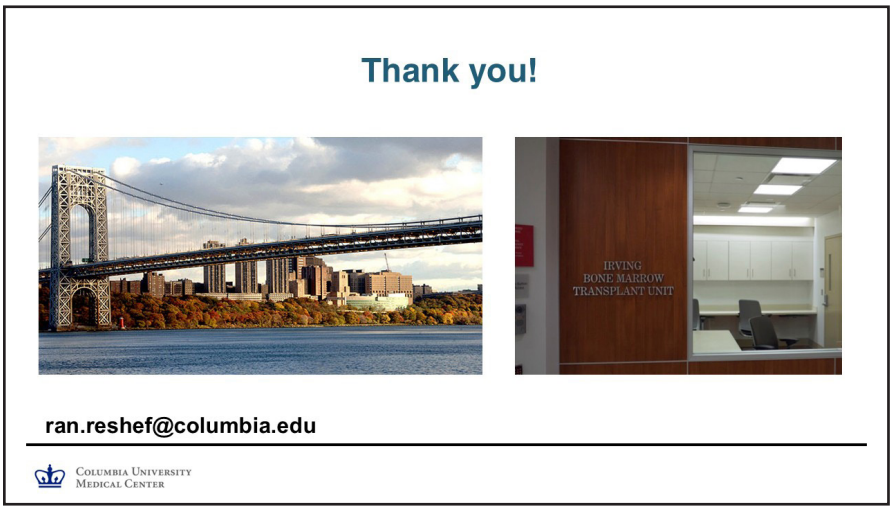
Now, no hard cutoffs. I've seen patients who are well into their 80s, who are completely appropriate and can benefit from CAR T cells. We've treated at Columbia up to age 90, and now in the registry data, that up to age 91, there are patients listed as getting CAR T cells. There's no hard cutoff. You can be someone on dialysis. You can be someone with heart disease or arrhythmias, heart rhythm issues. Talk to your physician about all of those. Don't consider yourself excluded before you're actually told by a CAR T physician that it might not be the best idea for you.

You should always discuss alternative options. There are so many other treatment options right now for these diseases. It's

important to distinguish which ones are truly ones that we have known curative potential versus other therapies that can only work for a while, but we don't know if they're not going to fail in the future. These are some of the things that may distinguish CAR T cells from other therapies.

Very importantly, there are other therapies nowadays that target the same markers, CD19, BCMA. We have other types of therapies, such as bi-specifics, antibodies, antibody drug conjugates (ADCs). To me, the general rule is that you should always use the most potent therapy first. In most cases, the answer will be CAR T by the way, but this is, again, something to discuss with your physician, is it a good idea to get a BCMA antibody, and then get CAR T? Well, I would actually sequence this the other way around. Why not get the more effective, more potent, more better therapy first, because by sequencing therapies against the same target, you may actually lose the efficacy over time? It's an important point to discuss with physicians.

Another thing we've learned that could make CAR T cells more effective and actually less toxic is smart use of bridging therapies. What we frequently do is we collect the T cells from the patient, we start the manufacturing process. During that time, which can be easily 4 or 5 weeks, we give some bridging therapy to reduce the amount of lymphoma or leukemia or myeloma in the body. That would make it easier for the CAR T cells to work. That would, in most cases, reduce the amount of side effects. Discussing how to intelligently use bridging therapy may help get a more favorable outcome.



Slide 60: THANK YOU

That was my last slide. We have 25 minutes to discuss a gazillion questions that came through. I'm going to pass control back to our LLS colleagues who are going to run through the questions now.

Slide 61: ASK A QUESTION

Lizette:

Thank you so much Dr. Reshef for your very informative presentation.

As you mentioned, it is now time for our question-and-answer portion of our program.

We'll take the first question from our web audience, Doctor. Abby is asking: "Are there any factors that can lead to higher success rates, such as gender, type of cancer, age, etc., or conversely make success less likely as determined through data analysis?"

Dr. Reshef:

Yes. Really good question. Absolutely, we have some known factors that can predict outcomes. The first one that was already noted by Abby is the type of disease that you have. Obviously, the success rate in an aggressive lymphoma like DLBCL is not the same as the success rate in follicular lymphoma or in CLL, although I would have to say that in all of them, success rate is probably greater than 50%, or at least the chance of getting a complete remission is greater than 50% in any of those diseases, seems to have a much higher chance in myeloma than in other diseases. Myeloma is definitely one disease where I encourage a lot of patients to go look for a CAR T option.

Other parameters are less well known. Gender is not a significant factor. Age is actually not a significant factor, and that's a huge relief for a lot of older individuals that are used to be told that, at their age, it may not work as well, or at their age, it might be too risky. The success in achieving a complete remission in older individuals is just as good as in younger individuals. They may have slightly more side effects, especially in the very older range, but not to a degree that becomes a barrier. In most cases, there's still side effects that can be manageable even in older individuals.

The one other factor, which I alluded to a little bit when we discussed bridging therapy briefly, is the amount of disease. Patients who have very bulky lymph nodes or a bone marrow that is completely packed with leukemia or myeloma, that tends to make it a little bit more challenging for the CAR T cells to work. What we do nowadays, which I mentioned, is use bridging therapy. We collect the cells, we let them get manufactured. We have 4 to 6 weeks usually to try and reduce the burden of disease. We can do that with radiation, we can use this with chemotherapy, we can use this with another form of immune therapy.

There are various ways of doing that, but if we're successful at reducing the amount of disease in the body, it gives a better chance for the CAR T cells to work, and actually reduces the side effect profile, because the overall battle is going to be less noisy and would require less inflammation to generate a favorable outcome. Thank you for this question. Very important one.

Lizette:

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

Operator:

Our next question comes from Michael from Florida. Go ahead.

Michael:

Yes. My question, I'm 87 years old. You said that there were approximately 150 locations where this therapy can be performed. Where in Florida are they?

Dr. Reshef:

Multiple locations. I'm not going to name them off the top of my head, but certainly the larger center is like Moffitt - University of Miami, University of Florida. Those definitely have our CAR T-cell options. I'm not sure if LLS has a comprehensive list on their website. Maybe the LLS staff can help with that.

Another place to look for that information is look at the websites of the specific CAR T-cell manufacturers. We have, for example, YESCARTA® for lymphoma, CARVYKTI® for myeloma, and these are just examples since, as I mentioned, there are 7 different ones. Each one of them maintains a website that has the list of all CAR T centers by geography, and you can put in and look up even using your own address to see which is the closest one. If you can't, then your oncologist should be able to do that as well. I hope that answers the question. Maybe LLS can give more information about that as well.

Lizette:

Yes, of course. Our Information Specialists can definitely provide CAR T cell centers in your area. Thank you so much for the question. Our next question, Doctor. Clyde is asking: "Can you please define what a line of therapy is, and what exactly constitutes a line of therapy? Please give some examples of what a line of therapy is and examples of treatment regimens that would not be considered a line of therapy."

Dr. Reshef:

Good question. A line of therapy is, for example, when you get, if you have diffuse large B-cell lymphoma and you get R-CHOP, that is considered your first line of therapy. If you have not gone into remission or you went into remission, your disease comes back, you will get a second line of therapy, which nowadays, pretty much everyone is trying to get their patients to get CAR T cells as second line. Even CAR T is considered a line of therapy.

There are some situations where something is not considered a line of therapy. For example, in myeloma when someone gets initial therapy in myeloma followed by a transplant, we consider them both as a predefined sequence. We call them one line. When we transition from one line to a second line, it's usually because either the disease did not respond well enough or the disease came back, or in some situations the patient could not tolerate the therapy for whatever reason and had to stop it and switches to the next line. That would also be considered a transition from first line to second line.

As I've shown you in some of these blood cancers, there are so many treatment options nowadays that it's not unusual for someone with myeloma, for example, to have had 9 lines of therapy, just switching from one to the next every time the disease is acting up.

Operator:

We'll go to the next question. Steven, your line is now live.

Steven:

Yes. Hello. I'm currently undergoing chemotherapy for CLL (chronic lymphocytic leukemia), and it's about to finish here in a couple of months while we'll get another test. How long and what criteria would I consider and evaluate with my oncologist to determine if and when's a good time to pursue CAR T-cell therapy?

Dr. Reshef:

Yes, good question. Since CLL has really seen a huge amount of development over the past couple of decades, we have therapies, either chemotherapy or targeted therapy, that can keep patients in remission for very, very lengthy periods of time. Without

necessarily even going into a remission, we have many therapies in CLL now that can just keep the disease under control, and as long as it's not causing symptoms and it is stable in their blood work, then it does not necessarily require going to the next therapy, in which case CAR T can be considered.

Generally, I would consider CAR T in patients who have had, at the minimum, an attempt to get one of the BTK (Bruton's tyrosine kinase) inhibitors, which is I think one of the most common forms of treatment for CLL and something like IMBRUVICA®. We have several others right now, and another therapy called the BCL-2 (B-cell lymphoma 2) inhibitor where the one we have is VENCLEXTA®, and probably additional ones will come in the future.

If someone had both of these therapies and they either stopped working or they could not tolerate them very well, this is the first time I would at least consider CAR T cells as the next treatment options, and it's not the only treatment option. It will be very cautious about giving a treatment recommendation. It needs to be considered along with any other treatment option that exists out there, and many clinical trials. There are a lot of clinical trials in CLL with regimens that seem to be working out quite well. The first time I would consider CAR T is if you've had a BTK inhibitor and a BCL-2 inhibitor and they either stopped working or not working well enough or there is some side effect that makes them difficult to tolerate.

Lizette:

The next question is from the web. Maggie's asking: "The phrase, harnessing the body's immune system, stands out to me. Two years out from a stem cell transplant, my immunity is low. I've had trouble building antibodies after a regimen of standard immunizations. Could such a compromised immune system be harnessed?"

Dr. Reshef:

Yes, great question. The short answer is yes, because when we say compromised immune system, it may have several components. For example, when you fail to respond to vaccinations, it might be because you haven't yet built enough B cells or plasma cells. It might be because on some people-- again, try not to answer this question specifically just about one individual patient, but in general, someone who needs immune suppressive therapies, steroids, there could be a variety of reasons why the immune system is not recovering well.

What we need in order to harness the immune system to make CAR T cells is very basic. We need a certain number of functional T cells, and the bar is not very high. We don't even need a normal number of T cells, we just need some T cells circulating in the blood so we can collect them and make CAR T cells for a patient. That would still work as harnessing the immune system, because keep in mind that we're not really relying on the healthy normal function of T cells.

You can even have some T cells that are not in the greatest shape. We're genetically modifying them, we're activating them aggressively in the test tube, and we're expanding them in numbers well above the numbers that they were in your blood to begin with. We're turning them into a completely different animal. It's really true that if someone has dramatically suppressed immune function, if your T cell count is less than 100, let's say, it might be challenging to even make CAR T cells from that mostly because of limitations in the manufacturing process. We need a certain minimum of numbers of cells. They need to be able to multiply, but that bar is pretty low.

We've made CAR T cells from patients who had a disease recurrence 2 months after a bone marrow transplant, not 2 years, 2 months, and had no problem making CAR T cells. We make CAR T cells regularly from patients with CLL who have a very, very dysfunctional immune system. All of those things are possible, and I would not consider someone like you excluded from an attempt to harness the immune system.

Lizette:

Our next question from Theresa. Theresa's asking: "Is CAR T-cell therapy harder physically on a patient than stem cell transplant, or is it easier?"

Dr. Reshef:

Very good question. We get that a lot because there is a lot of confusion out there. The treatments sound a little bit similar. They start by collecting cells, and they end by giving chemotherapy and administering cells. It is a completely different experience. In a bone marrow transplant, we really aim to give the highest doses of chemotherapy that a human can tolerate, and then the cells that we

infuse are not even the center of attention. They're basically intended to rescue the patient from those high doses of chemotherapy.

In the CAR T cell world, it's the other way around. The chemotherapy is very low intensity, very easy to tolerate. The CAR T cells are what's really doing the heavy lifting killing cancer cells and they're the ones who are causing some of the side effects. To give you a little bit of color, as I mentioned, we've treated patients up to age 91. I would almost never do a bone marrow transplant over age 75. There are a lot of patients in the age group between 65 and 75 that would not be good candidates for a bone marrow transplant because of heart function, liver function, kidney function, and again, many of those would not be a barrier for CAR T cells.

We've given CAR T cells to myeloma patients who have abnormal kidney function because myeloma typically affects the kidneys and is typically not normal in a myeloma patient. We've had no problem with that. We've even given CAR T cells to people with mild or moderate heart failure, people who had prior heart attacks, people who had certain levels of neurological dysfunctions, people who are bed-bound sometimes for reasons related to their disease.

If someone is bed-bound because of their lymphoma causing some neurological issue, I would not exclude them from getting CAR T cells because if the CAR T cells fix their lymphoma, that may help them recover and get out of bed and remove all of those barriers. These are not absolute cutoffs, and it's always on a case-by-case basis, and it's definitely, in my opinion, easier than a bone marrow transplant. If you take 100 CAR T patients and 100 bone marrow transplant patients, you'll get a pretty clear answer that CAR T-cell therapy was easier.

Lizette:

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

Operator:

Our next question comes from Rhonda. Rhonda, your line is now live.

Rhonda:

Hi. Yes. I have acute myeloid leukemia (AML), and I wondered if the CAR T cell was something that I could use in the future.

Dr. Reshef:

Great question. I'm sorry to hear that. I heard acute myeloid leukemia, and if that was the question, it is an important one to address. Acute myeloid leukemia is a relatively common disease in adults, and it is a fairly aggressive disease that we frequently use bone marrow transplants for. All of the diseases that I spoke about were from the lymphoid side, the non-myeloid type of diseases.

For myeloid diseases, such as acute myeloid leukemia, and I know some questions came in about myelofibrosis and essential thrombocytopenia (ET) and MPNs (myeloproliferative neoplasms), and MDS (myelodysplastic syndrome). I've seen a whole bunch of questions that I can now answer using your question, Rhonda. We don't yet have an FDA-approved CAR T for AML and for all of these other diseases that are on the myeloid side. There is very, very active research.

We at Columbia, for example, have a clinical trial that uses a certain type of cell therapy that can be built on top of a transplant and can help the transplant work better by removing any cells that the transplant failed to remove. That works seems to work well for AML and MDS, but that's a really unique type of cell therapy that has to be built on top of a transplant. It's not a stand-alone therapy yet.

There are other clinical trials in the very aggressive development to try and find good CAR T for AML. It's been a little bit of a longer development pathway. I think that, in the future, we will have CAR T cells in AML, but right now, they are all still in the clinical trial phase and not yet approved commercially available products.

Lizette:

The next question comes from Caroline. Caroline's asking: "Could you explain the difference between so-called off-the-shelf CAR T cells and patient-specific ones?"

Dr. Reshef:

Great question. All of the CAR T cells that we now have approved are made from patients' own T cells, which on one hand, is a little bit more straightforward because the patient can just give their own cells. We make their own cells, and that is what guarantees that these cells can persist in the body for long periods of time, and we know some of these cells can still be detectable 10 years after their giving.

Off-the-shelf T cells or off-the-shelf cell therapies are made from donors. These donors, what makes them off-the-shelf is that we don't tailor the donor to each patient. It's not like a bone marrow transplant. These are universal donors. These are healthy young individuals. I always give the example of you may want to get T cells from a 19-year-old Navy SEAL who's highly fit and has these superpowered T cells. That's really their main advantage that there might be better T cells.

Their other advantage is that you don't need to wait the manufacturing time. These cells have already been manufactured, they've been put in the freezer, and you could take them off-the-shelf and immediately give them. You don't need to wait for the manufacturing time, which may allow your disease to progress, you may develop a complication. It's a shorter way to getting the CAR T cells.

Their downside is that they're never going to survive 10 years in the body. They will ultimately get rejected like any type of foreign cell that we put in the system. One of the most active research priorities is how to make sure that they survive in the body long enough to kill all the cancer cells because once they did that, you may not need them for a long time. If you've really killed all cancer cells to the last one, you may not need cells, these CAR T cells to persist for 10 years. In fact, they might, at some point, cause some problems because they would also not allow your B-cell recovery to go through, and you may have trouble making antibodies on the long run.

Not to make this story very complicated, there are certain advantages and disadvantages to using these off-the-shelf approaches. We have a couple of trials using these approaches in certain types of lymphomas and leukemias, and in the future, we're probably going to see them in more diseases. It's an interesting strategy, but not yet FDA approved, not yet widely available.

Lizette:

Our last question today. John is asking: "What new aspects of CAR T-cell therapy have you learned in the last year as you've gained more experience?"

Dr. Reshef:

Great question. Where I think most of the developments are happening are maybe in 3 large buckets. One of them is what we just mentioned, the idea of using off-the-shelf therapies, which means as a patient, you don't need to undergo leukapheresis, you don't need to wait 4 to 6 weeks for the cells to be manufactured. Those are very important. There is a lot of progress in these off-the-shelf therapies, more methods to keep them in the body for longer. I think that would continue to evolve.

The second thing is just broadening the types of diseases we can treat. CLL is the one example that was only approved a year ago or less than a year ago. Before that, we did not have an FDA-approved therapy for CLL. We're continuing to broaden the number of indications, including outside blood cancers and including outside of cancer. We now have CAR T cells and we have a huge number of clinical trials at Columbia for lupus, multiple sclerosis (MS), myasthenia gravis (MG), a whole host of autoimmune diseases.

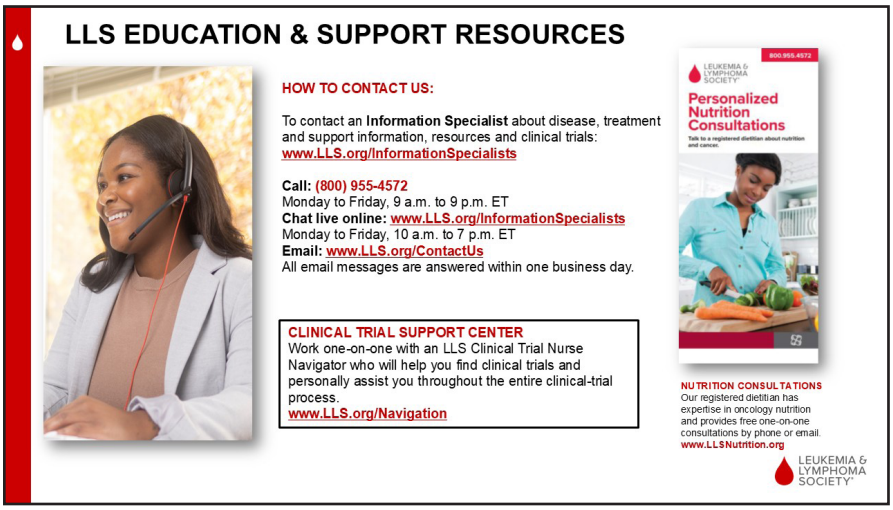
Maybe the third most important evolution is new targets and maybe developing CAR T cells that go after more than one target because why just go after CD19 or BCMA if you could potentially go after both at the same time? You might be able to that way capture more patients and eliminate some of the reasons that some cancers evade this treatment and manage to relapse despite the fact that we have an effective CAR T. These are maybe the 3 things that I've learned over the past year as potential developments in the next generation of clinical trials.

Lizette:

Thank you so much, Doctor, and thank you so much, John, for your question, which was our final question today. Dr. Reshef, thank you so much. We have a lot of positive feedback coming in through the chat. Thank you so much for sharing your expertise with us today.

Dr. Reshef:

Thank you for having me. I just have to say that you guys are so awesome. I'll do this anytime and any day. Thank you so much.



Slide 62: LLS EDUCATION & SUPPORT RESOURCES

Lizette:

We will take you up on that, definitely. Now, I know that we have a lot of questions, and I know if we weren't able to get to your questions today or you want more information or resources, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time, or reach us by email at LLS.org/ContactUs.

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 by calling an Information Specialist.

Slide 63: LLS EDUCATION & SUPPORT RESOURCES

We do have the information as to where these centers are that are available throughout the United States for CAR T-cell therapy, as well as what trials are open at this time for CAR T-cell therapy.

Slide 64: THANK YOU

Thank you again for support for this program from Bristol Myers Squibb, Johnson & Johnson, Legend Biotech, and Kite, a Gilead company.

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us in this program. Again, thank you, Dr. Reshef, for volunteering your time with us today.

On behalf of The Leukemia & Lymphoma Society, goodbye, and we wish you well.