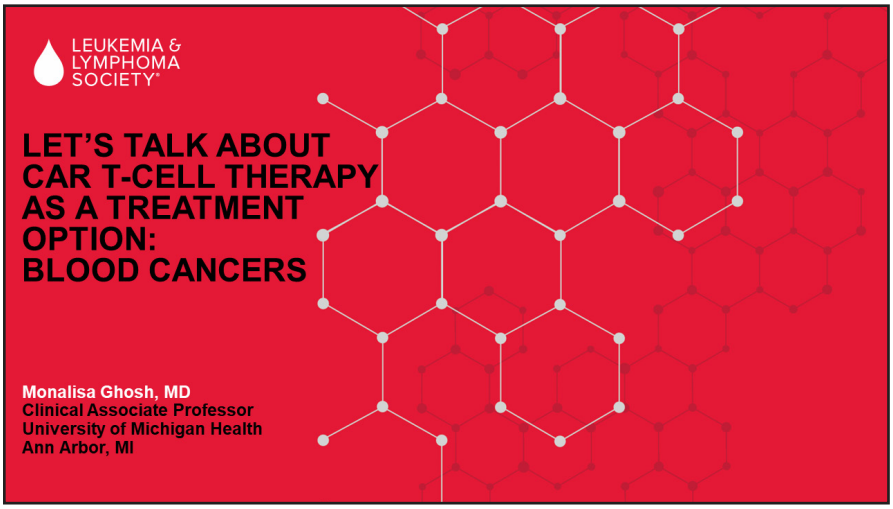
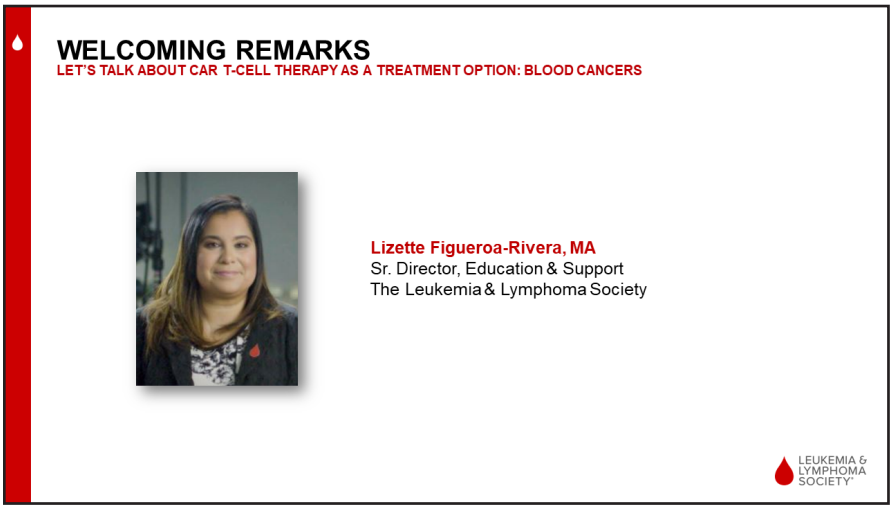


Slide 1: Let's Talk About Car T-Cell Therapy As A Treatment Option: Blood Cancers

Operator:

Greetings. Welcome to Let's Talk About CAR T-cell Therapy as a Treatment Option: 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

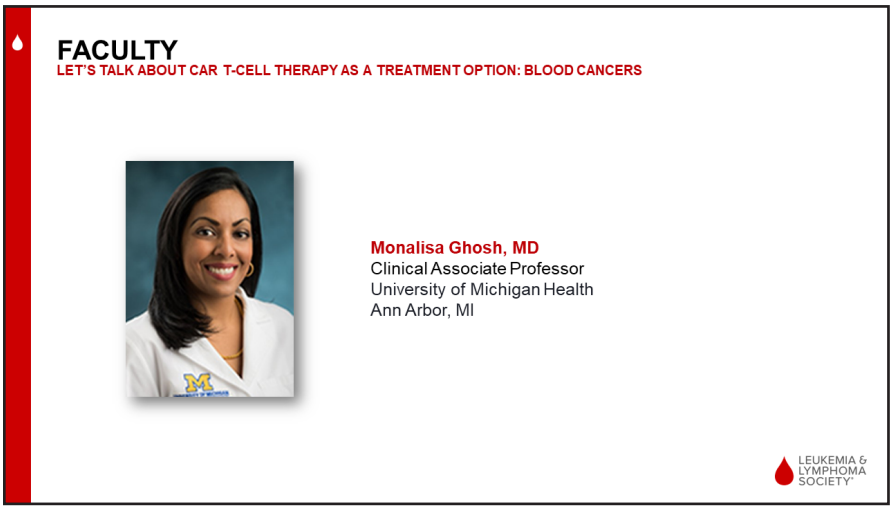
Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia and Lymphoma Society, I'd like to welcome all of you and thank you all for joining us today. LLS has invested over $1.5 billion in cancer research since our founding in 1949, leading to nearly every advancement in blood cancer treatment and breakthroughs in immunotherapy, genomics, and personalized medicine.

Our support of pioneering research at nearly 100 medical institutions worldwide is breaking new ground in the fight against cancer. Please continue to inform us of what you need during this time and please continue to let us be here for you.

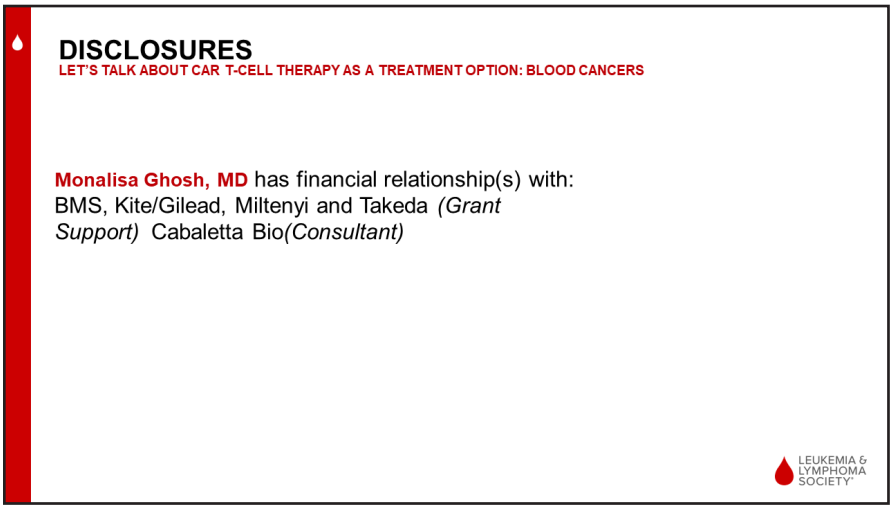
For this program, we'd like to acknowledge and thank Bristol Myers Squibb; Janssen Oncology and Legend Biotech; Kite, a Gilead Company; and Novartis for their support of this program.

It is my pleasure to introduce Dr. Monalisa Ghosh, Clinical Associate Professor at the University of Michigan Health in Ann Arbor, Michigan. Dr. Ghosh, I am privileged to turn the program over to you.



Slide 3: Faculty

Thank you so much and I am privileged to be here. I appreciate all of you coming onto this call and I appreciate LLS for inviting me to give you this talk.



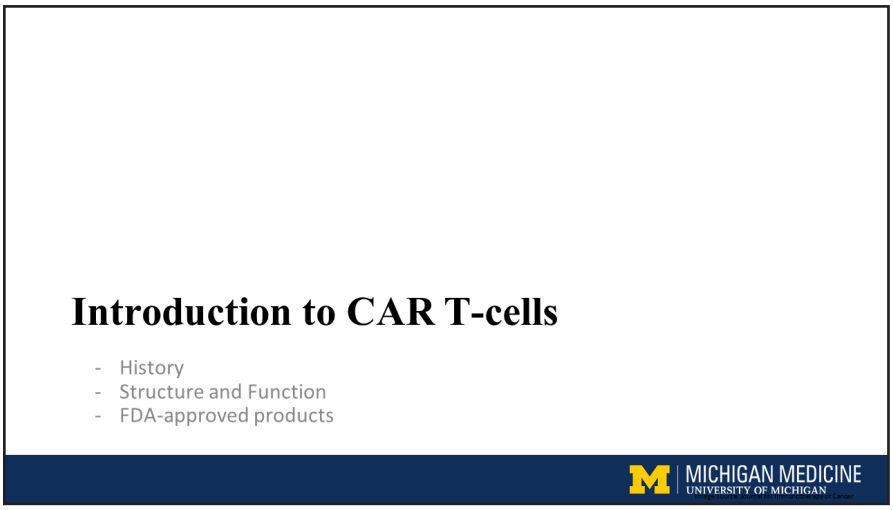
Slide 4: Disclosures

Dr. Monalisa Ghosh:

These are financial relationships due to research with various sponsors and companies.

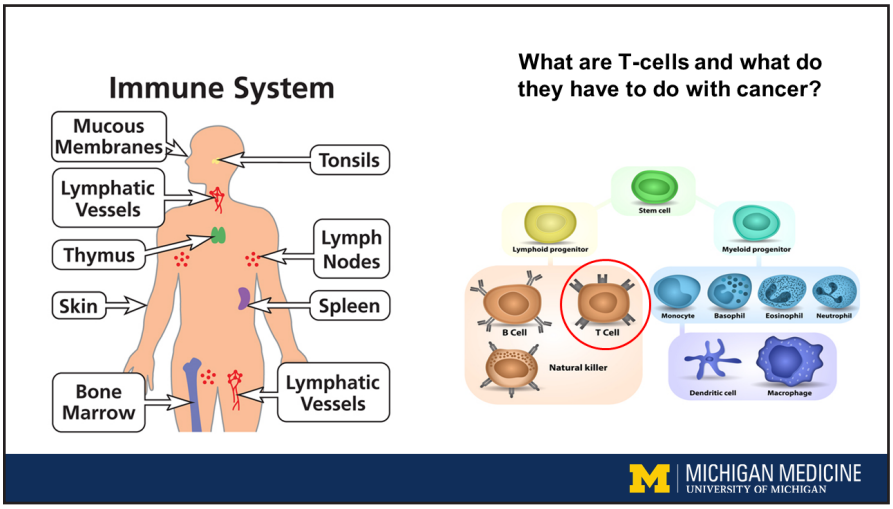
Slide 5: CAR T-Cell Therapy

Today, I will talk to you about CAR T-cell therapy, which is a very broad topic, but I will try to summarize for you the current data that is available and where we can go next to make CAR T-cell therapy better, for not just blood cancers but for other diseases as well.



Slide 6: Introduction To CAR T-Cells

First, I'll start with an introduction to CAR T-cells. Some of you may know quite a bit about it, some of you may have received CAR T-cell treatment already, but I will start with the basics and give you some history, and then discuss the products that are approved and the results of various studies.

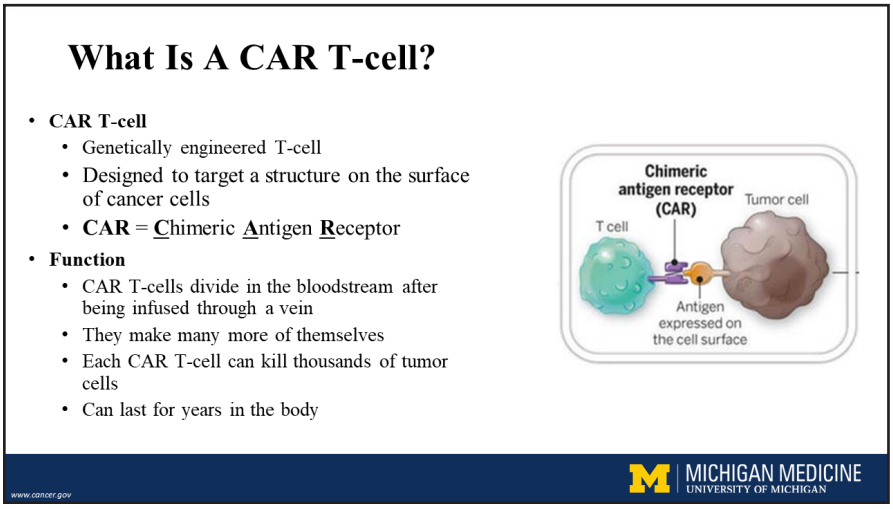


Slide 7: Immue System

Just to begin from the very beginning, I wanted to show you what the immune system has to do with cancer. The immune system is actually our first defense against cancer.

A lot of times what happens is various environmental toxins, it can be UV (ultraviolet) light, it can be various chemicals, or it can be something that's genetic, cause mutations in our cell's DNA, and then that leads to the formation of abnormal cells which can become cancer cells. Our immune system is supposed to be able to defend us from these cancer cells and get rid of them. One of the major ways that the immune system does that is through the action of T-cells.

T-cells are one of the major cellular components of the immune system. T-cells are found everywhere in the body in various tissues, in the tonsils, in the lymph nodes, in the spleen, in the bone marrow, and in the blood. These T-cells are supposed to be able to kill off these preliminarily potentially cancerous cells, but sometimes that doesn't happen. When that doesn't happen, what we think needs to be done at that point is potentially modifying these T-cells so they can do their job.

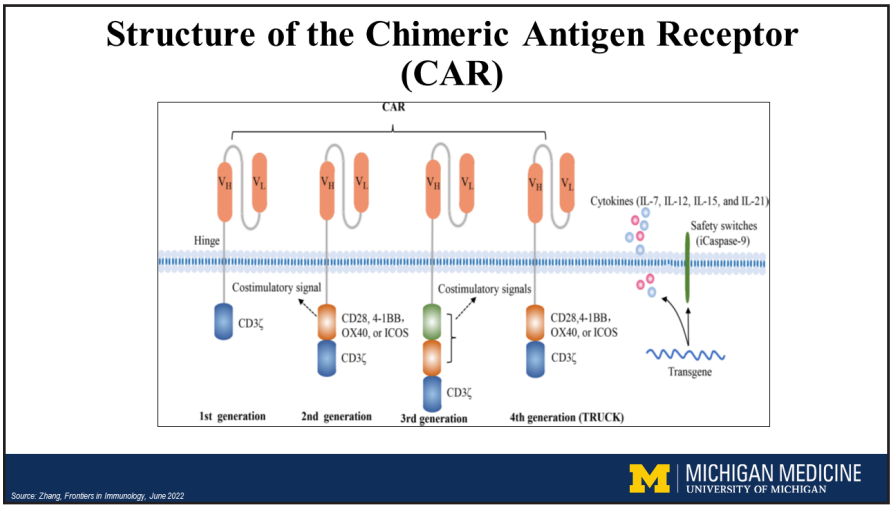


Slide 8: What Is A CAR T-Cell

What is a CAR T-cell? You can see this cartoon on the right shows a tumor cell on the right, that's just one tumor cell, and on the left is what's called a CAR T-cell. A CAR T-cell is a genetically engineered T-cell. The way that it's designed

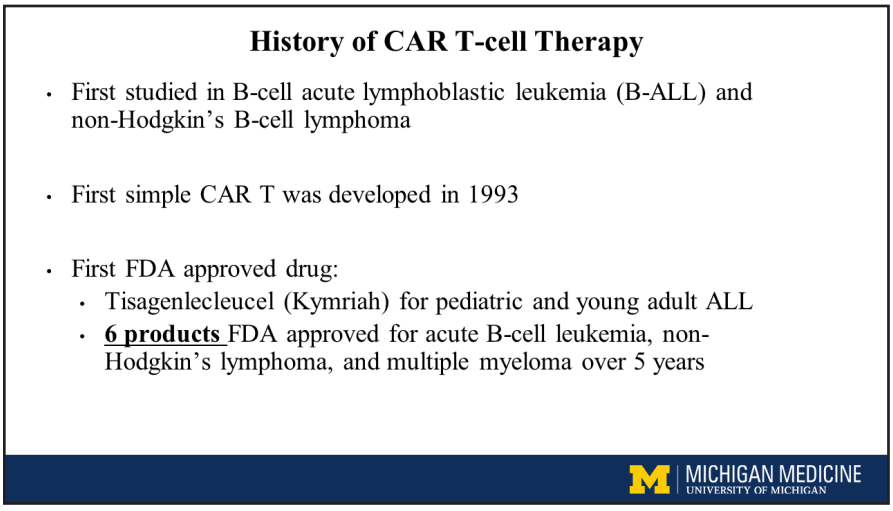
is to target specifically a protein structure on the surface of a tumor cell. You can see that purple in the cartoon, that purple extension from the T-cell, that is the actual CAR or what's called a chimeric antigen receptor.

That is something that is genetically engineered onto the T-cell and that points the T-cell toward the specific tumor cell, which then activates that CAR T-cell to directly kill that tumor cell. We know that after CAR T-cells are infused into the blood, they can divide in the bloodstream and make more of themselves and then each CAR T-cell can kill thousands of tumor cells and can last for years inside the body.



Slide 9: Structure of the Chimeric Antigen Receptor (CAR)

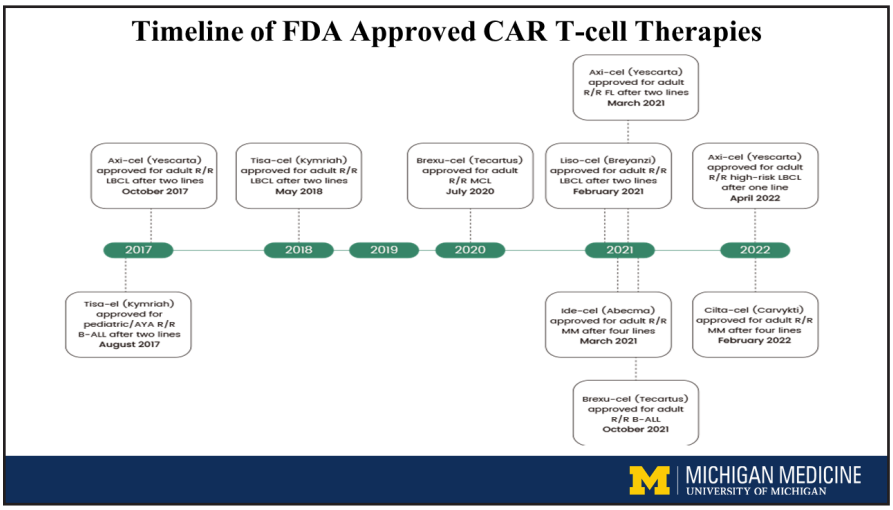
This is the molecular structure of the chimeric antigen receptor or CAR. The bottom half of the picture is the inside of the cell and the top half is the outside. The CAR structure consists of a couple of different components inside the cell and then the component on the outside of the cell detects the specific tumor cells. This just shows that there have been multiple generations or versions of CAR T-cells that have been developed over the years. The first one started in the late 1980s and now we're here and most of the FDA-approved CAR T-cells or all of them are second-generation CAR T-cells, but third-generation and fourth-generation CAR T-cells are in development and in clinical trials.



Slide 10: History of CAR T-Cell Therapy

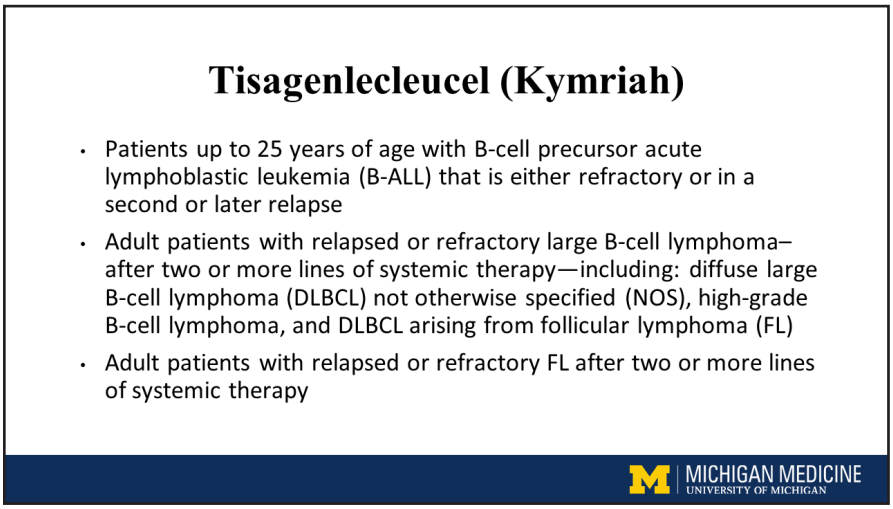
CAR T-cells were first studied in B-cell acute lymphoblastic leukemia (ALL) and non-Hodgkin's B-cell lymphomas, including CLL (chronic lymphocytic leukemia). The first simple CAR T was developed in 1993, developed at different institutions, and the first FDA-approved drug was in 2017 with the drug tisagenlecleucel or Kymriah®, which was FDA-approved for pediatric

and young adult acute lymphoblastic leukemia. Since then, over the past 7 years, 6 products have been FDA-approved for various malignancies, including acute B-cell leukemia, several non-Hodgkin's lymphomas, such as diffuse large B-cell lymphoma or follicular lymphoma and mantle cell lymphoma, as well as multiple myeloma.



Slide 11: Timeline of FDA Approved CAR T-Cell Therapies

This shows a timeline of the FDA-approved CAR T-cell products. As you can see on the bottom left, in August of 2017 the first CAR T was approved. It was tisagenlecleucel. Next axi-cel (axicabtagene ciloleucel, Yescarta®) was approved just a couple of months later, and then the tisa-cel, which was approved initially for pediatric and young adult leukemia and was then approved for large B-cell lymphoma in May of 2018. Then a couple of years went by and a CAR T product was approved for mantle cell lymphoma, followed then by another CAR T approval for non-Hodgkin's B-cell lymphoma, and then a couple more products that were FDA approved for multiple myeloma came in 2021 and 2022.

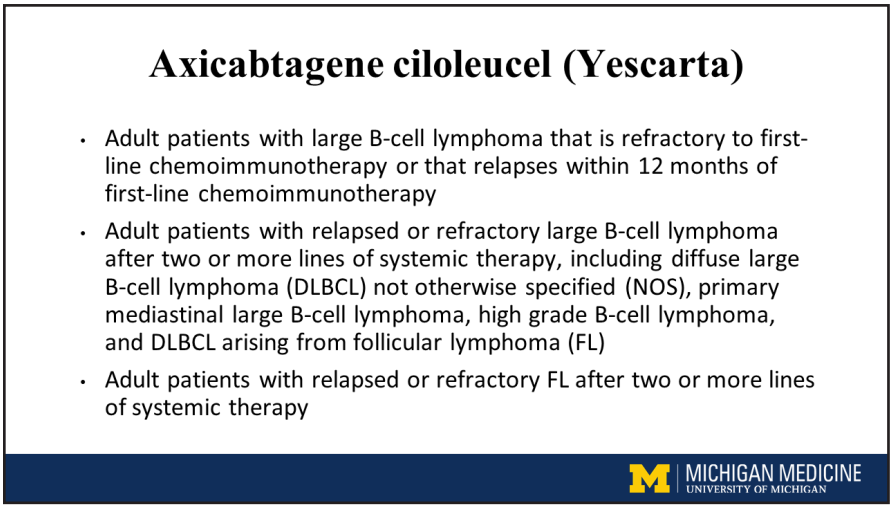


Slide 12: Tisagenlecleucel (Kymriah®)

To go through the list of these CAR T products, tisagenlecleucel or Kymriah was first used in patients up to 25 years of age who had a B-cell acute lymphoblastic leukemia. Either they had received at least 2 lines of therapy, meaning that they had received a chemotherapy regimen followed by relapse, followed by another chemotherapy regimen or even a stem cell transplant, and then relapsed after that.

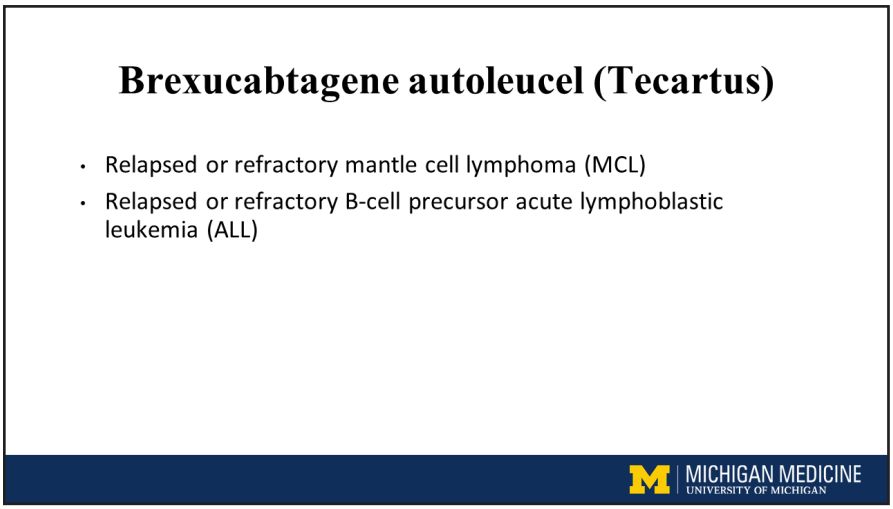
It was then approved for adult patients with diffuse large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma that converted over from follicular lymphoma. This was in the setting of having had 2 or more lines of therapy prior; that means at least 2 separate regimens of chemotherapy or even an autologous stem cell transplant.

Then it was approved for relapsed or refractory follicular lymphoma for people who had 2 or more lines of treatment.



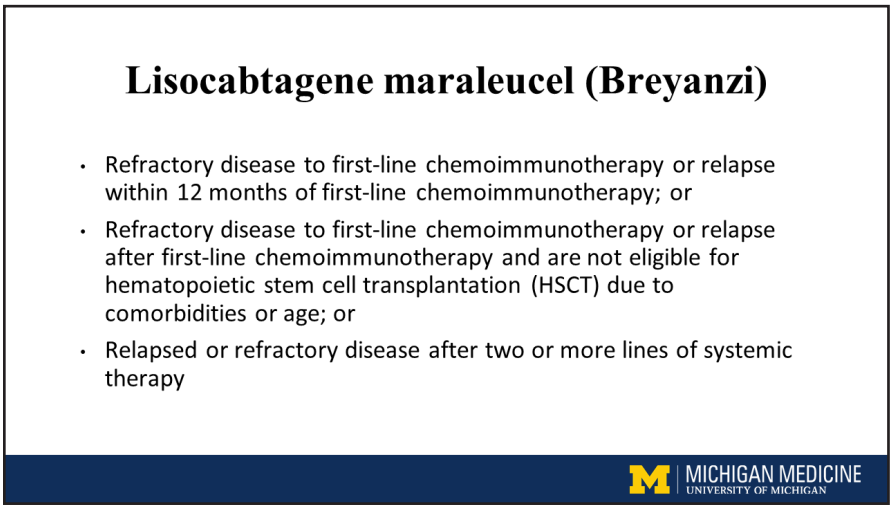
Slide 13: Axicabtagene Ciloleucel (Yescarta®)

Axicabtagene ciloleucel or Yescarta was FDA-approved initially for diffuse large B-cell lymphoma that had been relapsed or what we call refractory or basically not responsive to 2 or more different lines of therapy. However, a couple of years ago in 2022, there were 2 large Phase 3 studies that were done, meaning that they were randomized. On one arm of the study, patients received the standard treatment, which was an autologous stem cell transplant, and on the other arm of the study, patients received the CAR T-cell therapy. This was specifically for people who had diffuse large B-cell lymphoma that either relapsed within a year after getting the initial chemotherapy or did not respond to the initial chemotherapy. For those particular people, axi-cel was FDA-approved to use as the second line of treatment. Also, it was FDA-approved for adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of therapy.



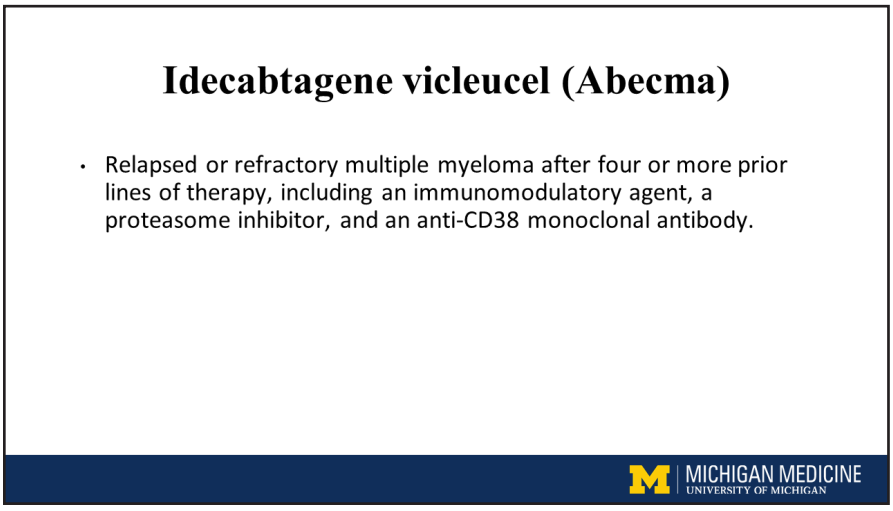
Slide 14: Brexucabtagene Autoleucel (Tecartus®)

Next is brexucabtagene autoleucel, also known as Tecartus ®. This is for people who have mantle cell lymphoma that has relapsed after at least 2 different lines of therapy, or for adults with ALL (acute lymphoblastic leukemia) that has relapsed after 2 or more lines of therapy.



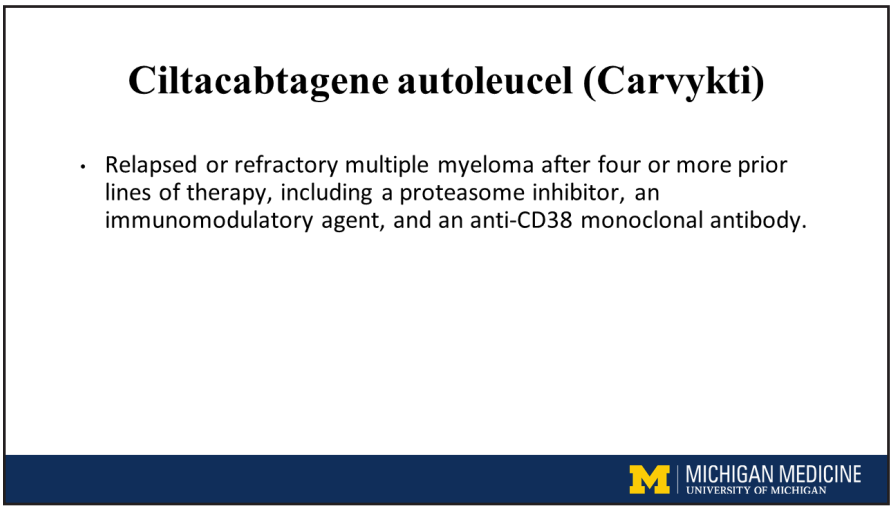
Slide 15: Lisocabtagene Maraleucel (Breyanzi®)

Lisocabtagene maraleucel or Breyanzi ® was FDA-approved. It was the third one that came onto the market for diffuse large B-cell lymphoma. It was also approved just like axi-cel was, for people who relapsed within the first 12 months of their initial chemotherapy or did not respond to initial chemotherapy. It was also approved for people who have received 2 or more lines of treatment.



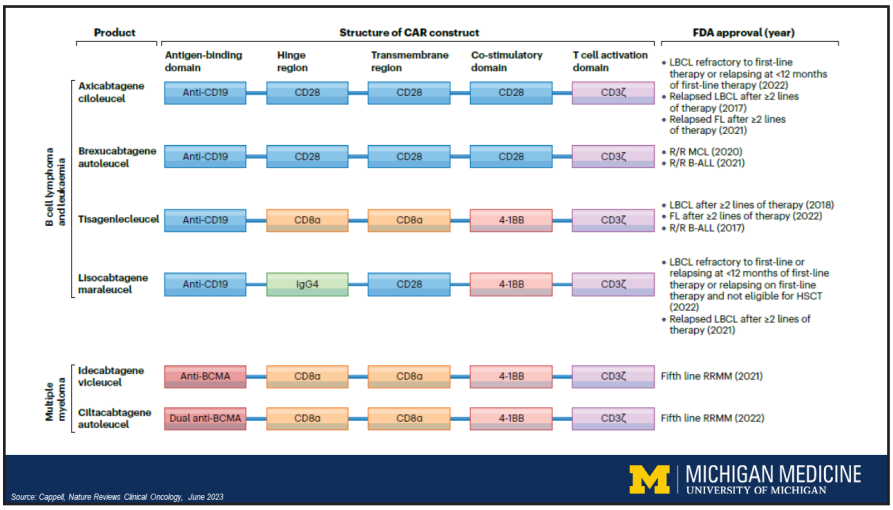
Slide 16: Idecabtagene Vicleucel (Abecma®)

Now, we get to the multiple myeloma CAR T-cell therapies. These are more recent. Idecabtagene vicleucel or Abecma® was FDA-approved for people who have had over 4 lines of therapy; that means 4 different systemic treatments. For instance, if you received 6 cycles of an initial treatment, such as RVD (Revlimid®/lenalidomide, Velcade®/bortezomib, dexamethasone), which is very common, and then had a stem cell transplant, if you relapsed after that, you would have to get another treatment and then if you relapse after that, you have to get another and yet another treatment. This is for later in the course in multiple myeloma, but there are studies ongoing that are looking at moving CAR T-cells earlier in the treatment course.



Slide 17: Ciltacabtagene Autoleucel (Carvykti®)

Another CAR T-cell therapy that was approved for multiple myeloma after 4 or more lines of therapy was ciltacabtagene autoleucel or Carvykti ®. This one is just a little bit different from the last one, and I'll go through that in the next slide, but this is also a more recent FDA approval and a more recent therapy that's become available.



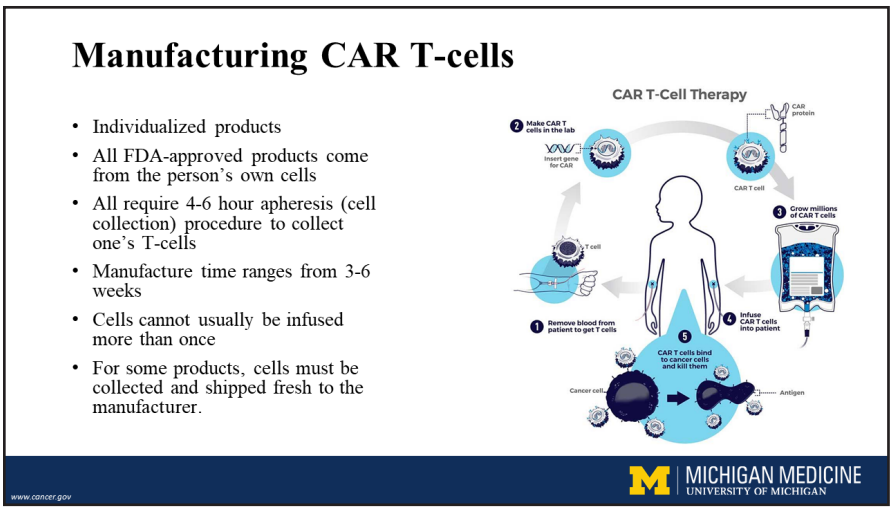
Slide 18: Difference Between CAR T-Cells

This slide here hopefully is visible. I know that the writing is very small, but what this shows is what is the difference between all of these CAR T-cells.

We have 6 different products. Aside from having different pharmaceutical companies that manufacture them, there are differences in the structure and function of these cells. For instance, for axicabtagene ciloleucel, the structure, of course, it's targeted against CD19. CD19 is the marker, that protein structure on the surface of the tumor cell that I showed a few slides ago, that is present on just about all B cells, including the cancerous B cells. Then there are all these other regions of the cell and then you have this, what's called the T-cell domain.

To put this in the simplest terms, the way they are different is these areas here. The structure here called the co-stimulatory domain is where some of these products differ. They also differ in the way they're administered. Some of them are given

as an infusion of a bag of liquid. Some of them are given as a syringe infusion. The 2 CAR T's that are FDA-approved for multiple myeloma, they target a whole different target than the other CAR T-cells. It's called BCMA or B-cell maturation antigen. This is a protein structure that's present on the surface of multiple myeloma cells specifically so it targets those cells.



Slide 19: Manufacturing CAR T-Cells

How are CAR T-cells manufactured? Right now, the ones that are FDA-approved are all individualized products. They come from the person who is getting the treatment themselves. This is from your own cells and it usually requires a collection of your cells that happens about 4 to 5 weeks before you get the CAR T-cells. It takes about 4 to 6 hours through a process called apheresis. This is where you are hooked up to a machine.

Usually, we will place an IV in one arm in one of your veins and an IV in the other arm in one of the other veins, and there will be tubing connecting you to the apheresis machine. The machine will pull blood out of your veins and extract the T-cells from your veins and then return the rest of your blood through the other 2. This is a continuous process that happens a lot like dialysis. It takes a few hours and then once the T cells are collected and we have the number of T cells that we need, we send them off to the sponsor, pharmaceutical company, that actually manufactures the CAR T-cells.

They do their magic and they manufacture these CAR T-cells and send them back to us. Then we prepare you by giving you a bit of chemotherapy ahead of time, 2 to 3 days of chemotherapy, which is a lot less of a dose than what you may have gotten in one of your previous treatments. It can be done in the outpatient settings, you don't have to be admitted to the hospital for that part. Then a couple of days after finishing that chemotherapy, we infuse the CAR T-cells into the veins, and then those CAR T-cells immediately go in and start attacking the tumors. Start attacking the lymphoma, or the leukemia, or the myeloma cells.

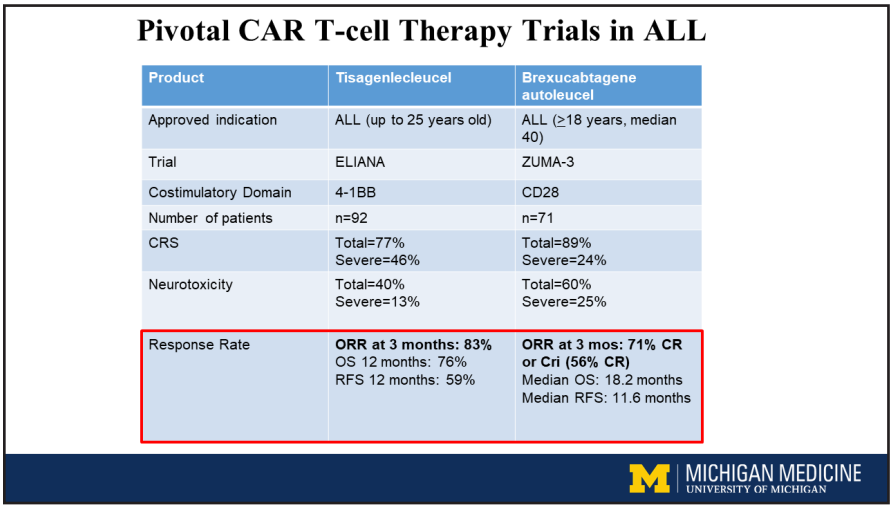
They do that by binding to those specific targets that they are created to bind, and then they directly kill off the tumor cells. Right now, CAR T-cells cannot usually be infused more than once and the reason for that is, first of all, it hasn't been tested extensively. As far as re-infusion goes, most of the products on the original trials were tested with just one infusion, and we have seen that people's response to the one infusion can last for a significant amount of time. I'll go into that in a little bit more detail.

We have not found the need to re-infuse for the most part, but there are certain occasions where we have been able to re-infuse. Sometimes of course, insurance companies also are not covering a re-infusion of cells, which with such an expensive product can become an issue. I'll also talk about other types of CAR T-cells that are in development that can be re-infused.

Most of the time, these CAR T-cells, they're shipped back to us either fresh or frozen, most of them are frozen. We can keep the CAR T-cells for anywhere from 9 months to a year. That way, for instance, if someone's disease goes into remission while they're waiting for the CAR T-cells, we could hold off technically and infuse them at a later date. They're not that many instances in which we do that, but it is possible.

Slide 20: How well do CAR T-Cell therapies work?

How well do CAR T-cell therapies work? I'll go through some data that we have in acute lymphoblastic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and multiple myeloma.



Product	Tisagenlecleucel	Brexucabtagene autoleucel
Approved indication	ALL (up to 25 years old)	ALL (≥18 years, median 40)
Trial	ELIANA	ZUMA-3
Costimulatory Domain	4-1BB	CD28
Number of patients	n=92	n=71
CRS	Total=77% Severe=46%	Total=89% Severe=24%
Neurotoxicity	Total=40% Severe=13%	Total=60% Severe=25%
Response Rate	**ORR at 3 months: 83%** OS 12 months: 76% RFS 12 months: 59%	**ORR at 3 mos: 71% CR or Cri (56% CR)** Median OS: 18.2 months Median RFS: 11.6 months

Slide 21: Pivotal CAR T-Cell Therapy Trials in ALL

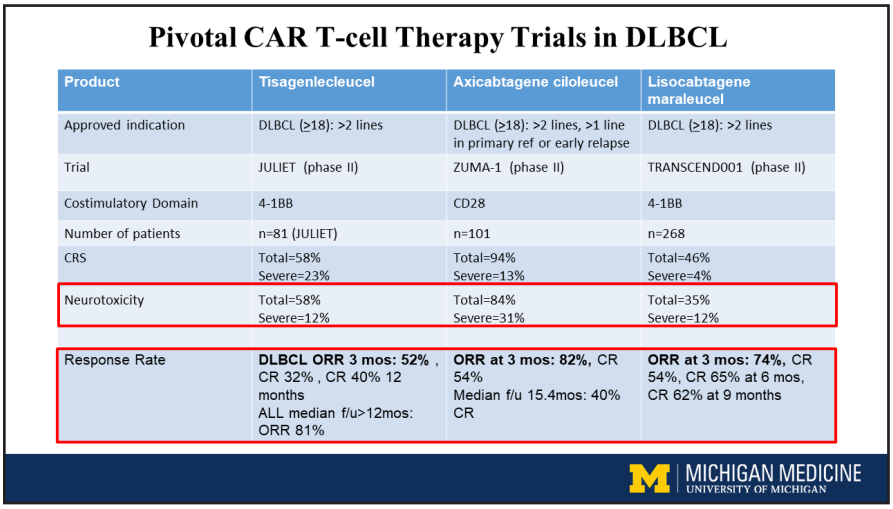
These are some of the pivotal CAR T-cell therapy trials in acute lymphoblastic leukemia. One of the first trials was a trial called ELIANA. This was done about 10 years ago. This was in pediatric patients with acute lymphoblastic leukemia. This is for pediatric patient children and young adults up to age 25.

What we found is the overall response rate, which you'll see here in bold as ORR, that's the number of people that responded. They either went into a complete remission or a near complete remission, meaning that there was no leukemia detectable in the blood or bone marrow or anywhere else in the body at the end of this treatment. 83% of people treated on this trial went into either a full remission or very close to a full remission, and the number of people surviving at 1 year was 76% of people on trial.

There was another trial called ZUMA-3, which looked at the drug brexucabtagene autoleucel in people who are over 18 years with acute lymphoblastic leukemia, and the overall response rate was 71%. 71% of people either had a complete remission or what we call CRi, which is a complete remission, no evidence of leukemia, but their blood counts have not recovered yet. The median overall survival, meaning the number of 50% or the majority of people that were alive were at 18.2 months after the treatment.

There's also some examples here. Above this column here, above this row, you'll see the levels of different types of side effects. There are 2 side effects we worry about with CAR T-cell therapy the most, one being cytokine release syndrome or CRS and another being neurologic toxicity. I'll talk about those in more detail. What this shows is that the majority of people treated on both of these trials did have some cytokine release syndrome. Severe amounts of cytokine release syndrome did occur in a fewer number of patients but was significant. Then neurologic side effects occurred in less than half of people on the pediatric trial and then a little more than half of people on the adult trial.

I will say that with this particular trial, we didn't really even know that these side effects were going to happen. They weren't something that we saw in for instance, when looking at mice with these early treatments in the lab, but it was something that we learned about and we've now gotten much, much better at managing this to the point that it usually does not progress and we see a lot lower rates of cytokine release syndrome and neurologic side effects.



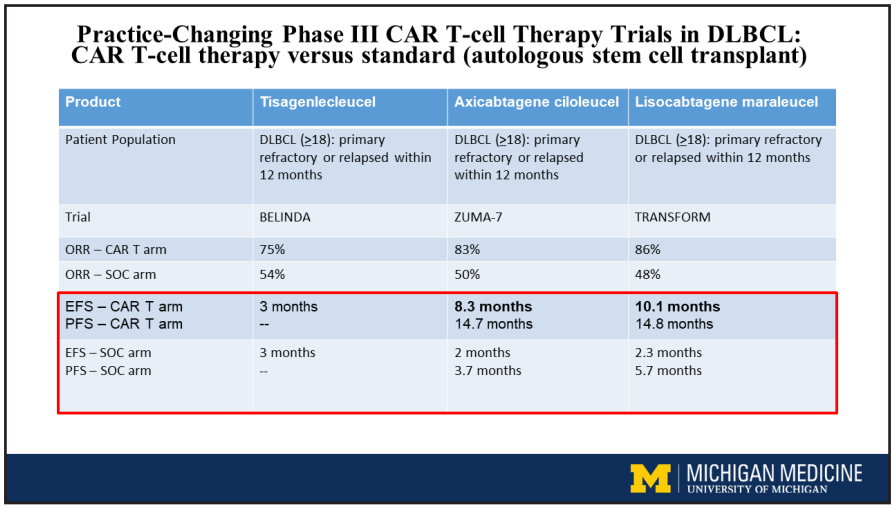
Slide 22: Pivotal CAR T-cell Therapy Trials in DLBCL

For diffuse large B-cell lymphoma, there are 3 CAR T products that are FDA-approved and they are tisagenlecleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel. These are based on 3 separate trials and here you will see the overall response rate. For this particular CAR T, these are for people who had gotten at least 2 different lines of therapy. Meaning they had gotten for instance, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), which a lot of people get as their initial chemotherapy.

Then they relapsed and then got another line of treatment, which could be something like RICE (rituximab, ifosfamide, carboplatin, etoposide) for example, and then relapsed again. These are people who had pretty rough disease, pretty resistant disease. 52% of people had a response to the CAR T-cell therapy, meaning the majority of those people had what we call a complete remission where we don't see any disease left on the PET scan or the CT scans that are done after a few months.

The rest of the people had partial response and then the other 48% of people did not respond to this particular CAR T. When you look at this study with this other CAR T product axi-cel, the overall response rate was 82%. There was a much higher response rate but what really matters is looking at the long-term remission rate. Long-term remission rates were very similar for these 2 products.

Anywhere from 40% to 50% of people are still in remission even now 4 to 5 years down the road after these trials. On this study using this other product, the overall response rate was 74%. The majority of people went into full remission and we don't have very much long-term follow-up on this particular trial yet, we have a couple of years of data and it looks like at least over 50% of people are still in remission.



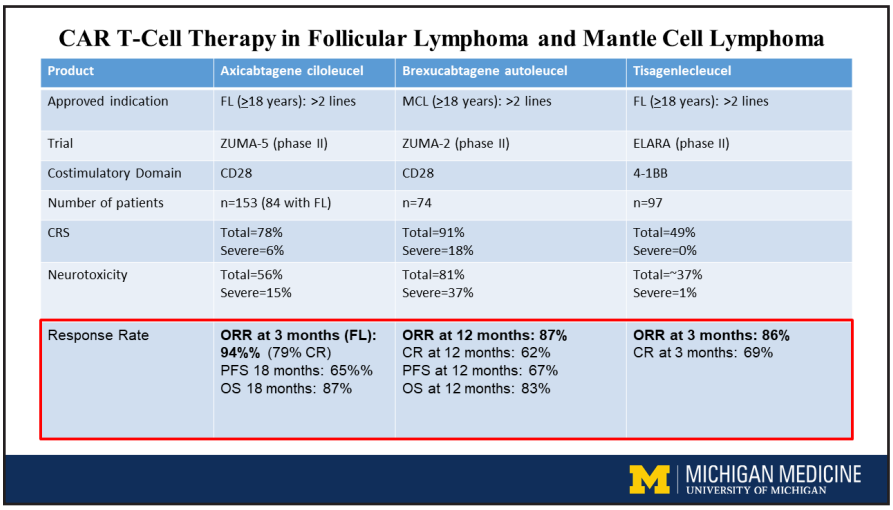
Product	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel
Patient Population	DLBCL (≥18): primary refractory or relapsed within 12 months	DLBCL (≥18): primary refractory or relapsed within 12 months	DLBCL (≥18): primary refractory or relapsed within 12 months
Trial	BELINDA	ZUMA-7	TRANSFORM
ORR – CAR T arm	75%	83%	86%
ORR – SOC arm	54%	50%	48%
EFS – CAR T arm PFS – CAR T arm	3 months --	**8.3 months** 14.7 months	**10.1 months** 14.8 months
EFS – SOC arm PFS – SOC arm	3 months --	2 months 3.7 months	2.3 months 5.7 months

Slide 23: Practice-Changing Phase III CAR T-Cell Therapy Trials in DLBCL: CAR T-Cell therapy versus standard (autologous stem cell transplant)

There were some of what we call practice-changing CAR T-cell therapy trials and I alluded to this earlier. These were trials where basically what was compared was standard treatment, which for someone who has relapsed diffuse large B-cell lymphoma, either that relapsed within a year after their initial R-CHOP for example, or did not respond to the R-CHOP. Usually, what we did in the past was something called an autologous stem cell transplant.

You would get more chemo and then have the stem cell transplant. However, we noticed that people who did relapse early or did not respond to their initial chemo actually tended to relapse early after a stem cell transplant as well. These 2 studies or these 3 studies compared doing a stem cell transplant versus doing the CAR T-cell therapy. What was found is that the response rate was much better with the CAR T-cell therapy and something called event-free survival, which is basically a marker that we use in lymphoma trials.

It was much better for the CAR T arm versus the patients or the people who got stem cell transplant. This led to the FDA approving CAR T-cell therapy for people with diffuse large B-cell lymphoma in this particular setting.



CAR T-Cell Therapy in Follicular Lymphoma and Mantle Cell Lymphoma

Product	Axicabtagene ciloleucel	Brexucabtagene autoleucel	Tisagenlecleucel
Approved indication	FL (≥18 years): >2 lines	MCL (≥18 years): >2 lines	FL (≥18 years): >2 lines
Trial	ZUMA-5 (phase II)	ZUMA-2 (phase II)	ELARA (phase II)
Costimulatory Domain	CD28	CD28	4-1BB
Number of patients	n=153 (84 with FL)	n=74	n=97
CRS	Total=78% Severe=6%	Total=91% Severe=18%	Total=49% Severe=0%
Neurotoxicity	Total=56% Severe=15%	Total=81% Severe=37%	Total=~37% Severe=1%
Response Rate	**ORR at 3 months (FL): 94%%** (79% CR) PFS 18 months: 65%% OS 18 months: 87%	**ORR at 12 months: 87%** CR at 12 months: 62% PFS at 12 months: 67% OS at 12 months: 83%	**ORR at 3 months: 86%** CR at 3 months: 69%

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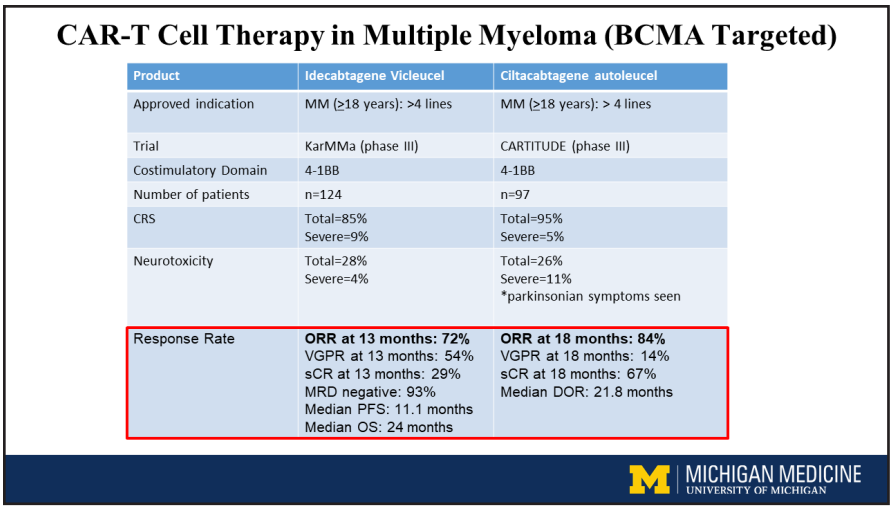
Slide 24: CAR T-Cell Therapy in Follicular Lymphoma and Mantle Cell Lymphoma

CAR T-cell therapy is also FDA-approved for follicular lymphoma and mantle cell lymphoma. Here I show some of the trials that were done in these particular diseases. For follicular lymphoma, we have here this trial called ZUMA-5, and then using a different CAR T product, we have the trial called ELARA. The overall response rate in these two, you can see at 3 months for follicular lymphoma, 94% of people had a response with nearly 80% of people in remission.

Overall response rate on this trial was 86% with at 3 months 69% of people maintaining a full remission. For mantle cell lymphoma at 12 months, 87% of people had a response to the treatment and two 62% of people were still in full remission at 1 year.



CAR-T Cell Therapy in Multiple Myeloma (BCMA Targeted)

Product	Idecabtagene Vicleucel	Ciltacabtagene autoleucel
Approved indication	MM (≥18 years): >4 lines	MM (≥18 years): > 4 lines
Trial	KarMMa (phase III)	CARTITUDE (phase III)
Costimulatory Domain	4-1BB	4-1BB
Number of patients	n=124	n=97
CRS	Total=85% Severe=9%	Total=95% Severe=5%
Neurotoxicity	Total=28% Severe=4%	Total=26% Severe=11% *parkinsonian symptoms seen
Response Rate	**ORR at 13 months: 72%** VGPR at 13 months: 54% sCR at 13 months: 29% MRD negative: 93% Median PFS: 11.1 months Median OS: 24 months	**ORR at 18 months: 84%** VGPR at 18 months: 14% sCR at 18 months: 67% Median DOR: 21.8 months

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Slide 25: CAR-T Cell Therapy in Multiple Myeloma (BCMA Targeted)

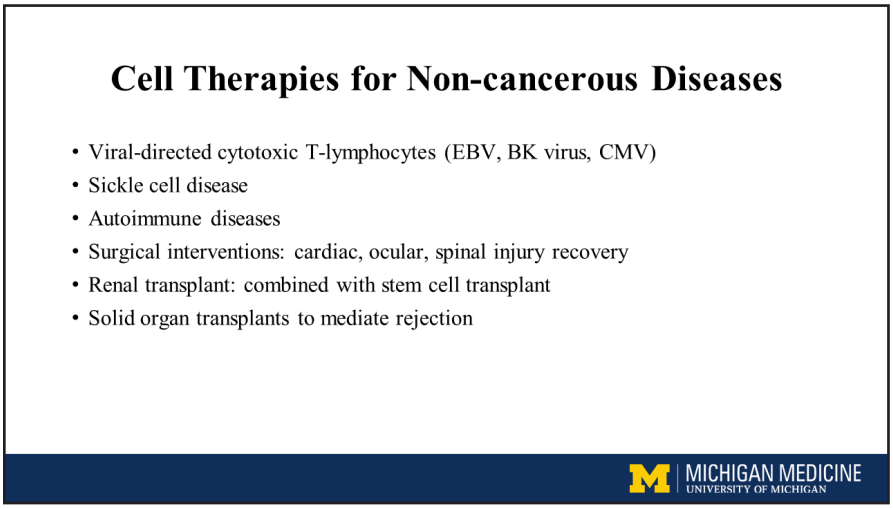
Now, multiple myeloma is a little bit different in how we think about disease control. We do think that certain CAR T-cell therapies may end up being curative in diffuse large B-cell lymphoma, but we don't know about that in multiple myeloma. Technically, we know that multiple myeloma at this point is not a disease that we can cure except in a few cases and some people who have a stem cell transplant from someone else, we have had some cases of cures.

However, we don't know yet if CAR T-cell therapy in multiple myeloma is going to be curative, but that's what we're shooting for of course. There are 2 different CAR T products that are available for multiple myeloma and the first one is idecabtagene-vicleucel, which the overall response rate at 13 months after infusion was 72%. 72% of people had responded.

For those who have multiple myeloma or are familiar, there's another type of response called a very good partial response. Which really essentially means that more than 90% of the myeloma has disappeared and that was 54% of this group of people. Another marker is something called a stringent complete response, which is where no evidence of any myeloma is detected and that's really what we're shooting for. That occurred in about 29% of patients or people on the trial at 13 months.

Looking at this other trial here for this other CAR T, the overall response rate at 18 months was 84%. You can see here the stringent complete response rate at 18 months was 67%. At the end of the day, it's difficult to really compare across 2 different trials because they had different requirements for entry into the trial, different groups of people with different diseases and different risks and it's just very difficult to compare 2 different trials, but there may be a signal that this particular CAR T product had a higher stringent complete response rate and may be more beneficial for certain people.

The side effects differ a little bit too. Some of the side effects occurred to a greater degree with this particular CAR T-cell therapy but we don't have enough years of follow-up on these studies yet to say what the long-term effects will be. It's only been a couple, about 2 or 3 years, since these studies have completed and so we're still waiting on data to see what the long-term response will ultimately be.



Slide 26: Cell Therapies for Non-cancerous Diseases

We're also looking at cell therapies, CAR T-cell therapies for non-cancerous disease. I've shown you all these statistics here and that's a little difficult to interpret sometimes if you don't know what the statistics are without using the CAR T-cell. Basically, we've been very, very impressed with the response rates using CAR T-cell therapy in diseases, such as diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, and acute lymphoblastic leukemia.

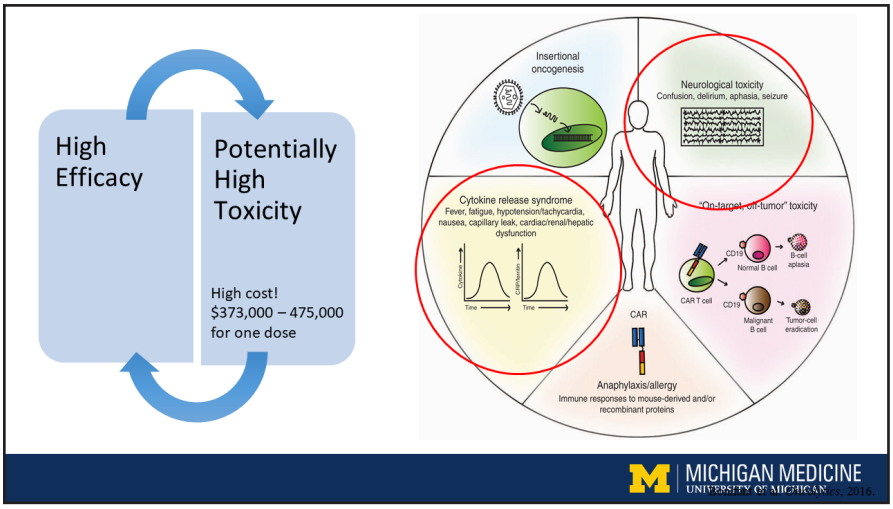
Because most of the standard therapies that are out there have very low response rates, usually less than 50%, we don't know if they will be long-term curative. That's why we feel that CAR T-cell therapy is usually the best next step when you have relapsed or refractory disease, meaning that you haven't responded to the standard therapies that are out there.

We're looking at different types of cell therapies for viruses. For instance, people can have lymphomas or other types of diseases that develop from Epstein-Barr virus. There's a type of virus called BK virus that can affect people who've had transplants of organs or bone marrow. There's another virus called cytomegalovirus, which can affect people who are immune suppressed and can cause lots of damage.

There are also newly FDA-approved cell therapies for sickle cell disease and thalassemia. We're looking at cell therapies now in autoimmune diseases, such as lupus or scleroderma. We're also looking at various transplants when people have a kidney transplant, lung transplant, etc., giving them stem cells from their donor as well so that they cannot take rejection or anti-rejection drugs. There's a lot of exciting work that's being done.

Slide 27: What are the major side effects of CAR T-cell therapy?

What are the major side effects of CAR T-cell therapy? I talked about that in the previous slides and I briefly mentioned cytokine release syndrome and neurologic symptoms. Those are the 2 main side effects and those usually occur within the first 4 weeks or so after CAR T-cell infusion. Other potential side effects include low antibody or immunoglobulin levels, low blood counts, and infections. There also is potentially the risk of a secondary cancer.



Slide 28: High Efficacy and Potentially High Toxicity

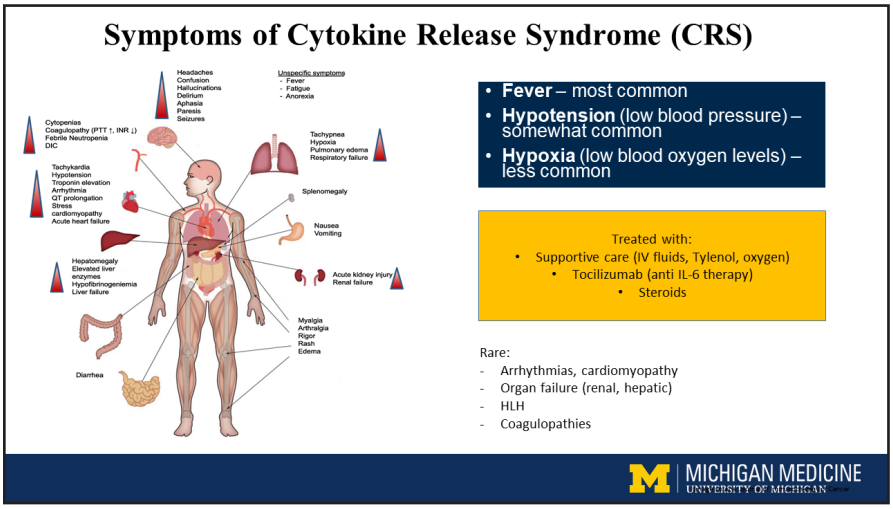
I'll start with the first with cytokine release syndrome. This is a schematic here of some of the various side effects that we can see from CAR T. Like I said, I'm going to focus first on the 2 major side effects we see within the first few weeks after CAR T-cell therapy. That is cytokine release syndrome and neurologic side effects.

Other effects we could see - some people can have an allergic reaction to the CAR T-cell infusion itself. This is usually something we would see right after the CAR T-cell goes into your veins and you may develop a rash or shortness of

breath, but that's very, very rare. I actually have not seen this in all of the patients that I have treated. There is the risk of something called on-target, off-tumor toxicity, which is where the normal B cells in your body, not the cancerous B cells, the normal B cells can be killed off by the CAR T-cells because unfortunately, the CAR T-cells do not discriminate between the cancerous cells and the non-cancerous B cells.

That leads to some immune complications because B cells produce antibodies that are very important in fighting infection. If your normal B cells are not there, then they can't produce those antibodies. Another risk is something called insertional oncogenesis, which we really have not seen much of this. This is very rare. This is where the part of the CAR T-cell that's genetically modified could potentially get inserted into other cells in the body and cause problems, even the possibility of some secondary cancers.

Again, this is very, very, very rare and we really haven't seen any major cases of this causing any issues yet. CAR T-cells, as I mentioned, high efficacy but potentially some significant toxicities or side effects. Another thing that comes into it is the cost. These are very expensive drugs; for one dose of drug it's priced at $373,000 to $475,000. Whether we like it or not, that does influence insurance companies for sure and it affects some people's ability to get treated with this. That's why there's the need for more access to CAR T-cells and for us all to be able to produce some of these cells in a cheaper manner.



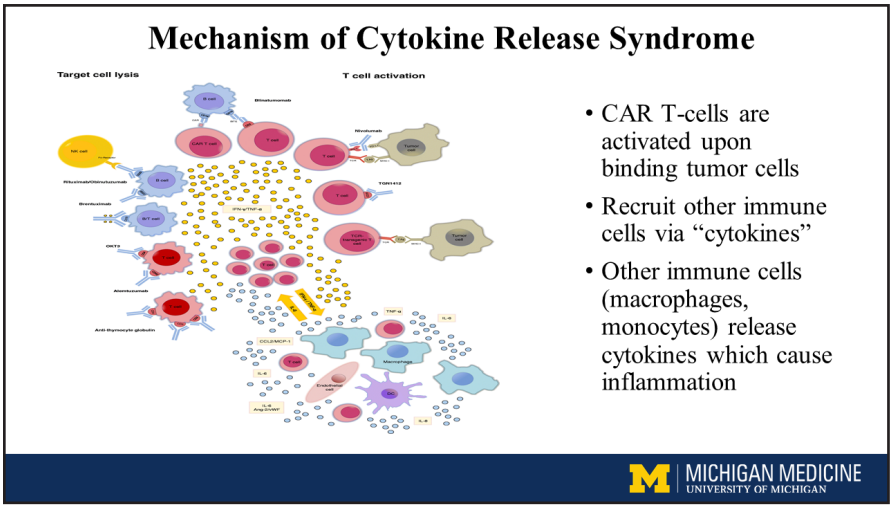
Slide 29: Symptoms of Cytokine Release Syndrome (CRS)

What is cytokine release syndrome? Cytokine release syndrome, when I describe it to people, it's really your entire body is inflamed. That's what's happening. When the CAR T-cells get into your body through your veins and they start targeting the lymphoma cells, then what happens is all different cells from the immune system come and join the party and create inflammation in the body.

That's how the body heals and that's how the body can help kill off the cancer. What a lot of people feel is, they feel like they have a bad infection, they have a really bad virus or the flu. This can manifest as various symptoms. You can get fevers, sometimes high fevers. We've seen 104°; for instance. Some low blood pressures, which can be responsive to IV fluids, meaning that we can give you some IV fluids and your blood pressure can improve, or the blood pressure will be persistently low despite giving IV fluids.

You can get hypoxia, which is low blood oxygen levels. That's less common but we do sometimes see that. If you can see - this is very tiny writing on the schematic - but if you can see it there, various organs can get affected by cytokine release syndrome, including the heart can develop abnormal rhythms, the liver, the kidneys, etc. The good thing about all of this is that we know a lot more about how to manage it.

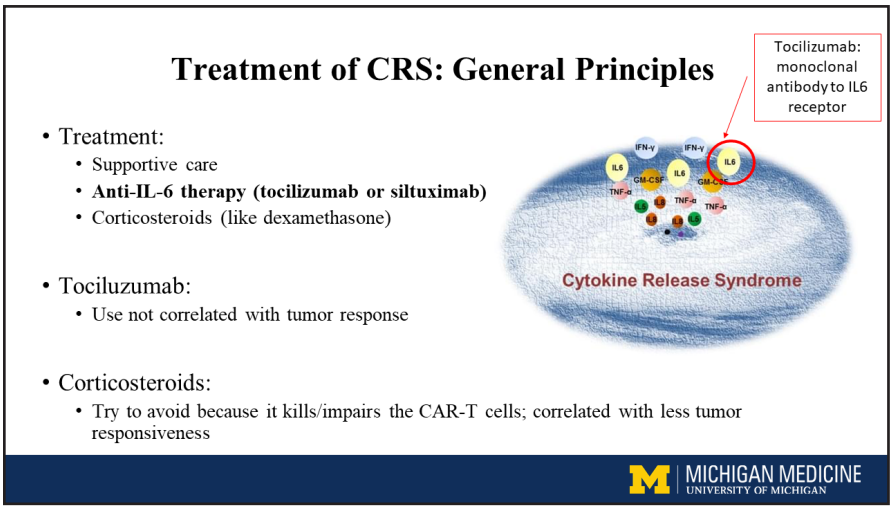
We know a lot more about how it works, how it happens, what causes cytokine release syndrome, and we have worked out systems to identify and manage and treat cytokine release syndrome. We do have a system that we use to grade cytokine release syndrome. It was a consensus system that was determined by a lot of people coming together and trying to figure out what is most important. We grade it by fever, low blood pressure, and low oxygen levels. I'll show you that system in just a minute.



Slide 30: Mechanism of Cytokine Release Syndrome

Going back to how this works - basically, cytokine release syndrome is just your body's immune system going into overdrive because of this very complex interaction that's happening between the CAR T-cells and the tumor cells and the rest of the immune system trying to clean everything up. The body releases these little factors called cytokines, which you can sort of think of them like hormones.

They're not exactly the same thing. There are these little protein factors that get released by various types of cells in the body and they are the way that the immune system communicates with itself. These cytokines can go to different tissues and organs in the body and tell those organs to create inflammation and create certain side effects.



Slide 31: Treatment of CRS: General Principles

The way that we treat cytokine release syndrome, if it's low grade, meaning there's just a fever that goes away within 24 to 48 hours, we usually just do IV fluids, maybe some Tylenol® or ibuprofen to try to keep you comfortable, but

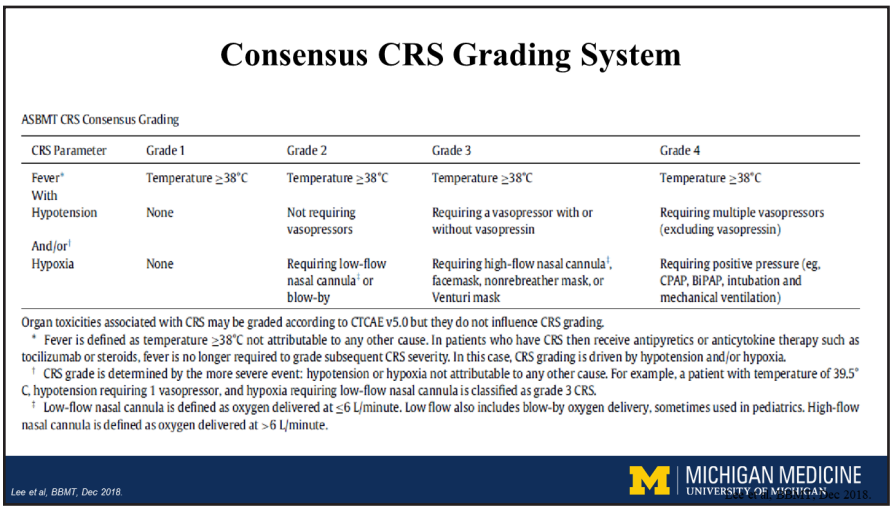
typically, don't intervene with anything at that point. If it becomes more significant, if the fever is lasting for a couple of days and not improving or if the blood pressure is dropping or the oxygen levels are dropping or various other things could be happening, such as abnormal rhythms of the heart, then we would start a treatment.

We call this anti-IL-6 therapy. IL-6 is one of those pesky little cytokines that causes a lot of the inflammation in the body during the cytokine release syndrome. These are antibodies, these are biologic agents that have been developed and designed to specifically get rid of that IL-6 cytokine. What we do is if we see that the symptoms are more persistent then we will administer either of these drugs usually as an infusion into the veins. Sometimes we administer it again after a few hours if we don't see improvement in symptoms. Then after a couple of doses, if we don't see any improvement, we start steroids, something like dexamethasone or prednisone; there are various steroids that we use. What the steroids do is they decrease the inflammation in the body and can help with the symptoms.

Using the anti-IL-6 treatment, tocilizumab (Actemra®) is the one that's actually FDA-approved for this particular use. We haven't seen any impacts on whether the CAR T-cells continue to do their job to kill the tumor cells.

However, we do know that the use of steroids can sometimes affect or impair the function of the CAR T-cells. In some of the early studies, we saw that people who got steroids maybe didn't respond as well to the CAR T treatment or their CAR T-cells were suppressed. However, we have learned more about this in the past 7 to 8 years. What we've learned is that if you time the steroids right, it may not affect the CAR T-cell function.

There's a little bit of an art to how you time the steroids, we can give it early. We actually give it as prophylaxis, meaning we give it right before giving CAR T-cells and then a couple of days after with some of the CAR T-cell products. It's been shown that that doesn't affect how well the CAR T-cells work and can help reduce the amount of severe symptoms. There are certain ways to use the steroids that we feel, and we have seen through the data, does not affect the function of the CAR T-cells.



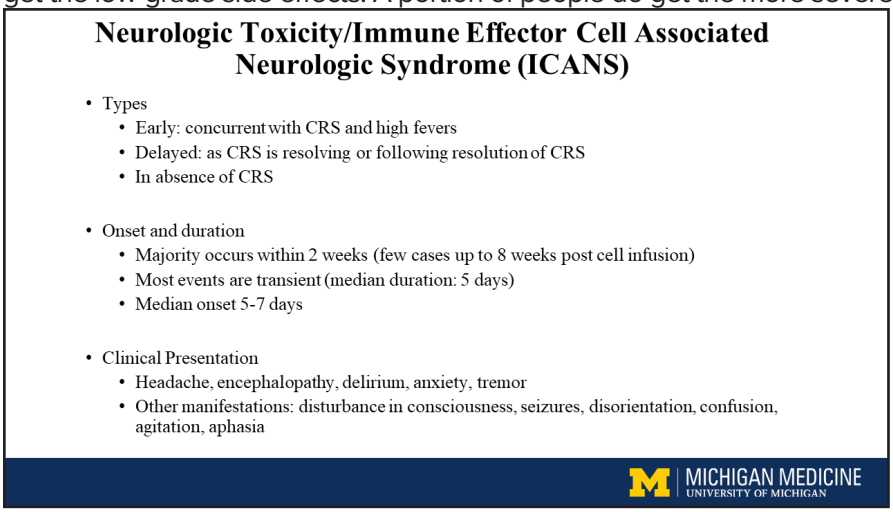
Slide 32: Consensus CRS Grading System

This is the consensus grading criteria. You may hear your physician saying, well you have Grade 1 cytokine release syndrome or Grade 2. What that means is, if you have Grade 1, you just have a fever. That's what we call low grade. Typically, we're not doing any treatment for that, but we may give you some treatment if the fever persists over 48 hours. If you have a fever and then you have lower blood pressure or you have some low oxygen levels that improve by giving you oxygen or low blood pressure that improves by giving you IV fluids, you have what's called Grade 2 CRS.

In some cases, we do treat that. If you have Grade 3 or Gade 4, that's more severe and we always treat that. Generally, if you have Grade 3, which is where you're a bit sicker, then you may have to be in the intensive care unit and may require

more monitoring. Sometimes that may involve in very severe cases being put on mechanical ventilation, meaning you're put on a ventilator or respirator. Typically, this is very short-lived. It usually lasts for a few days at a time.

The onset of these symptoms are anywhere from 2 to 7 days after the CAR T-cell infusion, depending on the product that we use, and can last an average of about 5 days, not necessarily severe. A lot of people just get, in fact the majority of people, just get the low-grade side effects. A portion of people do get the more severe side effects and we treat that more aggressively.



Slide 33: Neurologic Toxicity/Immune Effector Cell Associated Neurologic Syndrome (ICANS)

There's also something called neurologic toxicity or what we call immune effector cell-associated neurologic syndrome. We call it ICANS, which is a little bit easier to remember. There are different types. This is the neurologic or brain side effects that we see sometimes. This can happen at the same time as cytokine release syndrome, or it can happen a little bit after, or it can happen on its own without cytokine release syndrome. We treat it depending again on the grading and the symptoms. Typical onset can be somewhere in the first couple of weeks after CAR T-cell therapy. There even is one of the myeloma CAR T-cell therapies where a lot of these symptoms started even 3 weeks after the CAR T-cell.

For most of them, if it's going to happen, it'll happen in the first couple of weeks. There were early on a few cases of people developing some symptoms at about 8 weeks after the cell infusion. This was several years ago, but we haven't really heard reports or seen that recently. Some of you may be told to not drive for several weeks after CAR T-cell, and that's the reason, because we did see some of these side effects in the early studies, but we really haven't seen that recently now that we know better how to treat the neurologic side effects. Most of these events are transient.

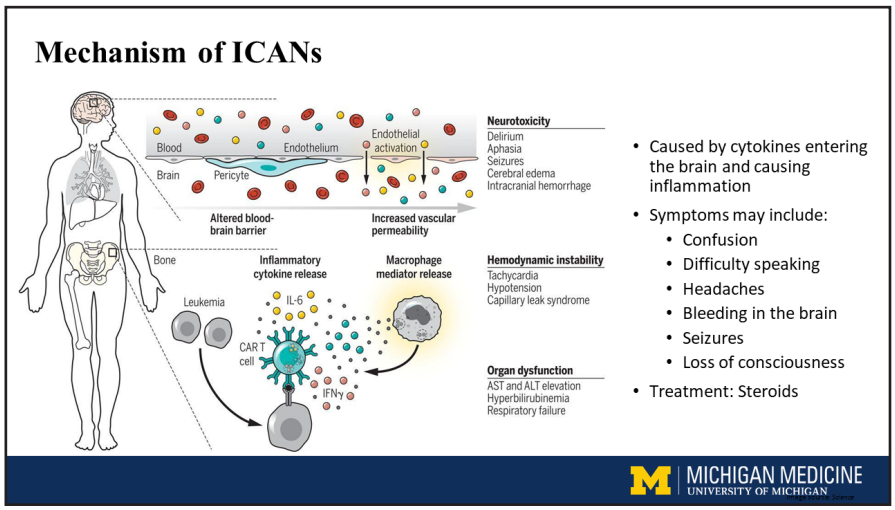
It usually lasts for about 5 days in most people and so far, we have not seen any long-term relation to any cognitive effects down the road, memory effects, things like that.

How does it look? Well, it looks different depending on the CAR T-cell that you use. For most of the CAR T-cell therapies that are out there, most people will experience some short-term memory loss and confusion. One of the most common symptoms that we see is people may forget what day of the week it is or the month, or the year, or may have difficulty expressing themselves. You know you're trying to get out a particular sentence, but you just can't get it out. We call that aphasia.

In some people it can be delirium, which is where you're just not very with it. You're not there, you're just kind of falling asleep and tired. That can be one of the symptoms we see as well. We can see tremors, some people get headaches, and then some people if it becomes severe, can get eventually loss of consciousness and there is risk of seizures. I have not actually seen any of my patients develop seizures, but it is a risk. We actually put everybody on some anti-seizure medication before CAR T treatment, and typically we're able to treat and intervene before anything like

seizures happen.

Again, really this is a transient issue. A lot of people have told me that when they've had this happen to them, they don't remember that period of time. We still don't truly understand what causes this. We have some ideas but there is still a lot of work that we're doing in trying to figure out this particular mechanism.



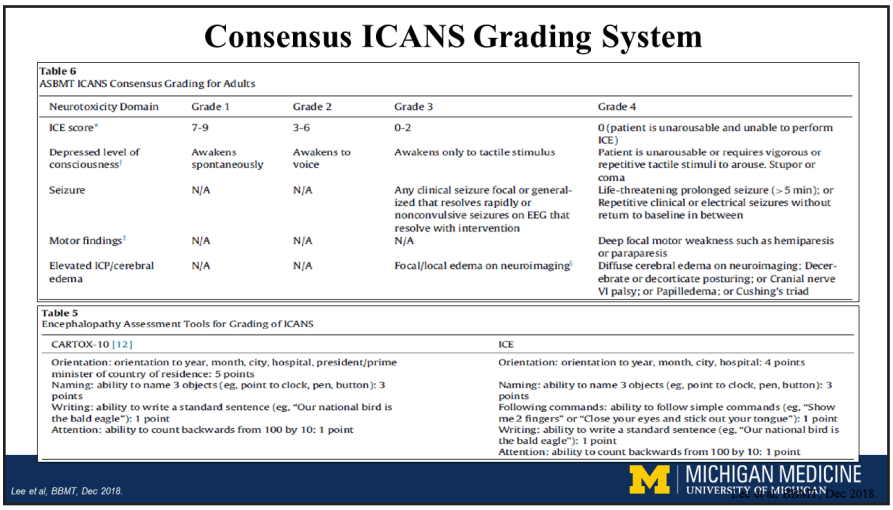
Slide 34: Mechanism of ICANs

This is a bit of a complicated diagram, but basically, what this is showing is that you're getting inflammation in the body from the CAR T-cells and your body tries to protect your brain as much as possible. Your body has something called the blood-brain barrier, which is basically like a border that is patrolled by all kinds of cells to prevent bad things from getting into your brain.

Your body tries to prevent drugs and various things from getting into your brain at all costs. However, when you get CAR T-cell therapy that can lead to breakdown of that blood-brain barrier and that can allow all of this inflammation to go from the rest of the body into the brain and it can cause some swelling and it can cause inflammation in the brain and that's the CAR T-cells themselves can get in the brain and these cytokines can get in the brain and then cause all of the symptoms that I mentioned before. We really don't have great treatments for neurologic toxicity except for steroids. Steroids can work wonderfully for this. It can actually reverse it.

People can feel a lot better with steroids. We have tried some other medications and some of them help and some of them don't. Usually steroids are going to be our main intervention. Sometimes we do have to do a lumbar puncture, which is where we put a needle into the fluid at the base of your back, into the fluid that surrounds the spinal cord and the brain, and we actually inject some steroids into that area. When we do that, we have seen that some people improve pretty quickly, but a lot of times the neurologic side effects really just take a little bit of time and improve on their own.

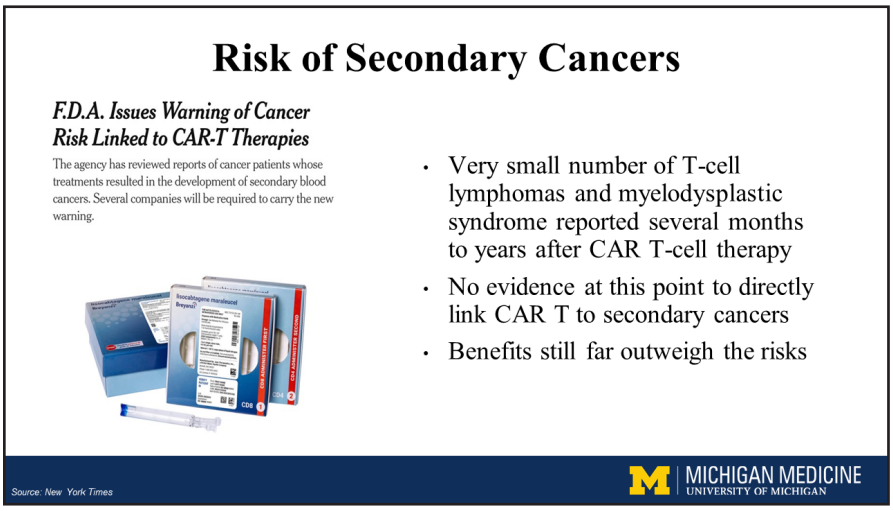
It can be incredibly scary and incredibly difficult for families, for sure, if you have severe symptoms, but the majority of people are not going to get severe symptoms. The rates of neurologic side effects vary depending on the CAR T-cell product that's used. For some of the CAR T-cell products, the rate is 20%, and some it's 60%. Even among that 20% or 60% of people, the majority of people will get what we call low-grade side effects. That is what we use on our grading scale here. Those of you that have received CAR T-cell therapy or may receive it in the future, we will be asking you questions called the ICE (Immune-effector Cell-associated Encephalopathy) score.



Slide 35: Consensus ICANS Grading System

What this is, you'll see here on the bottom right. The ICE score is a test that we give every day. Usually, at our center we do it twice a day at least, in the morning and in the evening. We ask you to identify the year, the month, the city, the hospital, name 3 objects, follow a simple command, and write a sentence. This adds up to 10 points. If you score 10 points, you're fine. You don't really have any signs of neurologic side effects. If your score drops to about 7 to 9, we consider that Grade 1, so that's mild. We oftentimes don't have to do anything for that, it usually resolves on its own.

However, if the score drops a little bit more to 3 to 6, or to 0 to 2, that's when we have to intervene. When we are at Grade 2, we intervene with steroids. Sometimes we'll give one dose of steroid and see if you get better. Sometimes we will continue with steroids every 4 to 6 hours in high doses. Of course, if we see any of these other symptoms here, we will treat those symptoms as well. The majority of people, if they get neurologic side effects, it's really going to be in the Grade 1 or 2 region. A very small number of people will get Grade 3 or 4, which is more severe.



Slide 36: Risk of Secondary Cancers

One other issue I wanted to address, which many people I'm sure there will be a lot of questions about this, and many of you may have seen this in the media recently. There is potentially a risk of secondary cancers after CAR T-cell therapy. To the left here, this was an article from The New York Times that was published just last week. What this states is that the FDA is now issuing a warning and will likely request updating of the labels of the CAR T-cells to state that there may be a risk of secondary cancers. What this is based on is, there have been observed a very small

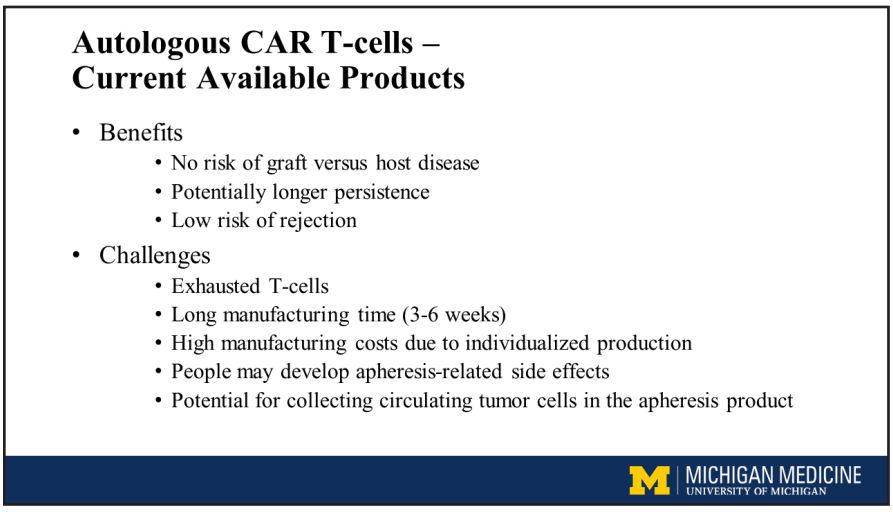
number of T-cell lymphomas - T-cell, not B-cell lymphomas, and something called myelodysplastic syndrome, which is a syndrome in which the bone marrow just stops working and stops making blood.

This has been reported in some people several months to years after CAR T-cell therapy. There's no evidence that we have at this point that directly links CAR T to these secondary cancers. Unfortunately, anytime you get any chemotherapy or radiation or stem cell transplant or anything, that actually puts you at a small risk of a secondary cancer. Then some people just have that risk anyway. Some people may have developed T-cell lymphomas anyway.

It's a very, very tiny number of people, which of course is always significant even if it's one person, but out of the thousands and thousands of people who have been treated, we are not seeing this as a large number of people being affected. The FDA is looking into these particular cases to see if they are directly related to CAR T, but we don't know that yet. We still feel that the benefits far, far, far outweigh the risks of getting these cancers down the road.

Slide 37: Emerging Immune Effector Cell Therapies

There are lots of different, what are called immune effector cell therapies, different types of CAR T-cell therapies that are being looked at.

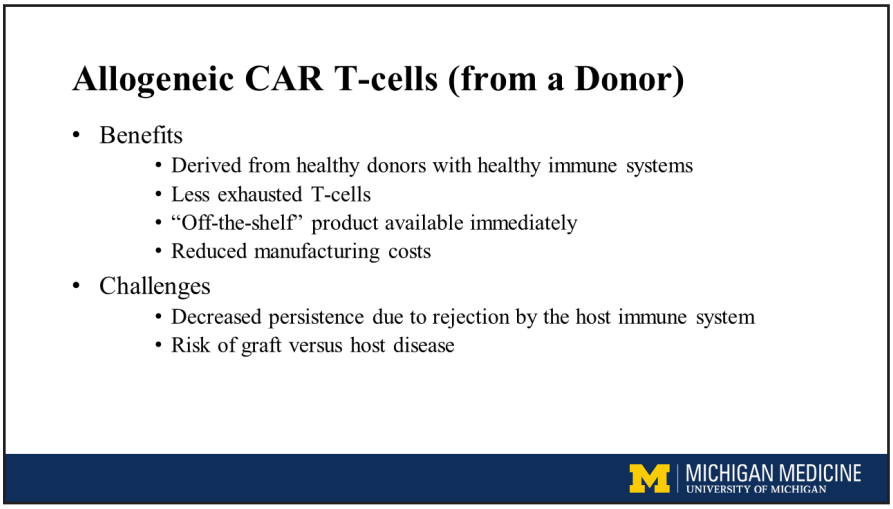


Slide 38: Autologous CAR T-Cells – Current Available Products

We have CAR T-cells, right now everything is autologous, meaning that the CAR T-cells are manufactured from your own T-cells. Right now, that's a good thing in many ways because you don't risk these T-cells coming in and attacking your body because they're your own T-cells. Potentially, the body also is okay with these T- cells because they're your own, so they can persist longer in your body and there's a very low risk of the body rejecting these T-cells. However, the problem is, once your T-cells have been exposed to chemo, they become exhausted. Over time, we're taking some older exhausted T-cells that may not be up to killing as much cancer as we want them to kill. Then the manufacturing time is an issue. It can take, at the quickest, usually about 17 days to manufacture CAR T-cells and at the latest sometimes 6 weeks.

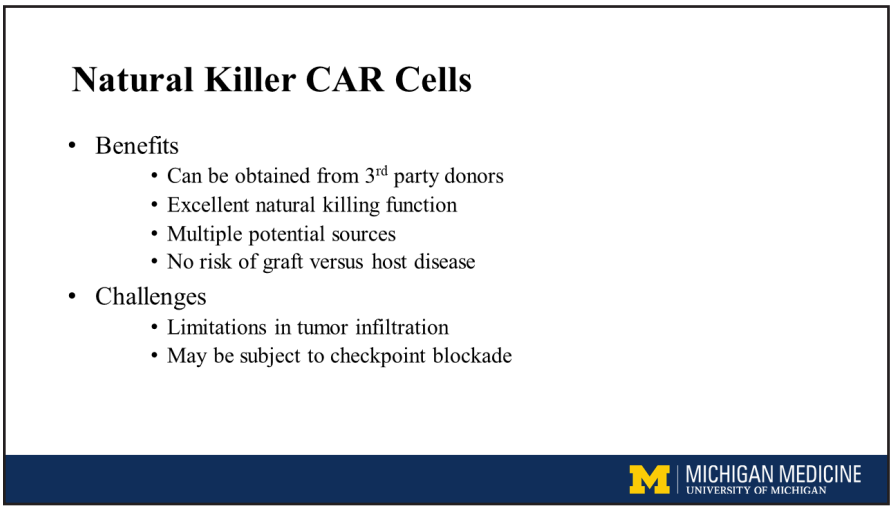
During that time, the cancer keeps growing, and you may have to get additional chemotherapy, which can lead to additional infections and side effects because you want to keep the lymphoma under some control before doing the CAR T-cell therapy.

We also know that it costs a lot to make these individualized products and then people can get some side effects from the collection of the cells itself. There's also the question, "Can you collect some of the tumor cells that may be in the blood in this product that you're sending to the company?" We haven't really seen that cause any major issues at this point, but theoretically, that could be an issue.



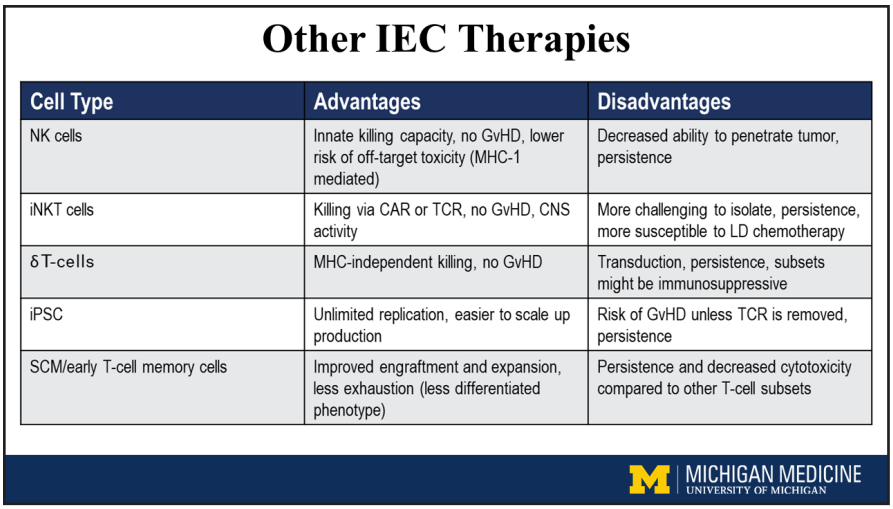
Slide 39: Allogeneic CAR T-Cells (from a Donor)

That leads us to looking to other sources. There are what are called allogeneic CAR T-cells. This is from a donor. None of these are FDA-approved at this point. These are all in the setting of clinical trials.



Slide 40: Natural Killer CAR Cells

What is done with these particular cells, healthy donors are taken, people who have healthy immune systems, and their T-cells are extracted and then modified so that they could potentially be used for treatment. There are other types of cells in the body called natural killer cells, which as their name suggests, are very good at killing things. They're very good at killing tumor cells. You can actually engineer a CAR - that receptors onto these cells so they can direct their function against the tumors. This can be obtained from other people. The good thing about these types of cells, which we're calling off-the-shelf cells, is that they're available. They're available quickly.

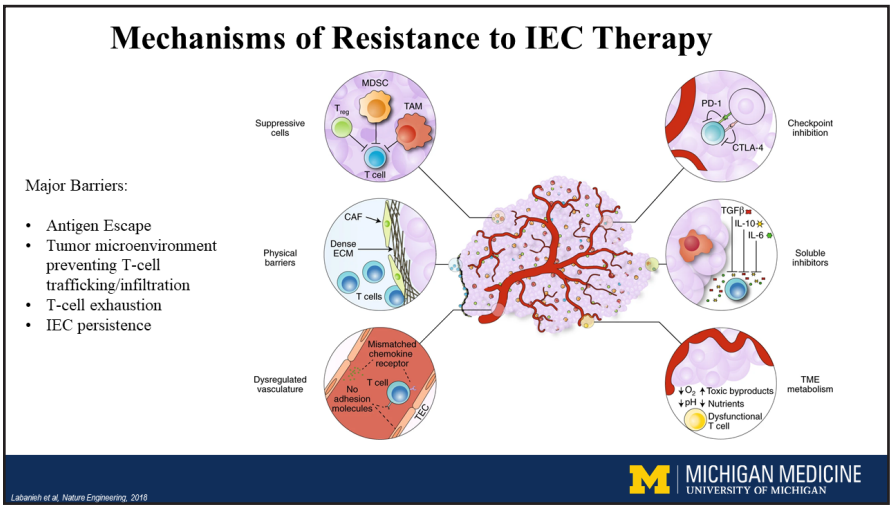


Slide 41: Other IEC Therapies

We can give them to people without having to harvest your cells and take time to manufacture those cells into CAR T-cells. The problem is that [with] some of these cells, we haven't perfected the method yet. Your body could reject them. They could come into your body and cause something called graft-versus-host disease (GVHD), which is where those T-cells attack some of the tissues and organs in your body. Then the body may just get rid of these. Sometimes we have to do multiple infusions of these cells, often every few weeks or so. There are advantages and disadvantages, but we need to work to make them better.

Slide 42: Future Improvements in Immune Effector Cell Therapy

We have a few minutes left, just to talk about some of the improvements in immune effector cell therapy. This includes CAR T-cells and various other types of cells. One of the issues with CAR T-cells, as you saw from the response rates I showed earlier, maybe 80% of people are responding initially, but there are 20% of people who don't. That is unfortunate that some people do get CAR T-cells, and the cancer does not respond to it. Why does that happen? There are many different reasons. One of the reasons I touched on just now is that the T-cells themselves may not be good, and that's why it may help to get T-cells from a healthy donor with a healthy immune system.

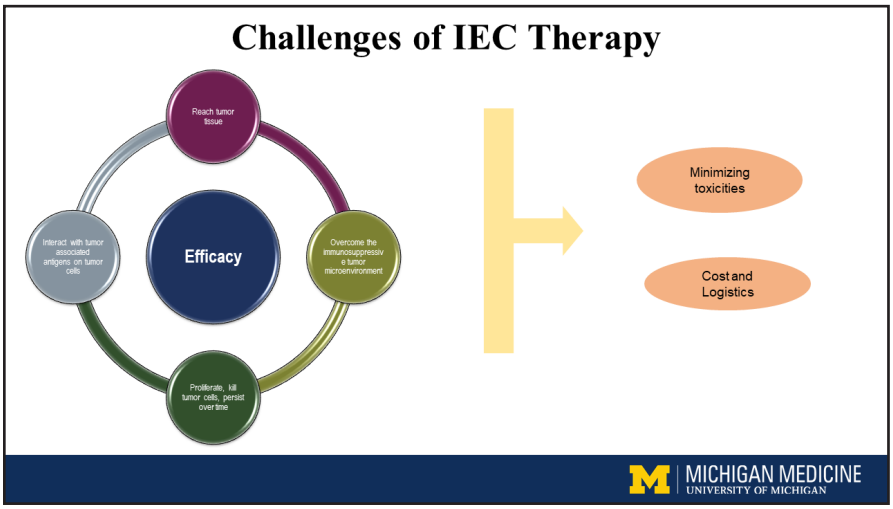


Slide 43: Mechanisms of Resistance to IEC Therapy

There's also something called antigen escape. That means that when that marker on the cancer cell is targeted by the CAR T-cell, cancer cells can be smart. They can actually then divide and grow without that particular marker on their cells. I have had some patients who received CAR T-cells that targeted the CD19 on the surface of their lymphoma cells and then the CAR T-cells either stopped working or didn't work. What we found down the road when we did another biopsy is that those lymphoma cells came back without that CD19 marker on them because they figured out that's the way to escape from the CAR T-cells.

Also, CAR T-cells have been tried in solid tumors. When we say solid tumors, we mean that cancers that are not blood cancer, so lung cancer, pancreatic cancer, things like that. Those are still in clinical trials, and some are very promising. One of the problems when you're trying to attack a tumor is that a tumor is a complicated environment, and the tumor

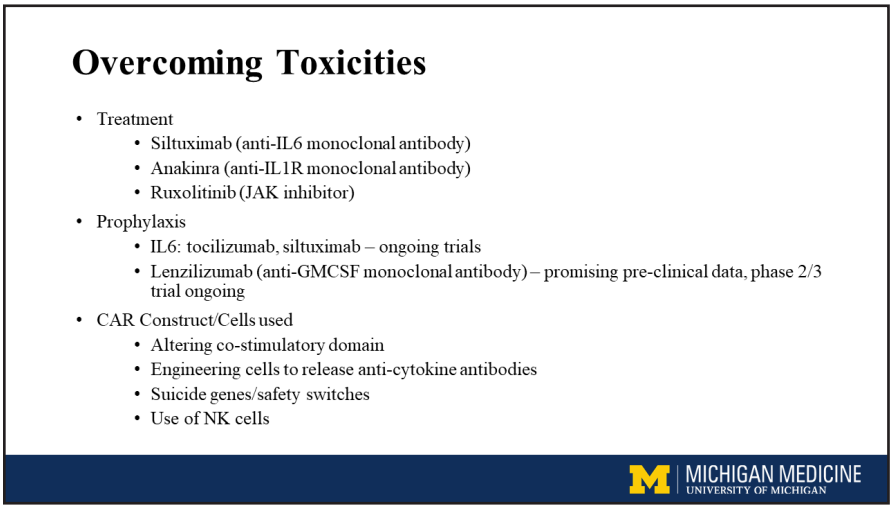
tries to keep out the CAR T-cells because the tumor doesn't want to be killed. There are ways that the tumor can keep the CAR T-cells out of it and can suppress it. These are all different avenues that very smart people, not me, are looking at in the laboratory to try to improve the efficacy and the positive effects of these different cell therapies.



Slide 44: Challenges of IEC Therapy

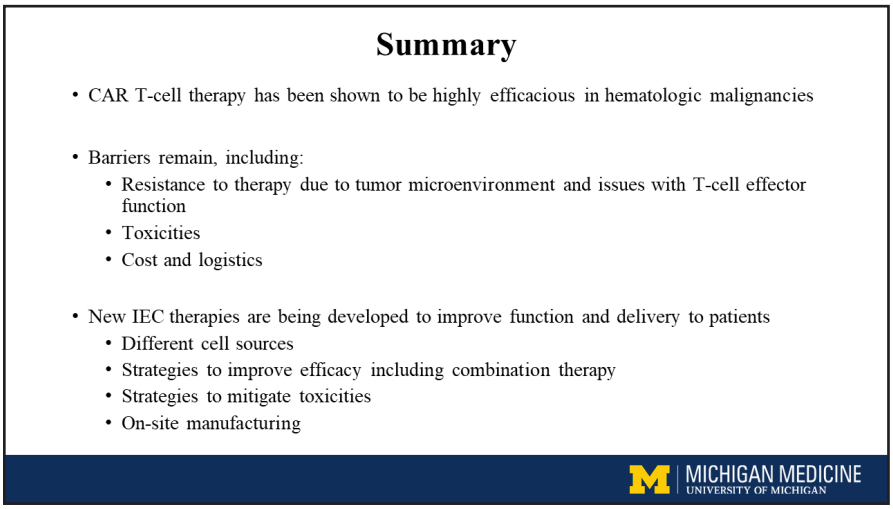
Basically in trying to improve CAR T-cells, the main things we want to do is we need the CAR T-cells to first of all be able to make more of themselves, proliferate, kill tumor cells. They also need to overcome the body's immune response and the body needs to allow the CAR T-cells or whatever other cells we're using come in and actually get to the tumor tissue, reach the tumor tissue, and kill the tumor cells. Then we have to have the right types of targets for these CAR T-cells to interact with. Then also very importantly is minimizing the side effects.

There are studies looking at using different medications as sort of prophylaxis, so giving some medications ahead of time, not just steroids to prevent even completely eradicate some of these side effects like cytokine release syndrome. Then of course bringing down the cost and improving the logistics of CAR T-cells, making the manufacturing faster, making it more accessible for people. These are the challenges, and these are things that we as a field are working on right now.



Slide 45: Overcoming Toxicities

As I mentioned, there are various strategies for trying to overcome the side effects. There are treatments that are being looked at, there are different prophylactic drugs that are given before the CAR T-cells are even infused. Then we have different ways of trying to construct the CAR T-cells so that they will not cause as many side effects.



Slide 46: Summary

In summary, we know that CAR T-cell therapy has been shown to be highly efficacious in blood cancers compared to the standard therapies that are available. However, we know there are many barriers, we could do a lot better with making CAR T-cells work better and last longer. We need to reduce the side effects of the CAR T-cells, which can make people pretty sick. We need to reduce the costs and improve the logistics. There are new therapies that are being developed right now from different cell sources, including from healthy donors.

We also have the potential of combining various types of cell therapies, combining with chemo, combining with other types of immune therapies, or just combining multiple cells together to get even more of an impact on tumors. We have lots of different strategies right now to try to decrease side effects, and a lot of people are trying, and we're working on this at our institution as well, of manufacturing our own CAR T-cells so that it's quicker, cheaper, and a little bit more accessible for people.

Slide 47: THANK YOU

That's all I have for today. We're just about at the end of our hour, and I believe we will be transitioning into the Q&A session.

Slide 48: ASK A QUESTION

Lizette:

Thank you so much Dr. Ghosh for all of that information.

It is time for our question-and-answer portion of today's program.

We'll take the first question from our web audience. Dr. Ghosh, there are many types of blood cancers and we have many blood cancer patients on the line. I know that there have been a lot of CLL patients, a lot of Waldenström's macroglobulinemia patients. People are asking about Hodgkin lymphoma and CMML (Chronic Myelomonocytic Leukemia), LGL (Large Granular Lymphocytic Leukemia), are all of these other types of blood cancers right now in clinical trials for CAR T-cell therapy?

Dr. Ghosh:

Yes, they are. The ones that I mentioned are the ones that are FDA-approved and available as standard of care. However, there are clinical trials for all of these blood cancers going on. There's a lot of data out there for CLL especially. Actually, the first patient treated with a CAR T was in CLL, and we're hoping that maybe one of the CAR Ts will get approval pretty soon in CLL. Right now, it's not FDA-approved yet. For the other diseases, yes, there are studies. For Hodgkin's, there are a few studies at a couple of different sites targeting something called CD30 on the surface of those cells. All of these are in clinical trials. They just aren't FDA-approved yet, and the clinical trials are at various sites across the country.

Lizette:

Thank you. We'll take our next question from our telephone audience please.

Operator:

Thank you. Our question comes from Larry. Larry, your line is open.

Larry:

First, thank you Dr. Ghosh. My wife and I are in the car. She's the patient. She had her stem cell transplant at the end of October, and we're literally driving to Mass General for our first appointment with our hematologist since then. It's for multiple myeloma. She started with the daratumumab treatment. We know that's 2 of 4. My question is: What do you recommend the agenda be for our appointment today? How do we approach this with our doctor? What are the points to make? We understand right now the FDA's going to require 2 more courses to treatment. What should we be discussing this early on? Thank you.

Dr. Ghosh:

This early on, it really depends on what her response has been to the transplant and whether she's in remission or very close to remission. There are some trials that are out there that are looking at CAR T-cell therapy in this setting using it as a preventative measure to keep the myeloma from coming back. There are a couple of trials. Most of those though you have to enroll in before undergoing the stem cell transplant. At this point, I would say that the main thing after a stem cell transplant is being put on a good maintenance therapy to keep the myeloma away and stay in remission longer.

There will probably be some data and maybe update to the CAR T approval for third-line or after third-line therapy fairly soon, so if she relapsed after getting even another line of treatment, then possibly at that point there may be some update to the eligibility for CAR T. Right now, the main thing is seeing what the response is right now and then starting a maintenance therapy to try to stay in remission.

Lizette:

Thank you so much and our next question comes from Renuka. She's asking: For how many years will the CAR T-cells be present in the patient's body and fight the cancer cells? Do we know that, Doctor?

Dr. Ghosh:

That's a very good question and that also again depends on which CAR T-cell we're using and what disease. There have been CAR T-cells that have been identified in people up to 6 years after the CAR T-cell was infused. CAR T-cells, the way that they work is, when they get into the body for the first few weeks they divide and make a lot of themselves. You see this peak of the number of CAR T-cells in the body. That's when a lot of the action happens, and then those cells start to die off, but a few of them are left over and can propagate and make more of themselves. Those few are the ones we can detect potentially years later.

As far as how many people will have these cells detectable in their blood, that's a very difficult question to answer because it really depends on the situation. Some people who have relapsed, we can see the CAR T-cell is no longer there in their blood, and then some people it's still there, and they have relapsed. We don't have a good way of making an association between the CAR T-cells still being detected on this test that we have and ongoing response to the treatment. CAR T-cells also can create what are called memory cells. They help create this group of other T-cells called memory T-cells.

We're not necessarily going to detect the CAR T-cell itself but there may be memory T-cells that are doing the job at the instruction of the CAR T-cell years later. Again, like all of the questions with these CAR T-cell treatments, it varies, but we have seen the CAR T in some people several years later.

Lizette:

Thank you. Nick is asking: How much are you immuno-challenged after CAR T-cell therapy and for how long?

Dr. Ghosh:

That's an excellent question actually, and this is probably the most frequent question I do get. There are different levels of immunocompromised depending on how far out you are from the CAR T-cell infusion. We do give some chemotherapy right before the CAR T-cell infusion to prepare the body, and that chemotherapy does make you immunosuppressed for about maybe 8 to 12 weeks after the CAR T-cell infusion, and that makes you fairly immunosuppressed to the point that's almost similar to having a stem cell transplant. Not quite that immunosuppressed but pretty similar. You can get bacterial infections during this time, some viral infections.

Then after that, you start to recover and your blood counts will recover, and you get farther away from that chemotherapy, but you're still going to be somewhat immunocompromised because the CAR T-cells keep killing off

your normal B cells, and those are the cells that you need to make those antibodies or immunoglobulins that can identify bacteria, fungus, viruses, and let your immune system know that those are present and need to be eradicated. That can last for years. That particular part of the immunosuppression where you might be more susceptible to pneumonias and sinus infections from certain viruses and bacteria and even some fungal infections.

We do monitor and people sometimes need intravenous immunoglobulin or IVIG, which is administered from other people who have donated their normal immunoglobulins and some people need it every month, some people need an infusion every few months, and that can help prevent infections.

Lizette:

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

Operator:

Thank you. Our next question comes from Cheryl. Cheryl, your line is open.

Cheryl:

Is there a special diet that you need to be on afterwards?

Dr. Ghosh:

We do recommend that you stay away from certain foods. Usually it's the same type of diet we recommend for people who've had a transplant, so well-cooked food. The main thing that we're concerned about is foodborne illnesses, so we ask you to stay away from raw or uncooked food, sandwich meat for a little while just because there's the possibility of listeria. Certain restrictions at least for the first 8 to 10 weeks after CAR T-cell infusion. Then after that, there really isn't any particular diet that you need to be on. We don't know of any diet or nutritional effects at this point that may make the CAR T-cells work better, just the main thing is to avoid infection.

Lizette:

Thank you. We do have a lot of listeners asking about nutrition. Thank you for the question. Now, Debbie is asking: I've read about some of the side effects that can happen with CAR T, and they're usually temporary, but does it ever happen that they are permanent?

Dr. Ghosh:

Not that we have seen. We actually do collect data. For those of you who may undergo CAR T or have already undergone CAR T, most institutions that do CAR T-cell therapy, we collect data for about 15 years or so, meaning that when we follow you up we're looking for things that may be going on. The side effects we have not seen that they are permanent in anyone at this point. There are some studies, we have a study right now where we're looking at long-term neurologic or cognitive side effects in people down the road who have had the neurologic side effects in the short term. We haven't found any permanent effects yet. I have not seen it and I have not seen reports of any of those being permanent.

Lizette:

Thank you. Lydia is asking: Are blood transfusions or blood products required for this type of treatment? If need to travel for this procedure, how long do I need to plan for staying in town?

Dr. Ghosh:

Blood products may be required, and it varies, again depending on the CAR T product used, how much disease you have. Some people require more transfusions than others. There are some people I have treated who have never

required a transfusion. That really depends on what effect you have from the chemotherapy that we give. The CAR T itself can cause your blood counts to drop. Actually most people end up not necessarily needing blood transfusions but needing injections to help boost their white blood cell count. We do see neutropenia in a lot of people after CAR T-cell therapy for several weeks, and then sometimes even a few months down the road we can still see low white blood cell counts. Yes, occasional transfusions are needed.

As far as traveling, it really depends on the center where you're getting your CAR T-cell treatment. Most centers, initially when we started doing CAR T-cell therapy, did require people to stay close by and close by can be defined in a lot of different ways in different centers, for about 8 weeks after getting the infusion. A lot of times, depending again on the institution you're getting treated at, the hospital, either you get treated and monitored inpatient in the hospital for a couple of weeks or there are outpatient therapy options where you can get treated in the clinic and just return for daily or every other day follow ups for a few weeks.

At our institution, we require people to live within 100 miles of here for 4 weeks after getting the CAR T-cell infusion. We used to require 8 weeks but then we found that most people did just fine, and so we thought that 4 weeks would be sufficient. Really depends on where you end up getting treated.

Lizette:

Thank you. Mary is asking about age and CAR T-cell therapy. She will soon be 80 and wants to know if CAR T is still recommended and if there have been many patients over 80 that have gotten CAR T-cell therapy.

Dr. Ghosh:

Not a problem, Mary. Really age is just a number at this point. Yes, there are effects. We do take age into consideration, but it's really your overall health. I've treated people who are 82, 83 years old, and they have done just fine with the CAR T treatment. It really depends on any underlying health issues, that's most important. There is always the question when you are in your 80s, how efficacious are your T cells? Because they've been through a lot and age does affect the immune system, we know that. There could be some effects on how good the CAR T-cells are depending on your age.

Age alone is not a factor that would disqualify you when you're 80. It depends on the institution you're at and the doctor who's treating you. There are some studies now where we've been collecting what we call real-world data outside of clinical trials. We've seen that a lot of older people, people 80 or over, are getting treated with CAR T and don't seem to do any worse than people who are younger.

Lizette:

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

Operator:

Thank you. The next question comes from Dan. Dan, your line is open.

Dan:

I have leukemia AML [acute myeloid leukemia] subtype TP53. How's CAR T-cell working with that?

Dr. Ghosh:

There are a couple of trials that are looking at CAR T-cells in that setting with AML. We don't have any FDA products approved yet, but I know of a couple of trials in which you can get the CAR T-cell plus an allogeneic stem cell transplant, a transplant from someone else down the road. Really, that's only in the clinical trial setting. We don't truly know how well that's working. In some of the early reports, there have been responses, but it is something that you would definitely have to get in a clinical trial.

Lizette:

Thank you. The next question comes from Susan, but we have had several questions where patients have more than one diagnosis. Susan is asking: If having MDS (myelodysplastic syndromes) as well as mantle cell lymphoma disqualifies her from a CAR T-cell therapy treatment?

Dr. Ghosh:

That is a tricky question, but it's something that really would have to be determined as a discussion between you and your doctor because it does not necessarily disqualify you, especially if there is a plan to maybe do an allogeneic stem cell transplant down the road. It depends on how severe the MDS is as well. Given that there is some risk that you could get MDS for more therapy or worsening of the MDS, then that would have to be an individual discussion with your physician. Some people may recommend to you not to do the CAR T, but it also depends on whether you have a lot of lymphoma right now and what risk level your MDS is or what stage your MDS is at.

Lizette:

Thank you. Dennis is asking: Will it ever be possible to eliminate the need for bone marrow transplant or stem cell transplant with advances in CAR T-cell therapy?

Dr. Ghosh:

Great question. Yes, there is a possibility. I'll never say never. I am a bone marrow transplant physician, so I do believe that bone marrow transplant is great for certain situations. It is a possibility. The thing with CAR T-cell therapy right now is the way that we are using it, it's not used in a lot of the diseases that require ultimately a bone marrow transplant for cure. We don't know yet, but it's possible, and we would love to either not have to do transplants where there are lots of risks or make transplants even better in conjunction with using CAR T-cell therapy to try to cure diseases.

Lizette:

Thank you. Along the lines of speaking about transplants, Karen is asking: I've had autologous and allogeneic transplants, will I still be eligible for CAR T-cell therapy if needed in the future?"

Dr. Ghosh:

You may potentially, yes. For the commercial products that are available out there, it does not necessarily matter. There may be some clinical trials you may not be included in, but you should not have an issue with getting CAR T-cells, and it also depends on the comfort of the oncologist treating you and the individual hospital or institution's policies, but generally should not be a problem.

Lizette:

Thank you. Debbie's asking: Instead of immunotherapy with IVIG, can I just move along to CAR T-cell therapy instead of all of these therapies that are making me constantly sick?

Dr. Ghosh:

It depends on what disease you're being treated for. Do we know?

Lizette:

No, I don't have that information.

Dr. Ghosh:

It depends on the disease. I don't know. Unfortunately, I can't answer that.

Lizette:

Amy's asking: Why would you want to infuse CAR T-cells more than once?

Dr. Ghosh:

One situation, which I have done this actually with one of my patients, this patient received a CAR T-cell product and went into remission for about 2 years, but then the lymphoma came back and still had the CD19 marker on it. That's the marker that the CAR T-cell targets. That told me that the lymphoma did not really figure out how to get away from the CAR T-cell. The CAR T-cells themselves just weren't very good. What we do in that kind of situation, we do consider giving CAR T-cells again because that person did get a couple years of remission and still has the CAR T-cell target. You can sometimes use a different CAR T-cell product. It is possible.

This is a very unique situation in someone who received one CAR T on a trial and then received another CAR T as a standard of care. However, there are some instances that people have been able to reinfuse CAR T-cells in similar situations using the same product. If you see that you have gotten a good amount of response, say a couple of years after the CAR T and that marker for the CAR T is still there on the tumor cells, then it's possible to get it again.

Lizette:

Thank you. A lot of people were asking if you can have CAR T-cell more than once. Tom is asking: Are vaccines, such as flu, COVID, RSV, pneumonia, tetanus, and shingles safe and/or effective after CAR T-cell therapy?

Dr. Ghosh:

Yes. We don't have really any evidence to say that these vaccines are not effective, and the reason that there was some concern and there have been studies that looked at it, is because the B cells play a very important role in creating immunity after you get vaccines. If you get the flu vaccine, for instance, your B cells create antibodies to help protect you against the flu virus. If the flu virus gets into your system after the vaccine, then those antibodies can bind to the flu virus and help the immune system get rid of it. However, there are other types of immunity that vaccines induce. They also induce immunity in your T cells.

B cells alone are not the only response that your body produces or antibodies are not the only response your body produces after vaccines. We recommend and believe that these vaccines are very important because there are other types of immune cells in your body that can create immunity. It may not be complete immunity, it may not be the same as the general population of people receiving these vaccines, but it provides some protection, which is still better than nothing.

Lizette:

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

Operator:

Thank you. Our next question comes from John. John, your line is open.

John:

Hi. If the CAR T infusion treatment doesn't work what's the next line of treatments out there to treat myeloma?

Dr. Ghosh:

It is disease-specific, so I'm glad you told me it was myeloma, not lymphoma because the answer would be different. For myeloma after CAR T, if you do have relapse or progression of the disease afterward, there are different chemo regimens that can be used. If you haven't gotten one before, then you could get a different chemo regimen or there

are other CAR Ts that are being developed. There are CAR Ts that are targeting different targets on the tumor cell. The ones that are available right now that are FDA-approved target BCMA (B-cell maturation antigen), which is a structure on the surface of myeloma cells. However, there are other structures that can be targeted and those are in the clinical trial setting.

That is one thing you could try, a different CAR T product on a clinical trial setting. Other things, there are something called bispecific T-cell engagers. These are immune therapies that are on one end, it's an antibody that targets one of these structures on the myeloma cell, such as BCMA, and on the other end it actually targets T-cells. What it does is, it basically binds to the cancer cell on one end and then it binds to your T-cells on the other end and grabs those T-cells and brings them toward the cancer cell so that the T-cell can try to kill the cancer cell. That is one option if you do have relapse after CAR T-cell for myeloma.

Lizette:

Thank you. Martha's asking: My husband had CAR T-cell treatment in March of 2023. The treatment was successful, but since then, his white blood cells are always very low. He suffers from anemia and sometimes his platelets are very low. Is it normal that after 10 months of treatment he continues to suffer from neutropenia?

Dr. Ghosh:

That is not that unusual actually, and we do see this in a certain number of people. It depends on the CAR T-cell product that was used in the disease. For instance, if someone had myeloma and got one of the CAR T-cell products, we've seen decreased blood counts in up to 30% of people even about a year later after CAR T-cell infusion. I have a couple of patients who still have occasional low white blood cell count 5, 6 years after CAR T-cell therapy. It's actually a very hot topic in this area that we don't have a great answer to. We know that there is some immune effect from the CAR T-cells themselves on the bone marrow that is potentially contributing to these longer low blood counts.

One thing that's done that if he hasn't had done yet, would be to consider doing a bone marrow biopsy just to make sure that the bone marrow itself is functioning okay. Sometimes, like I mentioned before, you can get things like myelodysplastic syndrome, which is where the bone marrow is just not working well. If he hasn't had a bone marrow biopsy yet, that would be something to consider, to look into. Otherwise, it's not that unusual. About anywhere from 10% to 30% of people may have some longer-term decreased blood counts.

Lizette:

Thank you. Priya is asking about bispecific antibodies. Those are newer, and how CAR T-cell compares to the newer types of treatment?

Dr. Ghosh:

There has not been any head-to-head comparison between bispecific antibodies and CAR T-cell therapy. I'm not sure that we have any trials that are looking at those. When you look at the types of patients that get, say somebody goes on to get a bispecific antibody rather than a CAR T-cell and then you compare to someone who has had 2 lines of treatment and gets a CAR T-cell, if you're comparing across studies, which we usually try not to do because there are lots of issues with doing that, there seems to be a higher response rate with the CAR T-cell therapy.

If you have the choice between a bispecific antibody and CAR T-cell, the standard practice right now, especially in lymphoma, is to recommend the CAR T-cell because we have more data, we have longer follow-up that shows what looks like better outcomes at this point. There are trials looking at combinations at doing CAR T-cell therapy plus bispecific antibodies and because theoretically they can work together to try to get a better response. No head-to-head comparison. We can't really say one is better than the other, but based on how much data we have, our standard of care preference is still to try to do CAR T-cell therapy rather than the bispecific antibody.

Lizette:

Thank you. Debra's asking: Does cancer have to be present for CAR T-cell therapy or does a clear PET scan need to be done to have it?

Dr. Ghosh:

No, cancer does not have to be present. For instance, if you have diffuse large B-cell lymphoma where you got 6 cycles of R-CHOP, and then you still had lymph nodes that were lighting up and were growing, in that situation before being able to get CAR T-cell therapy, maybe you had to get another cycle of some other chemo. Let's say you went into remission at that point based on the PET scan that there was no lymphoma visible. The data is pointing us towards still administering CAR T-cell therapy in that situation. Because there can be lymphoma that you're not seeing on the PET scan.

They're cells, small, very microscopic diseases that could be seen because when you don't respond to the initial chemotherapy, we know that most people are going to relapse even if they go into remission right after that pretty soon. Using CAR T-cell as a preventative measure can be helpful based on some data that we have. We don't have a definitive answer for that, but we do think that it still is beneficial in preventing the cancer from coming back.

Lizette:

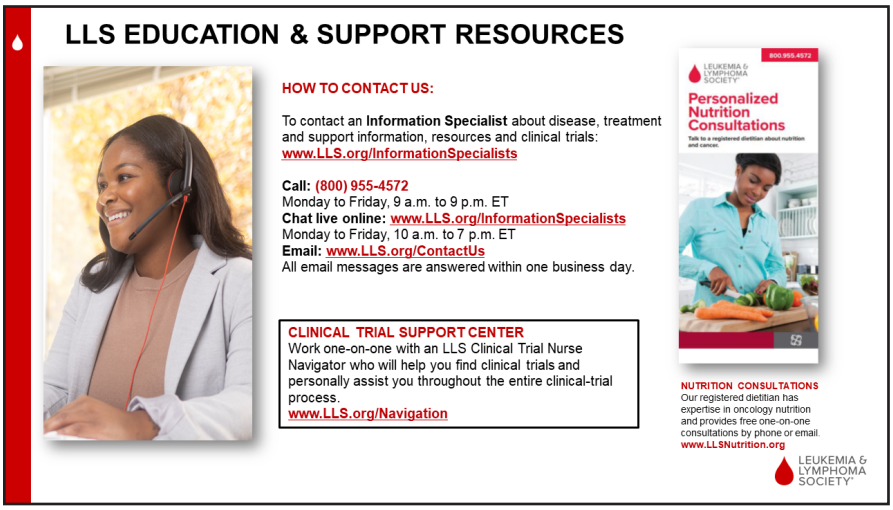
Thank you. Dr. Ghosh, what are you most excited about when you see all of the progress with CAR T-cell therapy?

Dr. Ghosh:

I am most excited about all of the different diseases that are being looked at with CAR T-cell therapy now. For instance, we are starting to look at things like autoimmune disease, which this can potentially even cure some of those diseases when we thought that there wasn't a cure. Then in solid tumors, such as lung cancers and breast cancers, etc., there's a lot of potential for CAR T-cells and other types of cell therapies. I'm excited to see that when we first started doing CAR T-cell therapy years ago, there were a few hundred trials that were starting, now there are tens of thousands of trials. There's just about a CAR T for almost anything you can think of in trials. It's exciting to see this because we see this as a huge shift in the way that we treat cancer and certain other diseases.

Lizette:

Thank you so much, Dr. Ghosh, for volunteering your time today and your expertise with us. We've heard so much about CAR T-cell therapy and we all are very excited, as you are, about the different blood cancer diagnoses as well as others that CAR T-cell therapy is really bringing hope to our patients and our caregivers. Thank you for being with us today.



Slide 49: LLS EDUCATION & SUPPORT RESOURCES

If we were not able to get to your question 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 you can 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 you may call an Information Specialist. As Dr. Ghosh mentioned, there are many clinical trials for CAR T-cell therapy. We do have Nurse Navigators to help you find a clinical trial if there is one available and if there is one that is right for you at this time.

Slide 50: LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society offers financial assistance to help individuals with blood cancer. For more information, you can visit LLS.org/Finances. We are also a proud partner with Dollar For, a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free.

Please visit www.lls.org/dollarfor, that's lls.org/DOLLARFOR, for more information.

Slide 51: LLS EDUCATION & SUPPORT RESOURCES

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

Slide 52: THANK YOU

On behalf of The Leukemia & Lymphoma Society, thank you for joining. Please consider sharing your story with us. Your words of encouragement can bring hope and confidence to others, and you may submit your story at LLS.org/Voices-of-LLS-submission. Again, LLS.org/Voices-of-LLS-submission. Dr. Ghosh, thank you again for volunteering your time with us. On behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye, and we wish you well.