Welcome & Introductions: CAR T-cell Therapy in Children and Adults with Blood Cancers

Ms. Lizette Figueroa-Rivera:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 2,500 people participating from across the United States as well as other countries, including Canada and Mexico. And a special thanks to Dr. Rayne Rouce and Dr. Loretta Nastoupil for sharing their time and expertise with us today.

Before we begin, our President and CEO, Dr. Louis DeGennaro, will make some remarks.

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

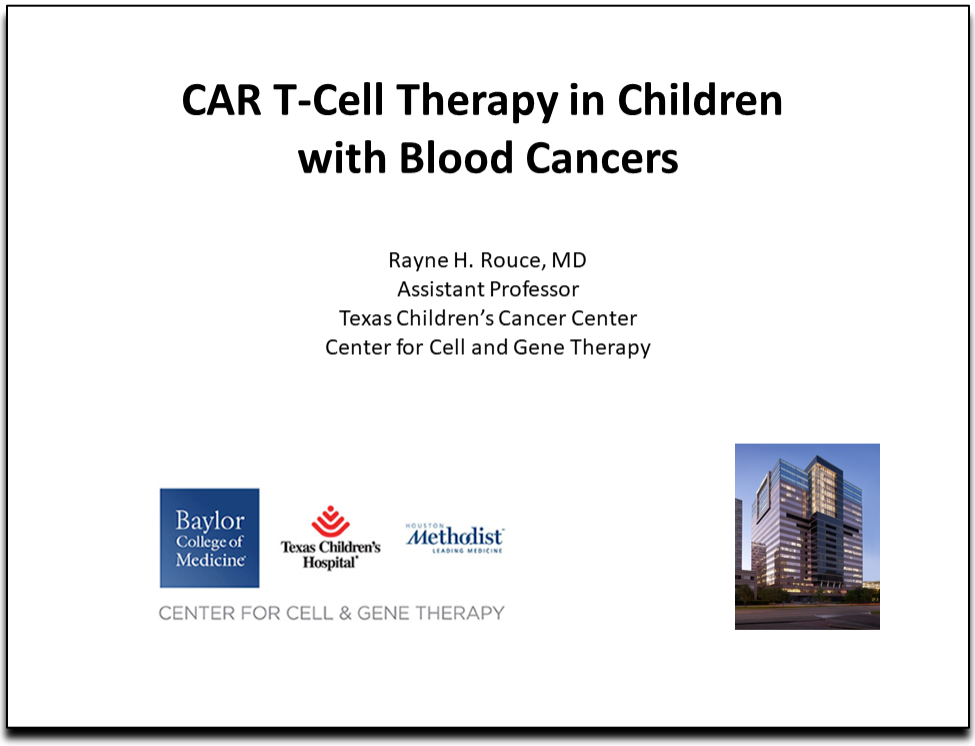
At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies, that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding ground-breaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care.

We're committed to working tirelessly toward our mission every single day. Today you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time and we

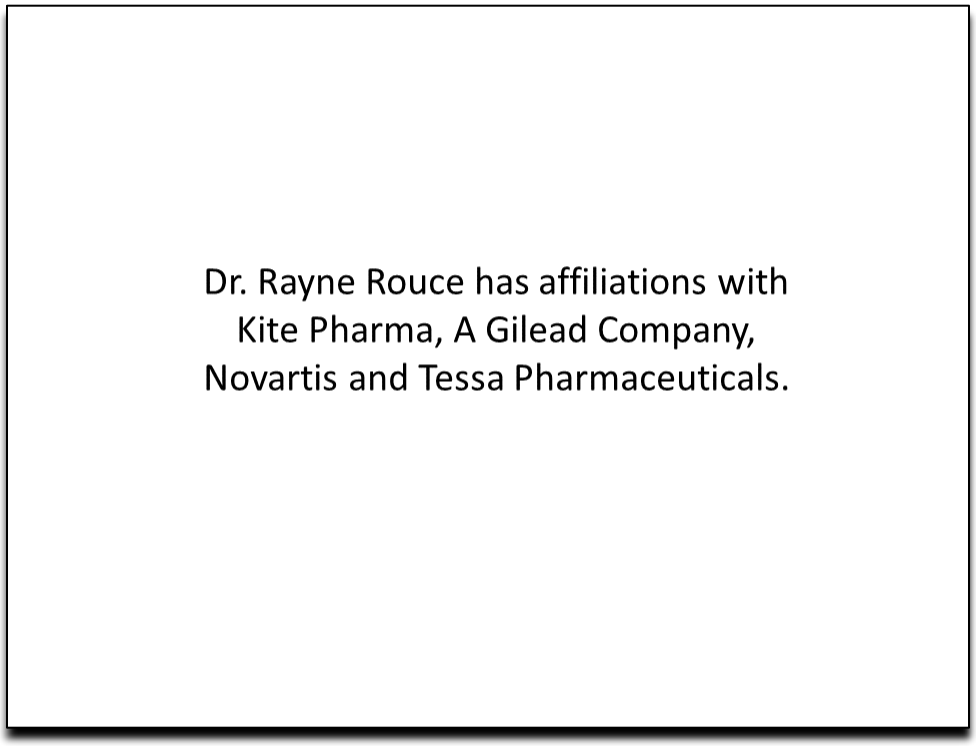
appreciate their dedication to supporting our mission [and], their commitment to caring for patients living with blood cancers. Thank you for joining us.

Ms. Lizette Figueroa-Rivera:
Thank you. And we would like to acknowledge and thank Celgene; Kite, a Gilead company; and Novartis for support of this program.



CAR T-Cell Therapy in Children with Blood Cancers

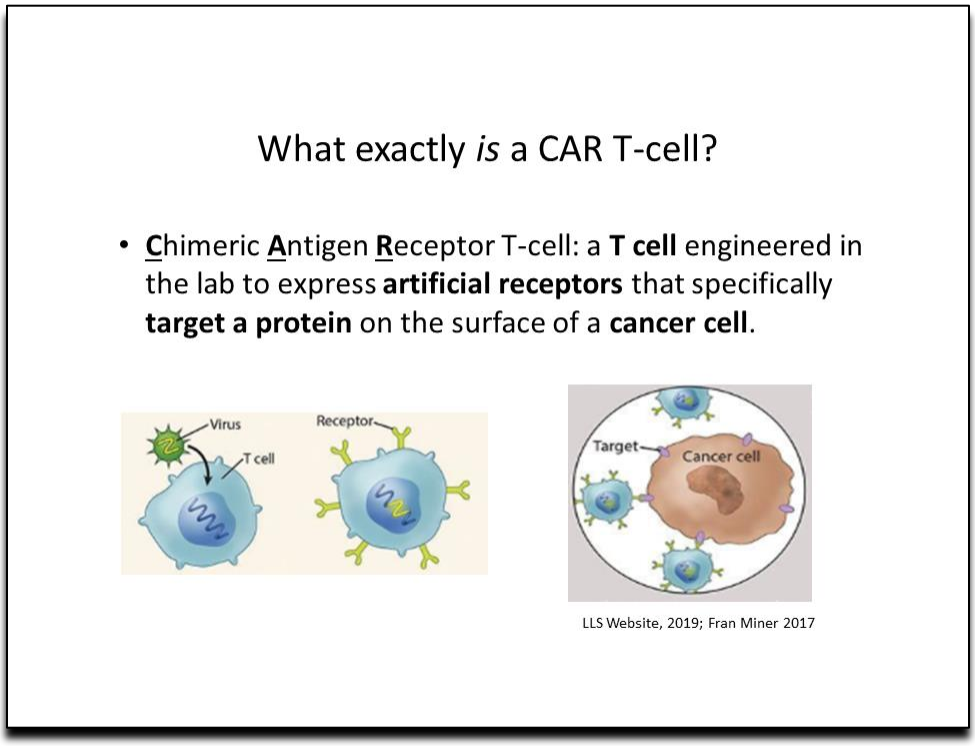
I am now pleased to introduce Dr. Rayne H. Rouce, Assistant Professor, Department of Pediatrics, Texas Children's Cancer Center for Cell and Gene Therapy at Baylor College of Medicine in Houston, Texas, who will be discussing pediatric CAR T-cell, and Dr. Loretta Nastoupil, Assistant Professor, Department of Lymphoma Myeloma, Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas, who will be discussing CAR T-cell Therapy in adults. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us. Dr. Rouce, I'm now privileged to turn the program over to you.



Dr. Rayne H. Rouce Disclosures

Dr. Rayne H. Rouce:
Thank you, so much and good afternoon, everyone. I'm excited to talk to you about CAR T-cell Therapy in children with blood cancers.

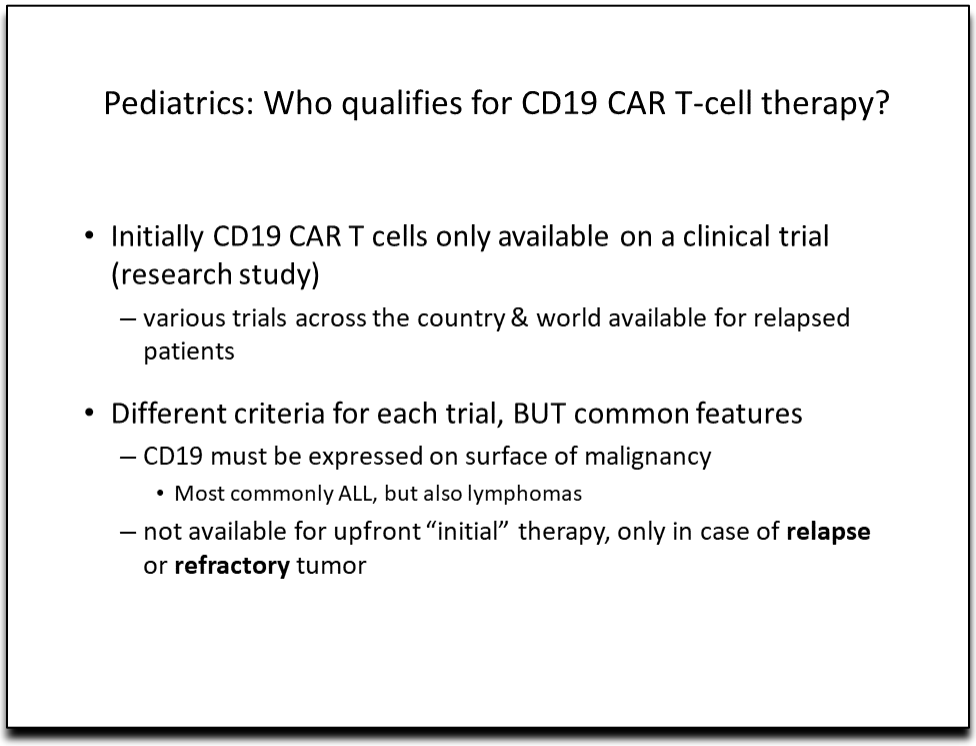
The main purpose of this program is to go through some of the frequently asked questions that I receive as a physician treating patients with CAR T cell and there will be an opportunity at the end, of course, to answer any additional questions that may be more personalized.



What exactly is a CAR T-cell?

So, I'll start with describing what exactly is a CAR T cell. Well, CAR stands for chimeric antigen receptor, and chimeric antigen receptor T cells are T cells that are engineered in the laboratory to express artificial receptors that specifically target a protein or antigen on the surface of a cancer cell.

In the laboratory, an inactivated virus is used to actually carry genetic machinery into the T cell that makes it produce these artificial receptors on its surface. Then in a laboratory, and both in the patient, when these CAR T cells come into contact with the cancer cell that expresses on its surface an antigen or protein that it's been specifically engineered to recognize, not only does it attach to the cancer cell but it can target it for kill.

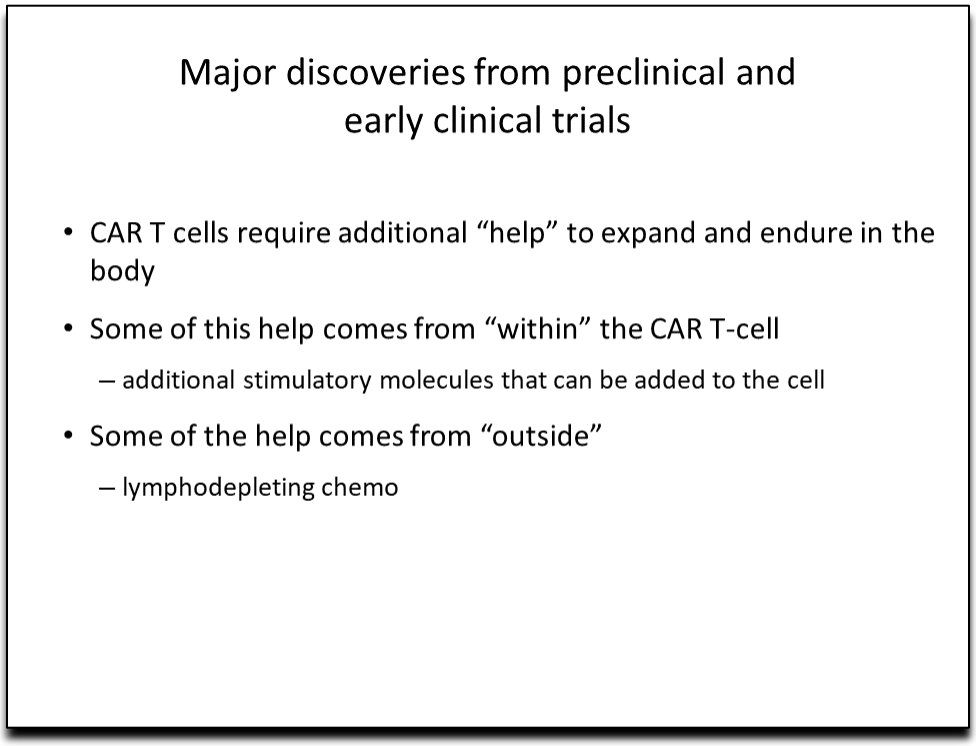


Pediatrics: Who qualifies for CD19 CAR T-cell therapy?

So, I'm going to talk mostly about CD19 CAR T-cell Therapy because by far it's been the most successful and has been the first CAR T-cell Therapy to be commercialized. So initially, until recently, CD19 CAR T cells were only available on a clinical trial basis or on investigative research studies. And so there are a number of trials across the country and the world that are available for relapse patients. And while there may be different criteria for each individual trial, such as inclusion criteria, there are several common features across all of the studies.

For one, obviously, if we've engineered these CAR T cells to specifically recognize CD19, the tumor that we're targeting has to express CD19, and so CD19 must be expressed on the surface of the malignancy. And fortunately, for the vast majority of pre-B-ALL, which is the most common type of acute lymphoblastic leukemia specifically in children, it is expressed, but there are also a number of lymphomas that express CD19 as well. So on different clinical trials sometimes there will be criteria or differences in how much CD19 expression has to be there, but this is a common feature that you will encounter.

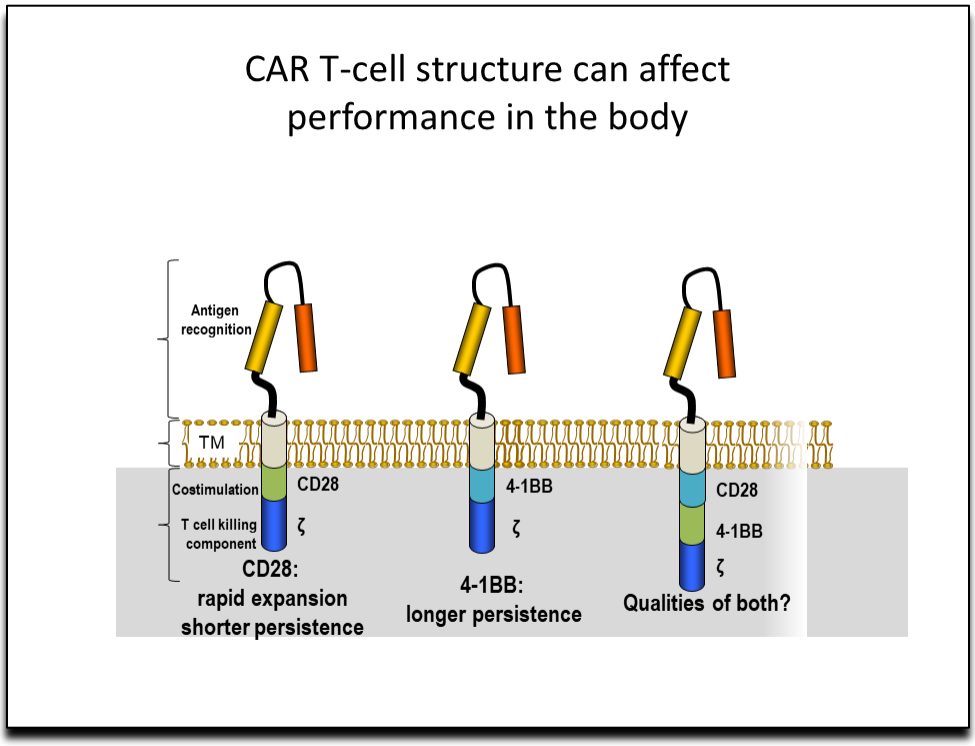
Also, it's important to emphasize that right now this therapy is not available for upfront or initial therapy at diagnosis, it's only available in the case of relapse, meaning maybe you've been treated and your cancer has come back, or refractory cases, meaning despite receiving a number of different lines of therapy, your cancer is still, unfortunately, there.



Major discoveries from preclinical and early clinical trials

So I want to talk about some of the major discoveries that have come from both preclinical laboratory work and early clinical trials in CAR T cells. For one, we've clearly recognized that CAR T cells do require additional help in order for them to expand and endure and continue killing leukemia cells in the body. And some of this help can come from within the CAR T cell. What I mean by this is when you build a CAR T cell or engineer it in the lab, you can actually build in additional costimulatory molecules whose job is to kind of keep that T cell going once it gets inside of the body.

Some of the help can come from the outside and what a number of studies have shown clearly is that preceding lymphodepleting chemotherapy, which some people call preconditioning chemotherapy, is absolutely necessary because what it does is we give a few days of chemotherapy and it clears out some of the T cells that are existing in the body to make room for the CAR T cells that we're putting in. One other important job of lymphodepleting chemotherapy is that it can actually free up some of the cytokines and nutrients that the CAR T cells need to continue to be activated, grow and expand, and kill their targets.



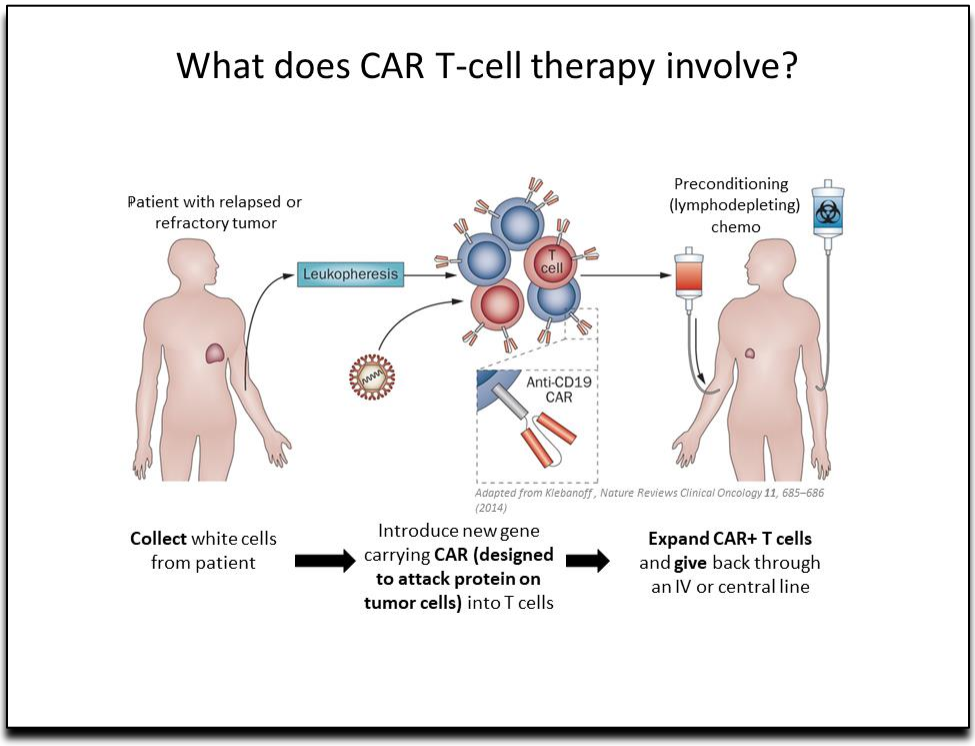
CAR T-cell structure can affect performance in the body

So, I want to pause for a second and talk a little bit about the structure of a CAR T cell. And one thing that has become very clear is that CAR T cell structure can actually affect their performance in the body. And I think it's important to highlight this because if any of you have been on a clinical trial or maybe heard about clinical trials, you'll often hear that there are differences between the CAR T cell and I want to break this down in a way that's easy to understand.

So in general, all CAR T cells have a few common properties, they have what we call an antigen recognition domain. And what this is, is it's derived from an antibody and this is the feature that tells the CAR T cell what it's targeting. So in the case of CD19 CAR T cells, for example, this antigen recognition domain is specific for CD19. They all also have the T cell killing component and this is called the zeta chain. So in normal T cells, they have this killing structure that's inherent to the T cell.

What I want to point out here on these slides is that since we know CAR T cells require additional stimulation once they get into the body, there are a couple of different costimulatory molecules that have become most commonly used. So this one is called CD28 and this one is called 4-1BB. And I point this out because Dr. Nastoupil is going to discuss this later, but there are differences in the currently commercialized product. There also, on an investigational standpoint, is the ability to combine both of these costimulatory molecules into a single CAR T cell and there's early evidence that this may provide the qualities of both.

So CD28 CAR T cells have been shown to have a bit more rapid expansion and they work very well but sometimes have shorter persistence then 4-1BB CAR T cells, which tend to last longer in the body.

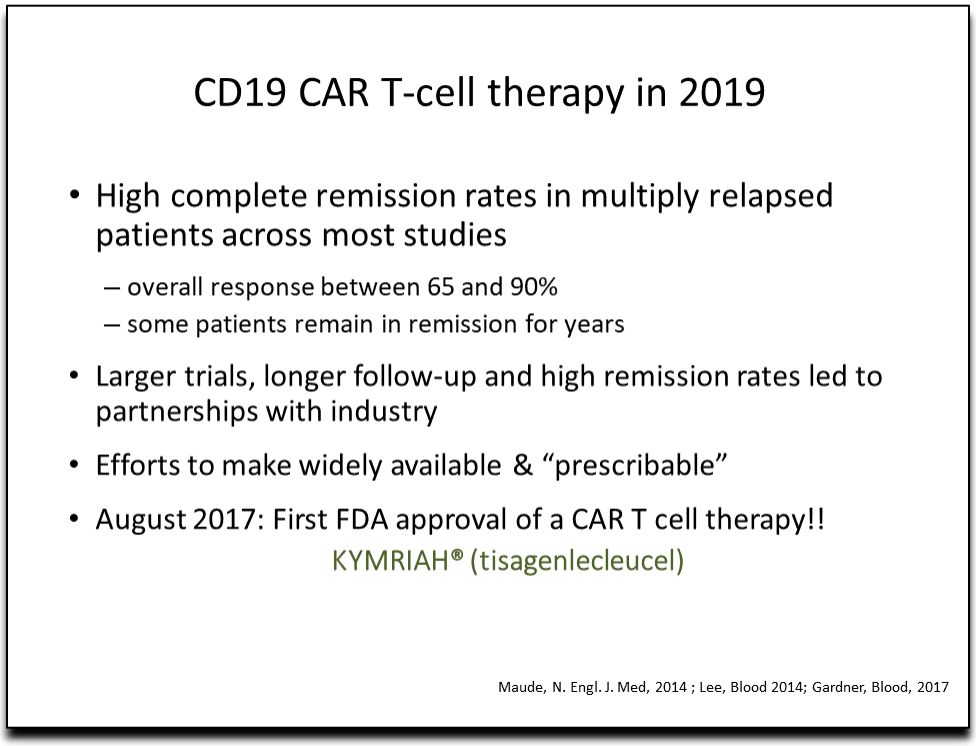


What does CAR T-cell therapy involve?

So, what exactly is involved in CAR T- cell Therapy? Well, we start with a patient typically with a relapsed/refractory tumor—in this case, we'll say this is a patient with CD19-positive acute lymphoblastic leukemia. We collect the white blood cells from the patient and this is usually performed by a process called leukapheresis, which involves placing a large IV in a patient—for pediatric patients this typically would be a large IV either in the neck or in one of the groin veins because you need a vein that's large enough to collect these cells—and then filtering out the white blood cells in a machine that looks similar to a dialysis machine and returning the cells that you don't need to the patient's body.

Next, this leukapheresis product is taken to the laboratory where the new gene carrying the CAR that we've designed—remember we used a virus to introduce these genes into the T cell is inserted into the T cell and then the T cells are expanded over time. And the time to expand these T cells will differ based on the different CAR T cell, but typically it takes upwards of 2 weeks long.

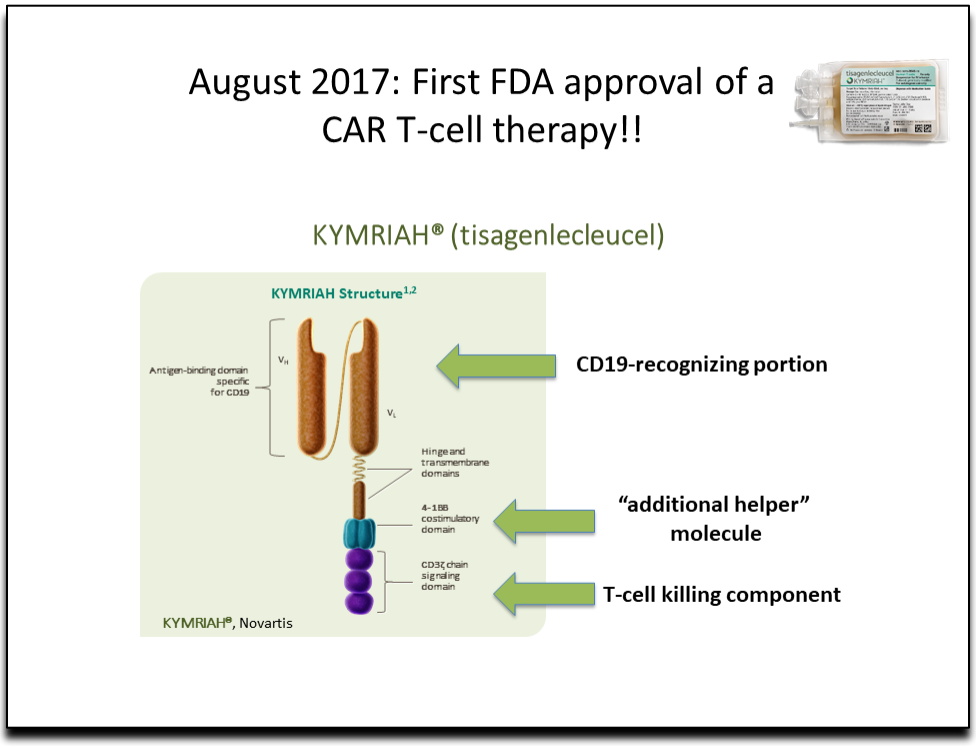
After the cells are made and they've grown in number we typically freeze them and then when the patient is ready, we can give these CAR T cells back to the patient through an IV, whether this be a peripheral IV or an existing port or central line, preceded by this preconditioning or lymphodepleting chemo, remember, because this is important to make room for the CAR T cell.



CD19 CAR T-cell therapy in 2019

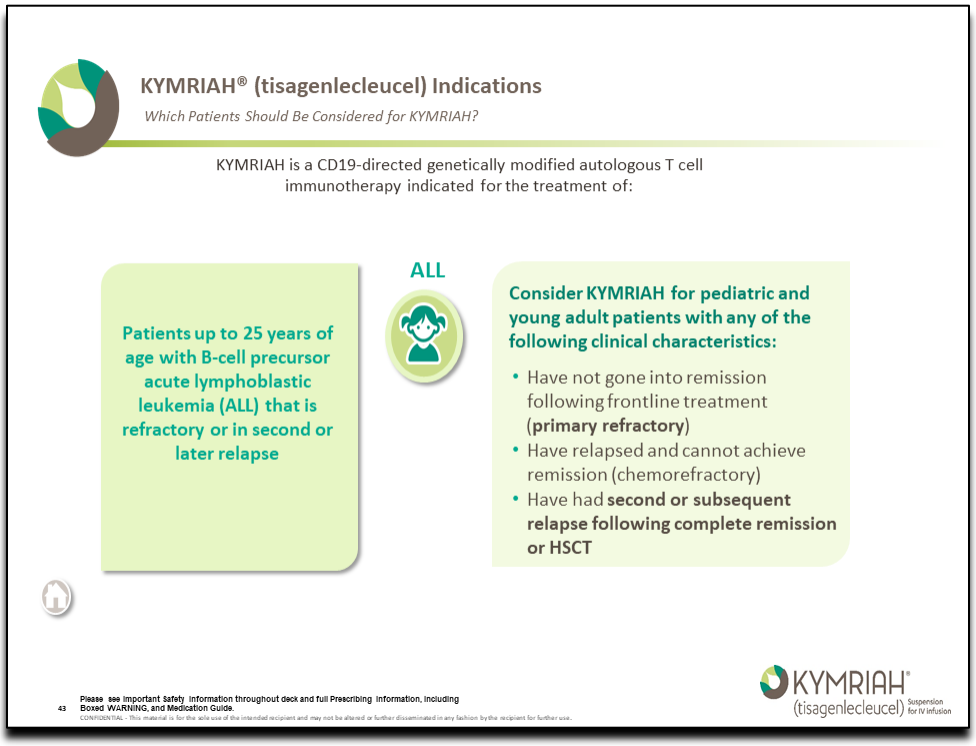
So where are we with CD19 CAR T- cell Therapy in the year 2019? Well, we've seen remarkably high complete remission rates in multiply relapsed patients across the vast majority of studies with overall responses ranging between 65% and 90%. Remarkably, some patients remain in remission for years, even after a single infusion of CAR T- cell Therapy. There have been much larger trials and longer follow-up and the high readmission rates and promise have led to partnerships between academic institutions and industry making an effort to make these therapies more widely available outside of a few specialized centers and actually prescribable.

So August 2017 was a really exciting time for the CAR T cell field and for patients because we had the first FDA approval of a CAR T-cell Therapy by Novartis called KYMRIAH®. It has a long fancy name but we usually typically call it KYMRIAH®.



August 2017: First FDA approval of a CAR T-cell therapy!!

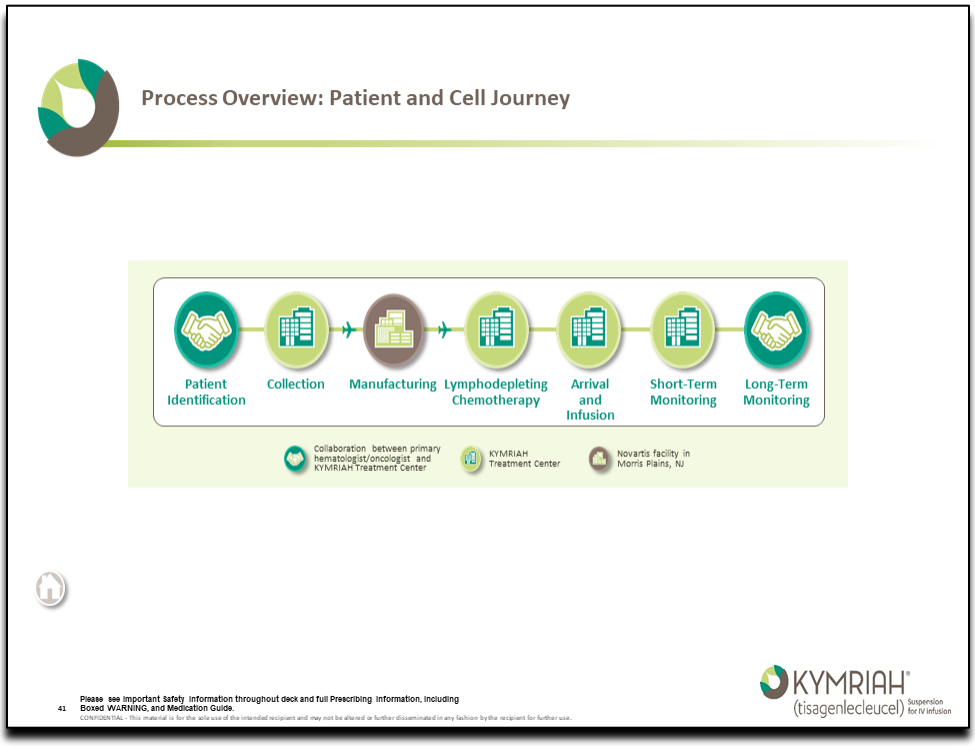
So let's talk about the structure of KYMRIAH®, what does it look like? Again, it's a CAR T cell and we already learned that there are a few common parts of every CAR T cell, one is the antigen recognition domain. So in this case, because KYMRIAH® is an anti-CD19 T cell, it, of course, has a portion that helps it recognize CD19, and it has the T cell killing component which is common to all CAR T cells. And in this case, we have our additional helper molecule and it's 4-1BB. Remember, this is the costimulatory domain that in studies has been shown to last a bit longer. And this is an example of what KYMRIAH® looks like after it's manufactured and sent back to the site, so it kind of looks like a platelet transfusion.



KYMRIAH® (tisagenlecleucel) Indications/Which Patients Should Be Considered for KYMRIAH?

So which patients should be considered for KYMRIAH®? So we already learned that this is a CD19-directed autologous, meaning it's made personalized from a patient, and it's indicated for the treatment of acute lymphoblastic leukemia in pediatrics. So any patient up to 25 years old who has pre-B-ALL also known as B-ALL, that's either refractory or in second or later relapse.

So if you're speaking with your doctor about your options you can consider KYMRIAH® for these pediatric and young adult patients who have any of the following characteristics. So number one, primary refractory. Again, this means that despite treatment patients have not gone into remission following front-line therapy or if you've relapsed and become chemo refractory and can't achieve remission. I point this out because even though at present KYMRIAH® is only approved for second or later relapse, it is important to look at this option because it may be something that you discuss with your doctor or health care professional if you've suffered one relapse. Also, any patient who's had second or later relapse following complete remission. And it's important to point out that patients who have never undergone bone marrow transplant but have second or later relapse or patients who suffered a relapse after initial relapse and transplant are also eligible.



Process Overview: Patient and Cell Journey

So, I want to take a few minutes to go over the process overview and the patient and cell journey, and Novartis was nice enough to provide these helpful slides. So it starts with patient identification and this can actually seem very similar to what you would do if you were going on a clinical trial. There is a specific indication for KYMRIAH® so you want to ensure that the patient meets that specific indication and so sometimes this may involve additional screening tests if you haven't had a bone marrow test in a while or spinal fluid collected, this may be involved, remember, because we want to make sure that your ALL still expresses CD19 on the surface.

And after this you typically undergo a process where you prescribe the actual KYMRIAH® and what this basically involves is usually getting insurance approval and a few more logistical things. And once that is all taken care of, we can actually arrange for a collection.

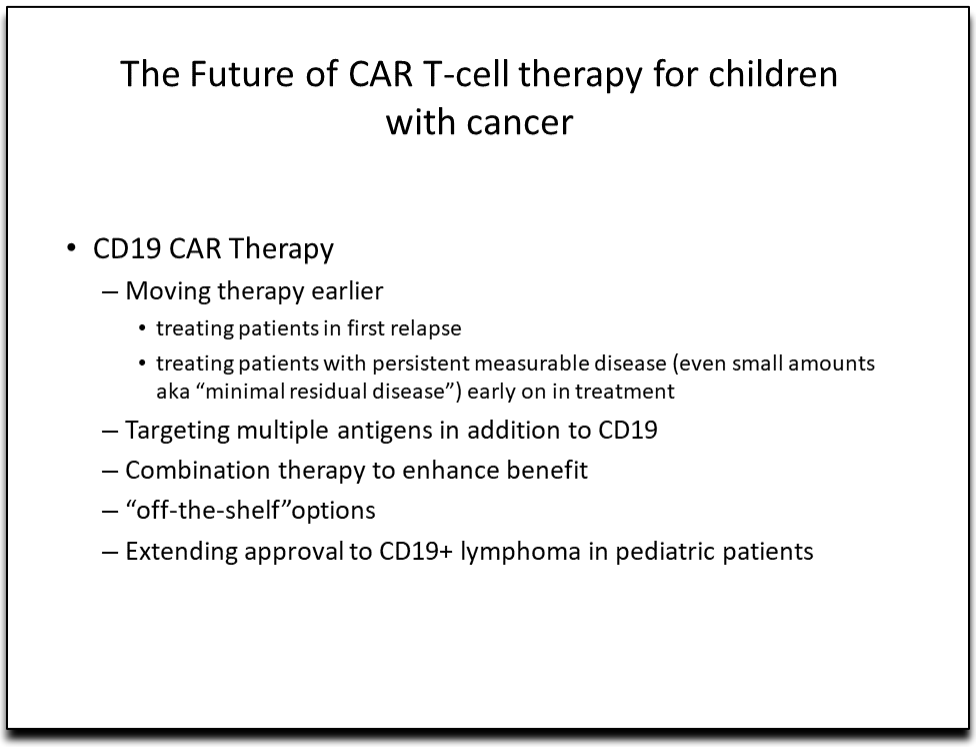
The collection is the leukapheresis process and KYMRIAH® is available at a number of institutions around the United States. And if you happen to live in a place that does not have a KYMRIAH® approved site close to you, Novartis can also help you identify one. So you undergo leukapheresis and once that is done, the cells are frozen and they're shipped back to the central Novartis manufacturing site that's located in New Jersey.

And manufacturing, again, this is personalized therapy from patients' T cells, so the times can vary but the target time for manufacture is around 22 days but could be shorter, it could be longer. So once the cells are ready for infusion, they're frozen down and the site is notified and they send the cells back to the site and typically then patients will undergo lymphodepleting chemotherapy which usually involves a few days of two chemotherapy medications, and then a short break before you get the cells infused.

So the infusion, again, I showed you a picture of what the product actually looks like. It looks like a little bag of platelets. It doesn't take long, usually under 30 minutes, to get these cells into the patient and afterwards there is short-term monitoring as well as long-term monitoring. And these monitoring

practices can differ from hospital to hospital. KYMRIAH® can be given as an outpatient in a clinic, and it can be given in the hospital. And again, it's important to talk to your hospital and your doctors to find out what their standard is.

And then, unfortunately, there is long-term monitoring. Remember, these are gene modified products so even though patients are not being treated on a clinical trial, they do require long-term monitoring.



The Future of CAR T-cell therapy for children with cancer

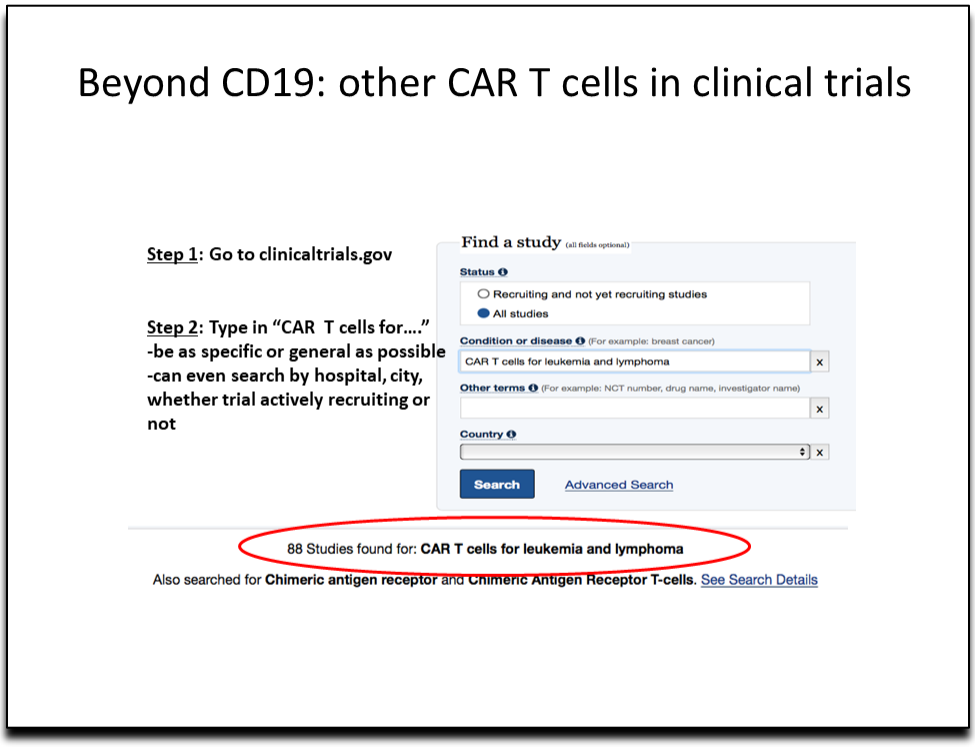
So where are we with the future of CAR T-cell Therapy? What does it hold for children with cancer? Well, as far as CD19 CAR T cells, a number of groups are looking at moving this therapy earlier, treating patients in first relapse, treating patients who have persistent measurable disease, even very small amounts, also known as minimal residual disease, treating them earlier on in treatment.

Also, a number of groups are looking at targeting multiple antigens in addition to CD19 and the point behind this is, leukemia cells can be very tricky, they can be very smart. Initially they may respond to CD19 CAR T-cell Therapy, but unfortunately, those cells may come roaring back and suddenly not express CD19 on their surface anymore. So there's a big push to target a number of antigens as opposed to just one.

And then combinatorial therapy to enhance benefit. There are some drugs that have been shown to either enhance activity of CAR T cells or they can actually enhance persistence. And the majority of these efforts is still in the research realm.

And then off-the-shelf options. Despite the fact that it may take only a few weeks to generate these CAR T cells, sometimes it can be difficult to collect enough normal T cells to start the process or sometimes patients may be too sick where they can't wait that amount of time. So being able to create a product that's automatically ready either from a healthy donor or from cord blood.

Lastly, extending approval to other CD19-positive malignancies like lymphoma and pediatric patients. And Dr. Nastoupil is going to talk about this more because there are approved uses in adults for lymphoma.

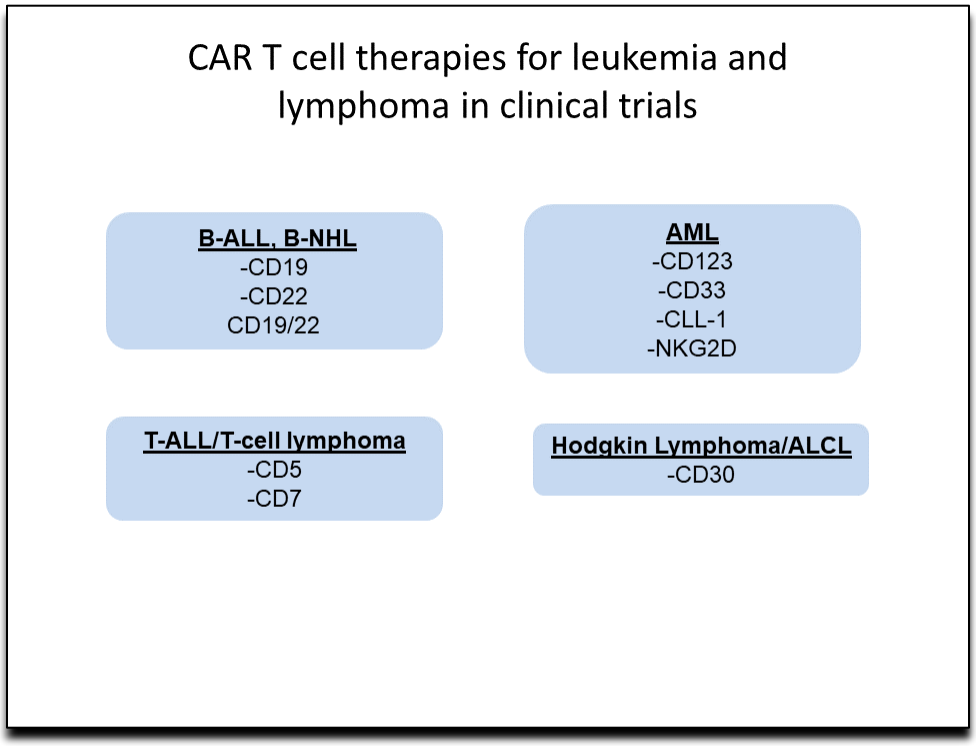


Beyond CD19: other CAR T cells in clinical trials

So, I want to talk for a minute about moving beyond CD19 CAR T cells and what other types of CAR T cells are in clinical trials. And I wanted to share with you a way that you can actually search at home on your search engine to look for CAR T cell studies that are actively recruiting.

So, step one is, you can go to *clinicaltrials.gov* and what pops up is a search engine box and you can see here that I've typed in "CAR T cells for leukemia and lymphoma." And next, you can type in "CAR T cells for (blank)" and you can be as specific or general as possible. If you've seen on the LLS website, or somewhere else, where you've heard about a CAR T cell targeting Hodgkin lymphoma, or AML, or at a specific hospital or city, you can actually start specifically there and add as much or as little information as you like. And you can even filter between studies that are actively recruiting versus those that are still undergoing some testing prior to recruitment.

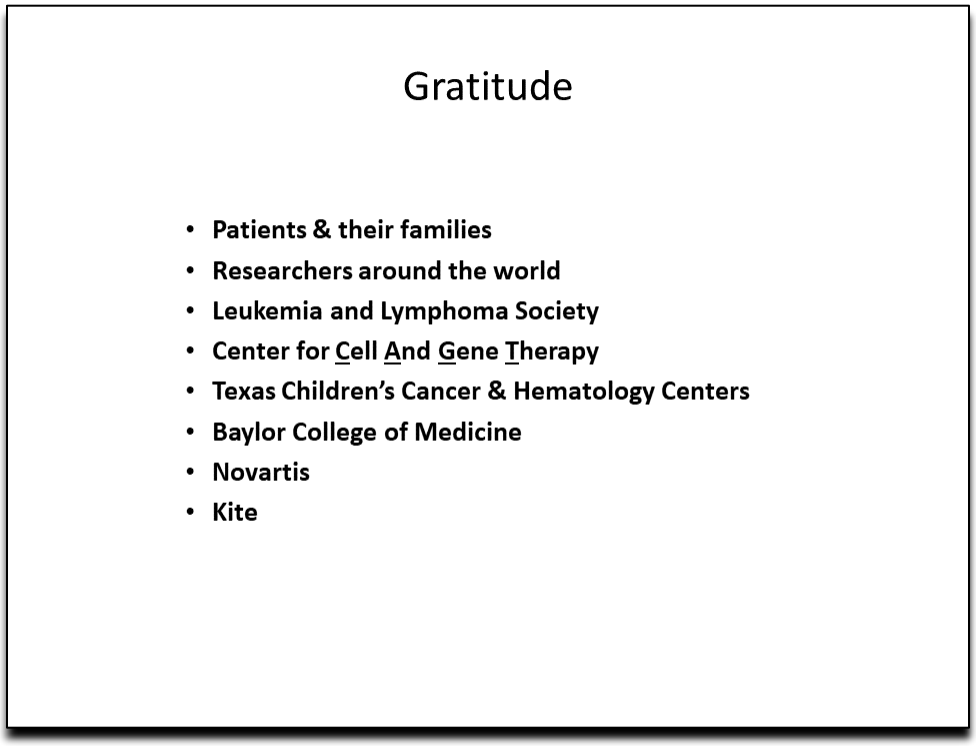
And so here when I typed in "CAR T cell for leukemia and lymphoma," I was able to find 88 studies and then it also gave me some helpful tips about searching in the future.



CAR T cell therapies for leukemia and lymphoma in clinical trials

So just for a few minutes, I'll talk about some of the other CAR T-cell Therapies available for leukemia and lymphoma and clinical trials for pediatric patients. So we've talked a lot about CD19, and of course, it's available for B-ALL and also for B-cell non-Hodgkin lymphoma, usually in the research standpoint. But another target that's growing promise is CD22 and it has very early promising results. And again, we talked about combining antigens and combining this target where we can actually have a CAR T cell that targets not only 19, but 22 as well.

For T-cell leukemias and lymphomas, our group has a study that's open right now that's recently opened to children that can target CD5, which is present on the majority of T-cell leukemias and lymphomas and an upcoming study with CD7. And then there are a number of targets in AML that have been studied in adults and recently moved into the pediatric forum. And then for Hodgkin lymphoma and anaplastic large cell lymphoma as well, CD30 is a promising target.



Gratitude

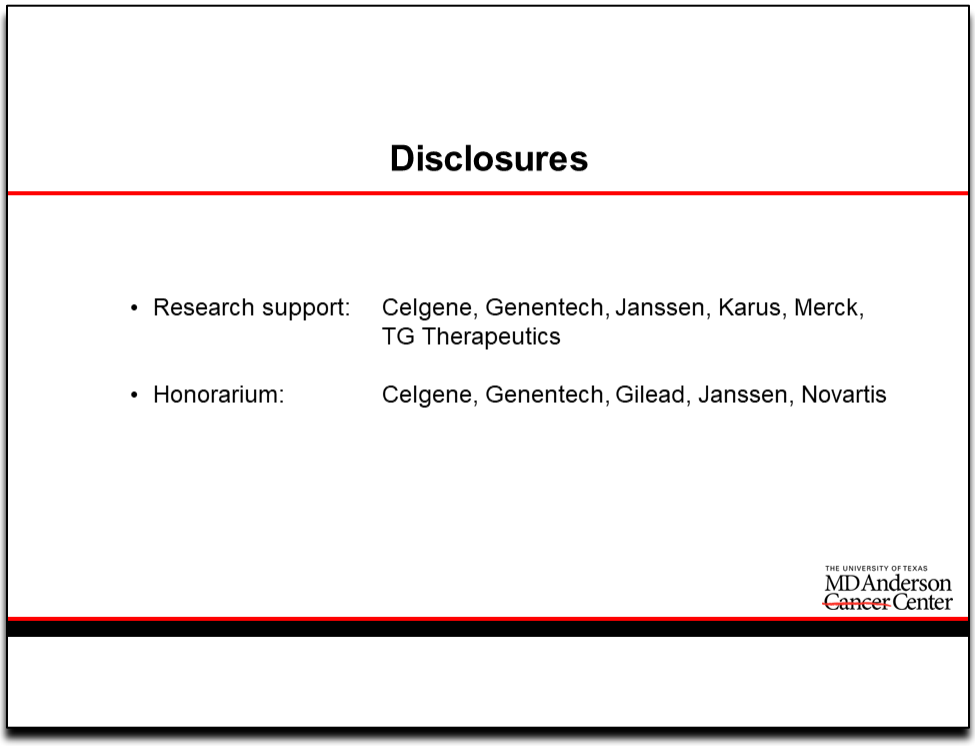
So I will close there. And obviously, there are lots of people to thank, primarily patients and their families. This research would not be possible without you, researchers all around the world, societies like The Leukemia & Lymphoma Society, my center, the Center for Cell and Gene Therapy, Texas Children's, and Baylor College of Medicine, as well as the industry sponsors for this program.

And it is my great pleasure to introduce Dr. Loretta Nastoupil, who is my colleague from right across the street at MD Anderson, and she is going to discuss CAR T-cell Therapy for adults, primarily non-Hodgkin lymphoma, as well as future directions. Thank you.

CAR T-Cell Therapy for NHL: Current and Future Directions

Dr. Loretta Nastoupil:
Thank you, Dr. Rouce. You made my job very easy. You did a very nice overview of what constitutes a CAR T cell and these principles apply in adults as well.

So I'm going to spend the next 20 to 25 minutes discussing the clinical trials that led to the FDA approval of two CAR T-cell Therapies for adult patients with non-Hodgkin's large B-cell lymphoma and also discuss some of the future directions in terms of where we see the field moving, potentially what other patient populations might stand to benefit from this therapy.



Disclosures

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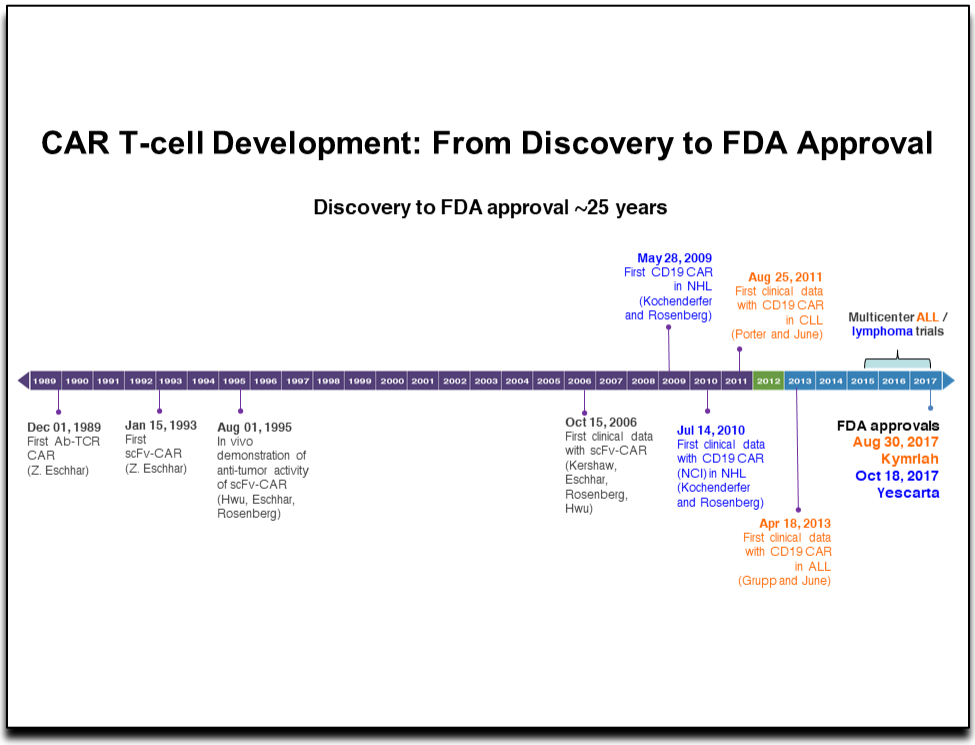
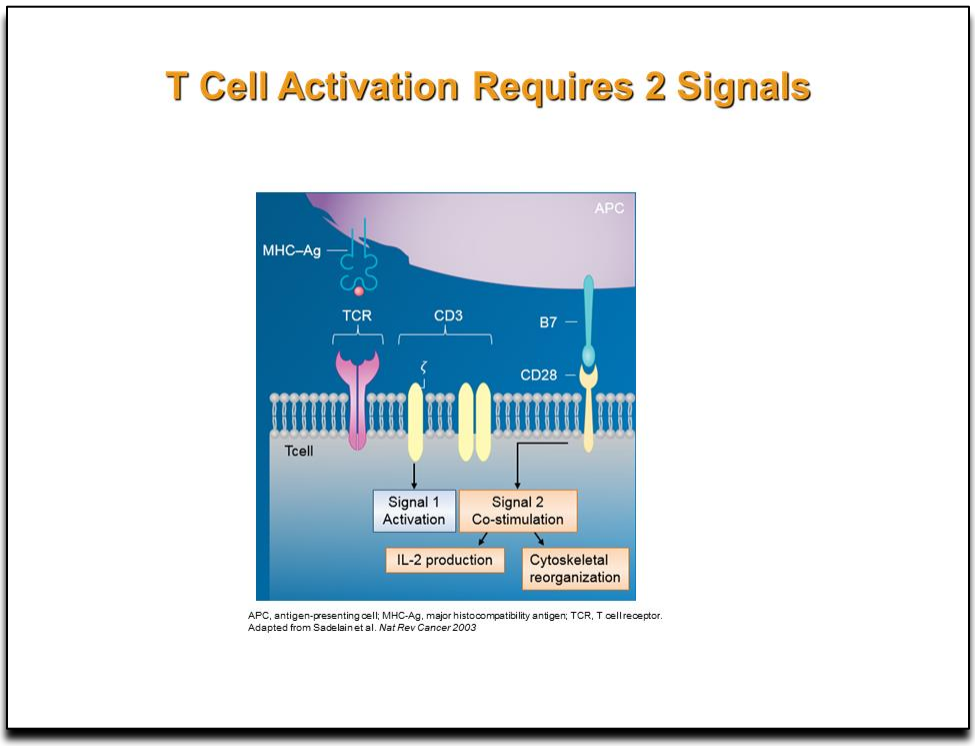


CAR T-cell Development: From Discovery to FDA Approval

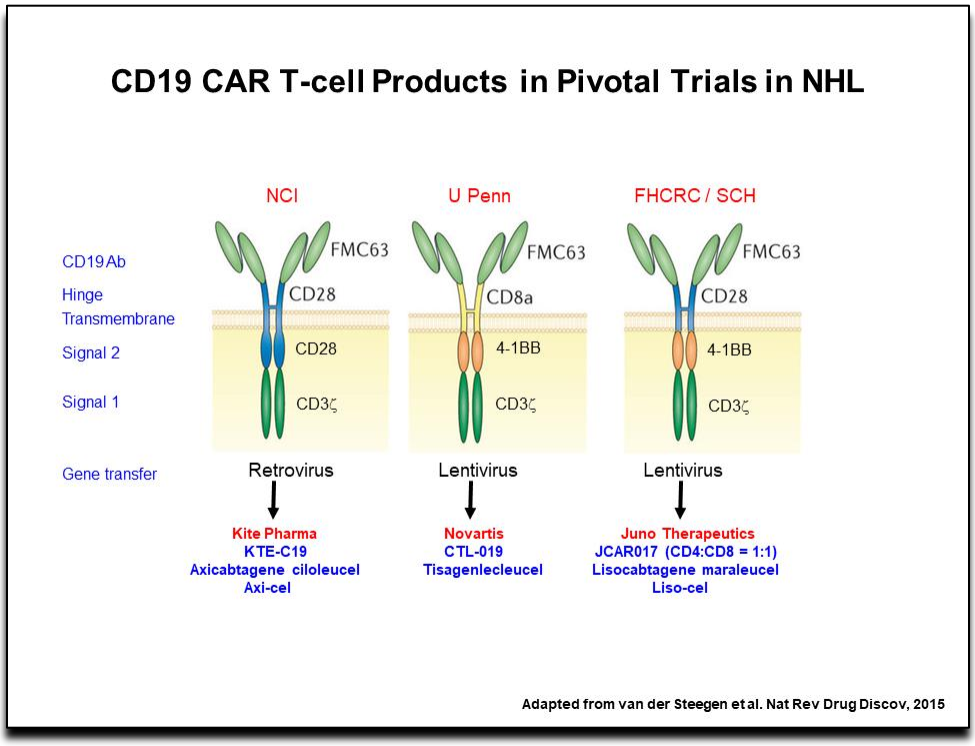
I think this is a fundamental slide and I think it's important, particularly when we partner with agencies like The Leukemia & Lymphoma Society, to remind everyone that this is something that had been in the works for 25 years and many of these projects are funded initially by the government or through organizations like LLS and it's not until late in the game where industry might join in to broaden the application and expand access to a larger number of patients. But oftentimes the science starts at a university and there are oftentimes, many, many years put into the research that goes behind these agents before we introduce them into patients.

So clearly, I'm biased, but I think it's important because some people will ask, “What is the benefit or the risk involved with going on a prospective clinical trial?” And there's a lot of responsibility on those of us who perform clinical trials to make sure that the science is sound and that the safety of a given agent is worth exploring in patients. But just keep in mind that there may be 25 years of work put in before we get to the point where we even introduce it into patients. And then, as you can see on this timeline, once drugs start to look very promising in early phase studies, oftentimes it will be a very short time until we can have access to it to a broader patient population.



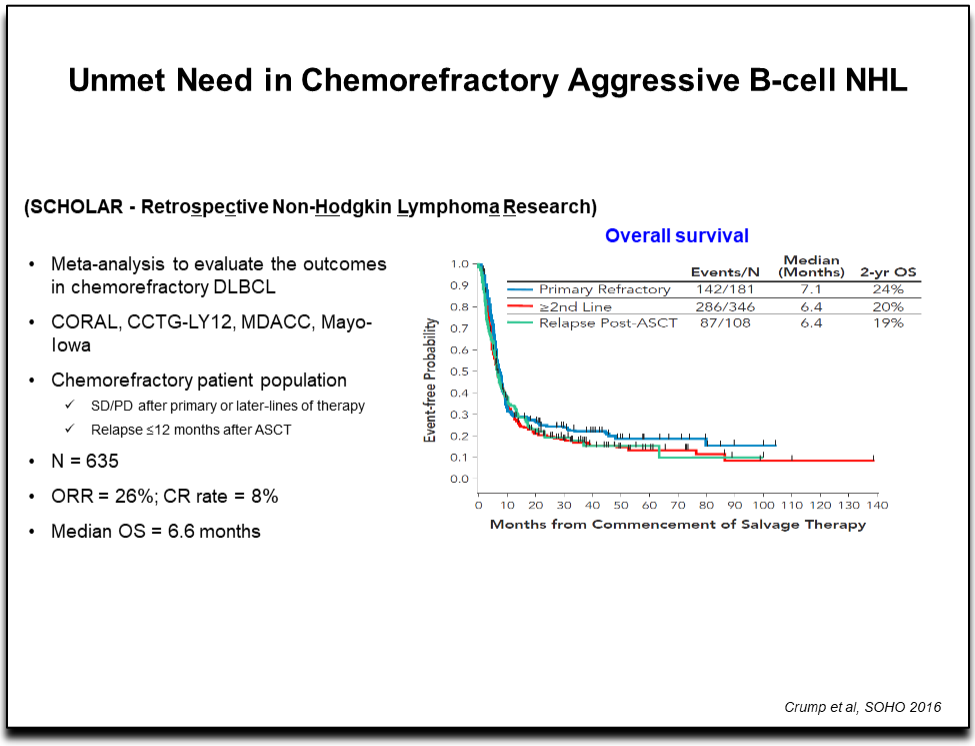
T Cell Activation Requires 2 Signals

As you heard by Dr. Rouce, what a CAR T is, is essentially we're genetically modifying patient's own T cells to perform outside of their normal function, which is usually restricted in terms of their ability to see and remove cancer cells. So this figure describes what a normal T cell goes through in terms of seeing a target, whether that's an infection or a cancer cell, which is usually presented to them in the form of an antigen or a protein, to receive additional signals that gives them the green light that this is okay to remove, this is not something important like normal tissue. And then that leads to an internal cascade of events that will result in the signal to go ahead and kill this cell that that protein is being expressed on.



CD19 CAR T-cell Products in Pivotal Trials in NHL

What a CAR T does, is we essentially bypass that normal process by building in a receptor on the surface of the T cell and then we build in those internal signals so that it automatically gets that costimulatory molecule so that when this modified T cell binds its protein target, and as you've heard, most of them-- the two that are FDA approved, target CD19, it will get a signal to kill and it will also secrete things like cytokines that will bring in other T cells, not even specifically CAR Ts, to the area so that you have this augmented T cell reaction to a tumor and sometimes can bypass where normal T cells can be dysfunctional. And the result has led to a lot of excitement and enthusiasm around this new therapy.

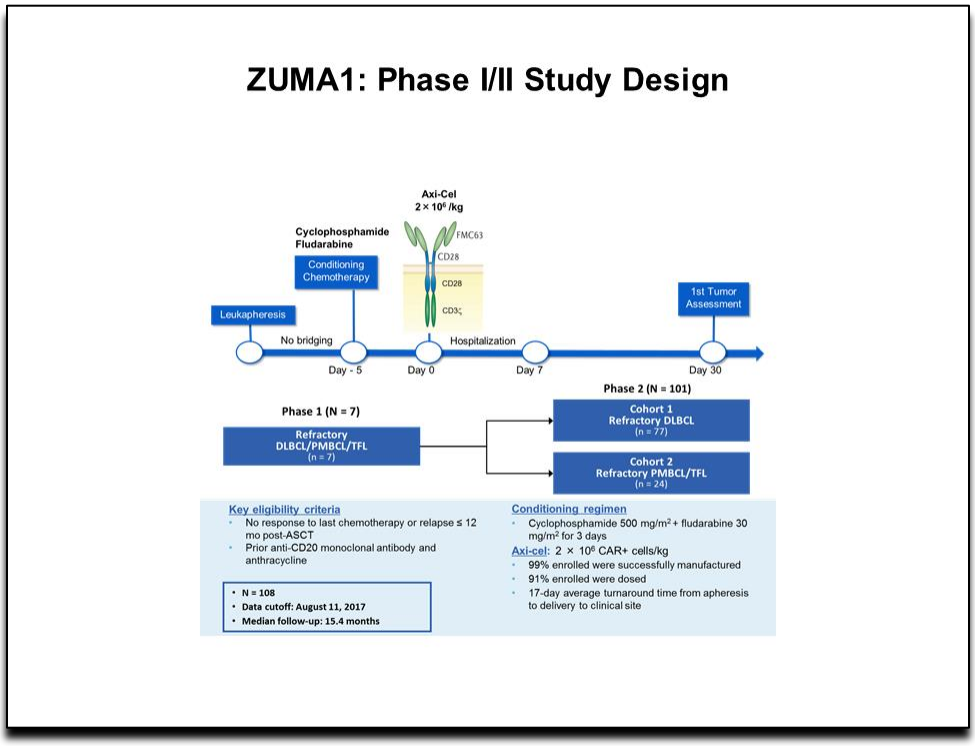


Unmet Need in Chemorefractory Aggressive B-cell NHL

What this slide highlights is what we consider the unmet need. So this was a collaboration in which MD Anderson participated, but it was a large number of investigators and studies that combined data from individual patients who had relapsed refractory diffuse large B-cell lymphoma, which is our most common lymphoma.

And fortunately, most patients are cured with front-line chemo-immunotherapy but about 20% to 40% of patients who are not cured with front-line treatment, they were facing very dismal outcomes. And what this curve shows, is only about 20% of patients with relapsed refractory large B-cell lymphoma had meaningful outcomes with standard treatment and that standard treatment oftentimes consisted of salvage chemotherapy followed by high-dose therapy and autologous stem cell rescue.

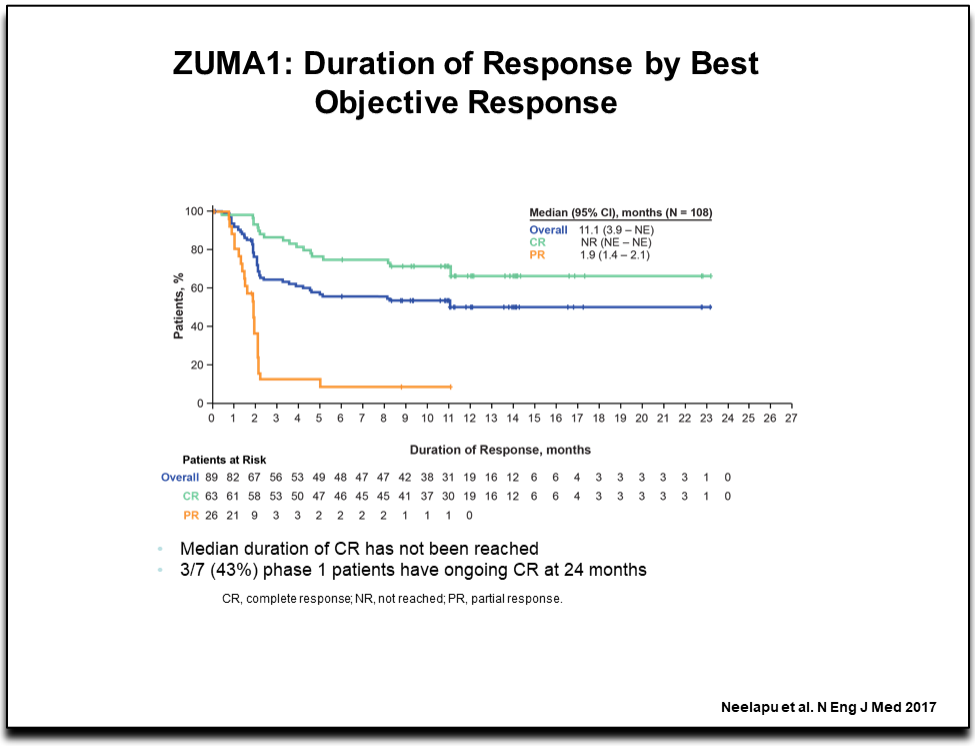
So this suggests that for patients with relapsed refractory large cell lymphoma most of them were facing a median survival of only about 6 months and less than 20% to really expect to do well, therefore signaling that chemotherapy was not good enough for these patients.



ZUMA-1: Phase I/II Study Design

ZUMA-1 was the phase I/II study that enrolled patients with that exact patient population, those that were refractory to chemotherapy with diffuse large B-cell lymphoma. And there are some subtle differences across the studies in terms of which patients were enrolled, which also has resulted in some subtleties in the indication for which these patients the drugs are FDA approved for. But ZUMA-1 did allow for patients with relapsed refractory, primarily refractory, diffuse large B-cell lymphoma that included a subgroup of primary mediastinal large B-cell lymphoma patients and transformed follicular lymphoma patients.

And as you heard previously, patients when they met the eligibility criteria, they underwent leukapheresis, where T cells were collected, they were sent off to manufacture. And when the T cells were successfully, the CARs were generated the patients were brought back in for 3 days of conditioning chemotherapy and then they received their CAR T infusion on day 0 and then they were monitored in the hospital for a minimum of 7 days. Now, side effects may have warranted longer observation in the hospital, but that is generally how the ZUMA-1 study was conducted.

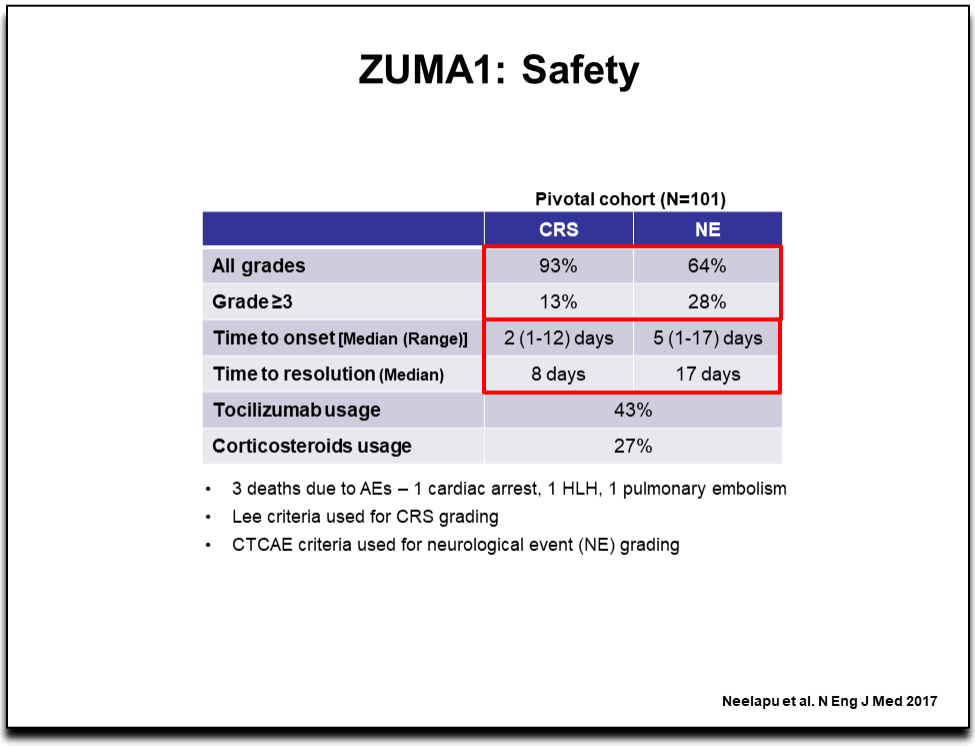


ZUMA-1: Duration of Response by Best Objective Response

And what we learned from ZUMA-1, you know, which started as a dose escalation and then there was an expansion, is at the time of the *New England Journal of Medicine* publication, there were 111 patients that had been enrolled. And for those patients who achieved a complete response, which is defined by a PET scan where there's no measurable lymphoma, you can see here in terms of their duration of response, it was quite good.

Early on when these studies were being conducted there were viewpoints that CAR T may be a bridge to transplant and this again, are some subtle differences between the pediatric population and the adult population. But what these curves suggest and now with longer follow-up, if you can achieve a complete remission with CAR T-cell Therapy there is a good chance that you will remain in a complete remission and may even potentially be cured. And there are different time points where we can be much more confident about using the term cure. But these curves do suggest that if you maintain your complete remission at 3, 6, and even 12 months later, there's a good chance you're not going to pass away from your lymphoma, which again, was quite striking when I just showed you the curve, that most of these patients would have been facing a median survival of only 6 months.

Now, this curve also highlights of the patients who fail to achieve a complete remission, which is this orange curve, the partial remission, they, unfortunately, are not seeing those favorable outcomes. And so in this setting, and we usually get a scan at day 30, we're starting to think about strategies to get them into a complete remission. And there are ongoing prospective studies looking at various strategies to accomplish that.



ZUMA-1: Safety

The safety of CAR T cells is different than what we traditionally see with chemotherapy, though there are some similarities, but cytokine release syndrome, which is one of the sort of impacts of generating these CARs, that they're augmented and then they release cytokines when they bind their target and this manifests in patients as severe flu-like symptoms, so oftentimes fever, muscle aches, headaches, fatigue, and that is very common. Almost all of patients, it's outlined here, 93% experienced some form of cytokine release syndrome.

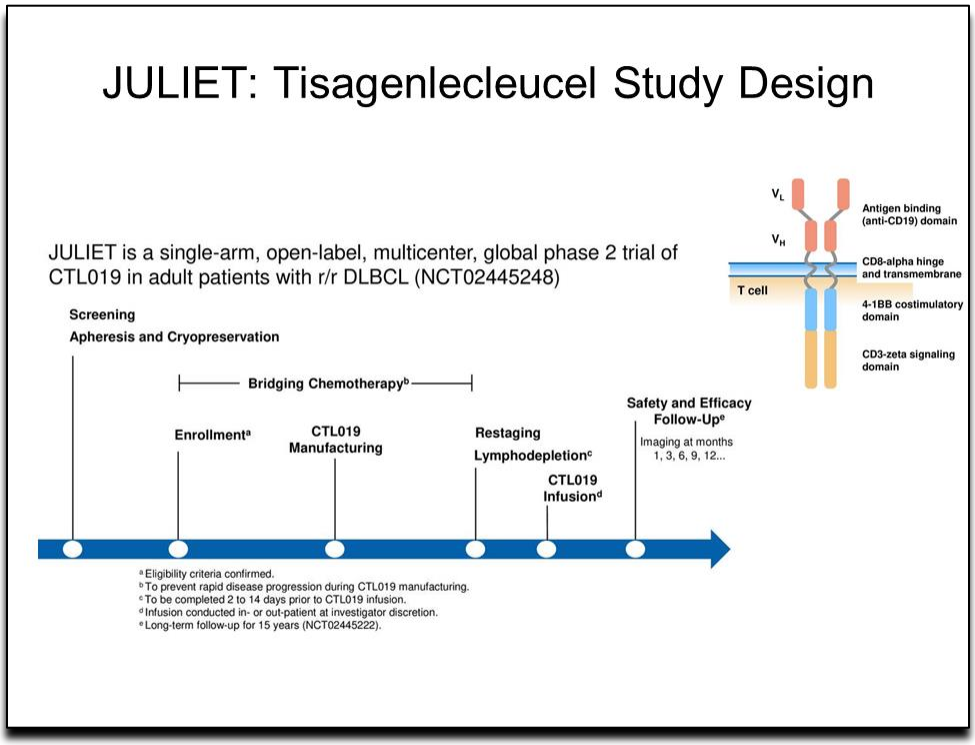
The severity in terms of grading, which we use across clinical trials—so what that means for patients and others that are caring for their loved ones, is that they may require ICU care. Fortunately, that is less common so only 13% of patients had grade 3 or higher cytokine release syndrome.

But neurotoxicity, which again, is a unique side effect of CAR T-cell Therapy, which may manifest as confusion, word finding difficulties, and even as severe as seizure activity or patients being unresponsive, again, the severity was about 28%. Now, the important thing is nearly all of these side effects were reversible. The time to it going away varied depending on the severity, but most patients were in the hospital approximately 2 weeks.

There are drugs we can use to abort these side effects and they're outlined here in terms of tocilizumab and steroid use. This is important because I'm going to discuss the other agent that's FDA approved. And there are differences across the studies in terms of the grading in the management of the cytokine release syndrome and the neurotoxicity and these agents have not been compared head-to-head. And so now that we have 2 that are FDA approved, how do you decide when they're approved for similar patients, to use one over the other?

So oftentimes as clinicians, we talk about how likely it is to cure someone or you may consider the side effect profile. And I just caution folks that because these studies were done slightly differently, and management was different it's really hard to compare across the trials to conclude whether one is safer

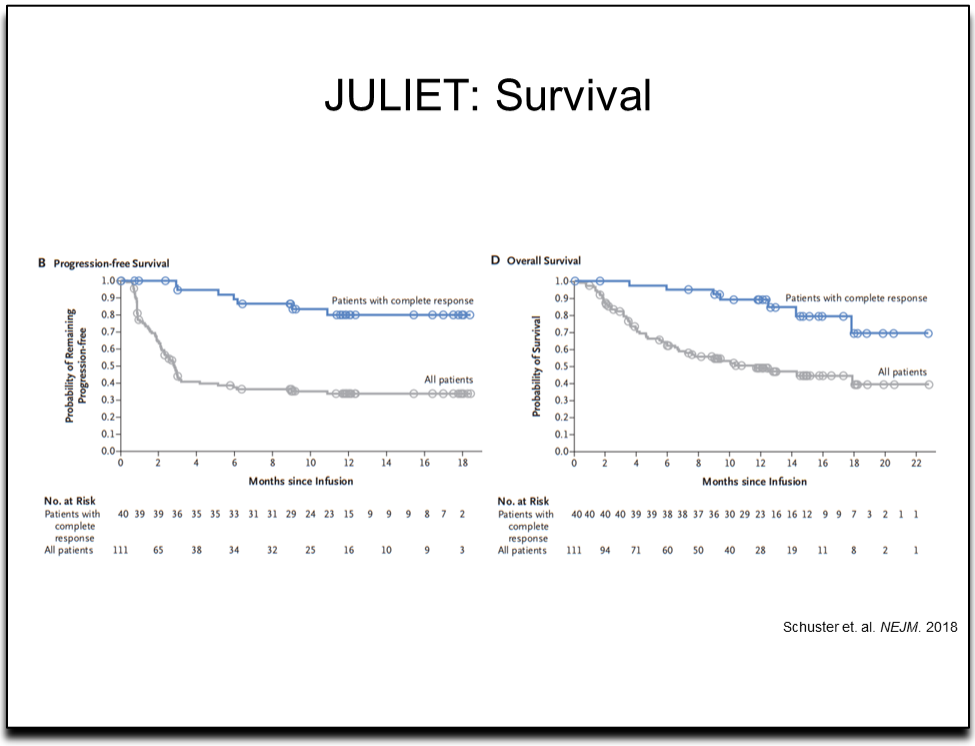
or not. But based off of this study and the safety profile of ZUMA-1, it is currently FDA approved for patients with relapsed diffuse large B-cell lymphoma who have had at least 2 prior lines of therapy.



JULIET: Tisagenlecleucel Study Design

The other agent that's currently FDA approved is the KYMRIAH® agent, which you've already heard Dr. Rouce discuss, because it was first FDA approved for pediatric patients with ALL and she discussed the patient population for whom it is appropriate. The study design was very similar in terms of ZUMA-1 with some subtle differences.

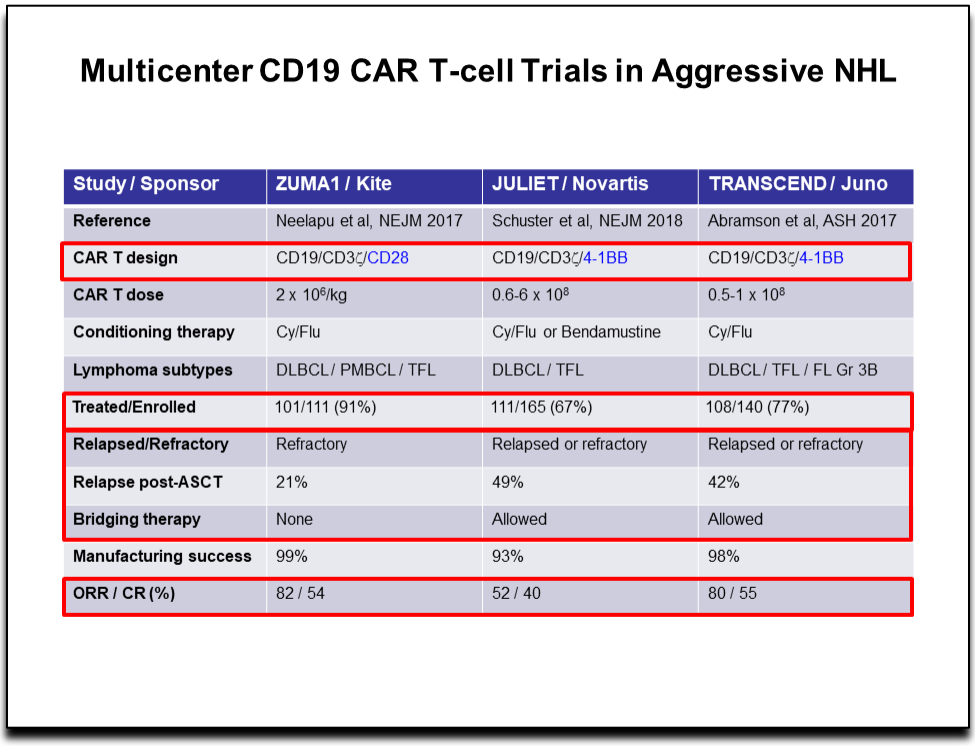
Some patients did not have to be refractory to their last treatment so there were some patients in the study that were relapsed. And the time period from enrollment to the start of conditioning chemotherapy and CAR T-cell therapy was slightly longer due to the study design. So there were patients that were allowed to undergo bridging therapy, meaning they could continue on their lymphoma treatment up until there was a point where they were cleared to proceed with the CAR T-cell Therapy on study. Which again, may result in some differences in terms of the outcomes of the trials.



JULIET: Survival

But very nice response for those patients who achieved a complete remission in terms of progression-free survival and overall survival and solidifying that if you're able to have a nice response to treatment that will likely result in a prolonged remission and again, potential cure.

KYMRIAH® is also FDA approved for patients with relapsed large B-cell lymphoma or transformed follicular lymphoma who've had 2 prior lines of therapy.



Multicenter CD19 CAR T-cell Trials in Aggressive NHL

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al, NEJM 2017	Schuster et al, NEJM 2018	Abramson et al, ASH 2017
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	0.6-6 x 10^8	0.5-1 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL Gr 3B
Treated/Enrolled	101/111 (91%)	111/165 (67%)	108/140 (77%)
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	49%	42%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	93%	98%
ORR / CR (%)	82 / 54	52 / 40	80 / 55

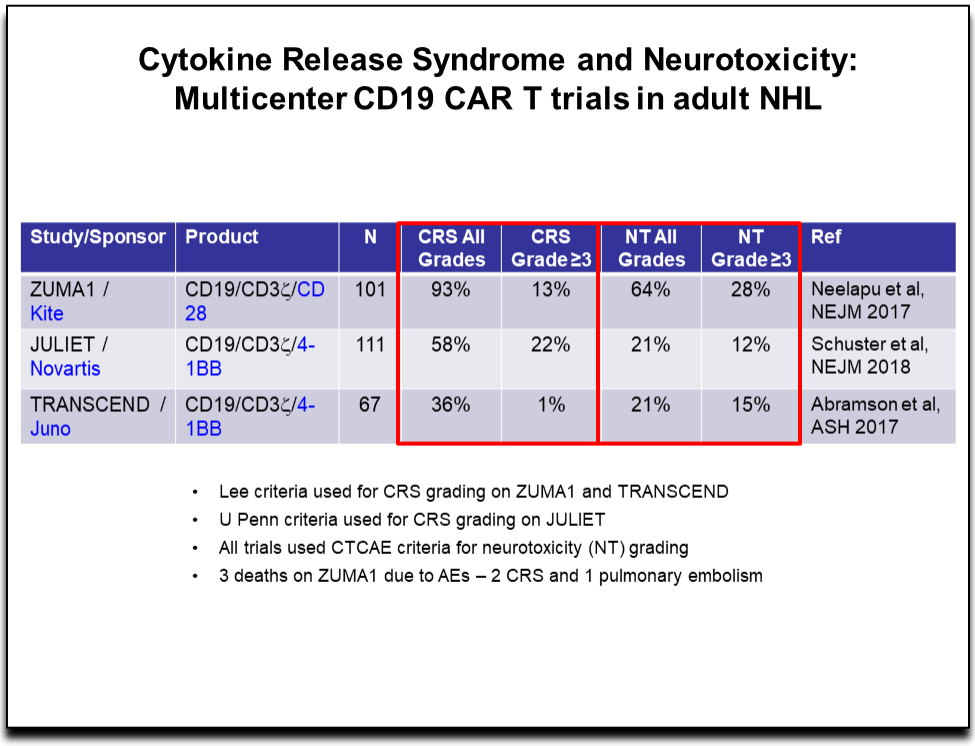
Multicenter CD19 CAR T-cell Trials in Aggressive NHL

This next slide discusses, again, though difficult to compare, the current FDA approved products. There are two of them and the third one that is pretty far along in terms of clinical study, which is the JCAR017 agent in the TRANSCEND study which has been reported, at least preliminary findings.

Again, there are differences in the CAR T construct, which Dr. Rouce did a nice description of the CD28 versus 4-1BB and what that translates to in terms of persistence in T cell expansion. There are differences in the dosing. There are differences in the conditioning chemotherapy. And also differences in terms of the baseline patient characteristics with ZUMA-1 restricted to patients that were refractory to their last treatment and that resulted in fewer that had undergone prior autologous stem cell transplant. Also, the JULIET and the TRANSCEND studies allowed for bridging chemotherapy.

The important thing when you look through this is at the end of the day the efficacy so far appears to be very similar across the different constructs. There are differences in terms of successful manufacturing and again, this may speak to how these cells may be collected and processed. With ZUMA-1 these are usually fresh cells, meaning as soon as they undergo leukapheresis, generally speaking, the cells are shipped to the manufacturer as opposed to KYMRIAH® where you could collect the cells weeks or months in advance and freeze them before they're actually processed.

The toxicity profile, again, can vary across the constructs, according to the studies. But again, a word of caution in terms of differences in regards to grading and management. There is a new consensus that will be published soon that should minimize the heterogeneity across these trials and may allow, in the future, for us to do a better job of comparing across studies.



Cytokine Release Syndrome and Neurotoxicity: Multicenter CD19 CAR T trials in adult NHL

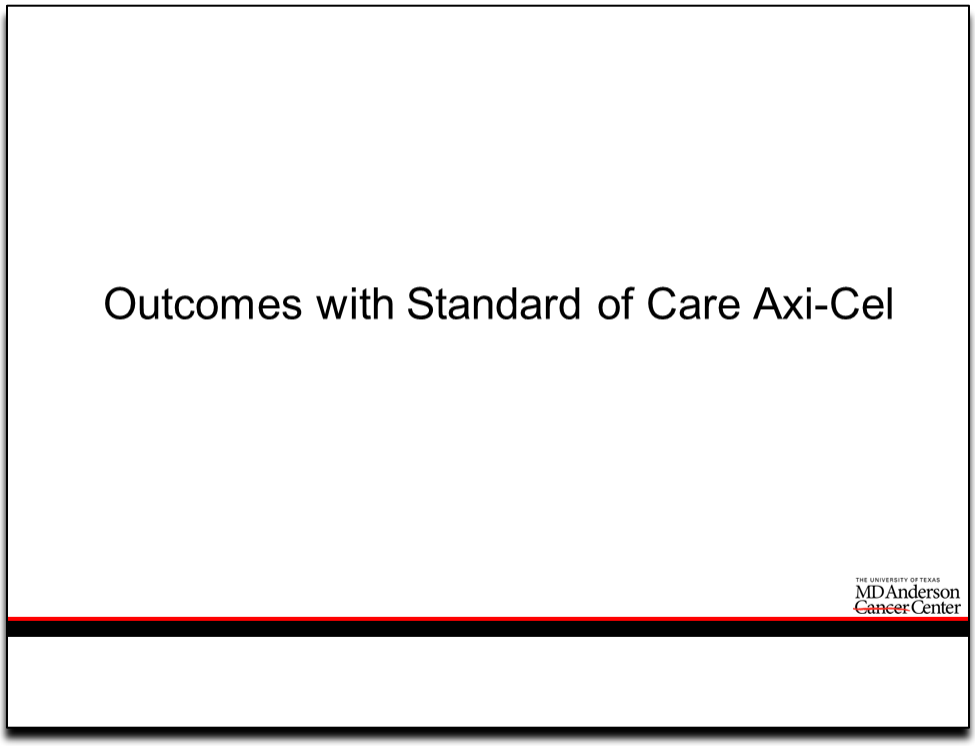
Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Ref
ZUMA1 / Kite	CD19/CD3ζ/CD 28	101	93%	13%	64%	28%	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/4-1BB	111	58%	22%	21%	12%	Schuster et al, NEJM 2018
TRANSCEND / Juno	CD19/CD3ζ/4-1BB	67	36%	1%	21%	15%	Abramson et al, ASH 2017

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

Cytokine Release Syndrome and Neurotoxicity: Multicenter CD19 CAR T trials in adult NHL

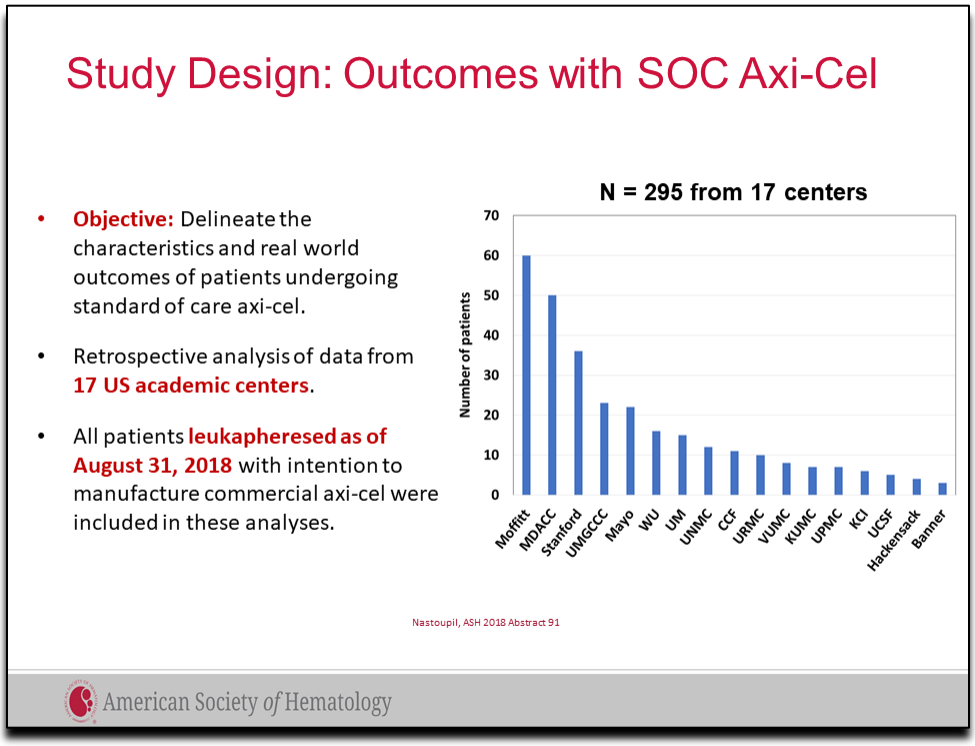
At the end of the day, we're getting better at managing cytokine release syndrome and neurotoxicity and we're less concerned about initiating some of these abortive medications due to fears that it may impact how well the CARs worked. Again, with more years of experience and more data emerging, the use of corticosteroids or tocilizumab at this time does not appear to impact the efficacy, therefore being more generous in terms of utilizing them to minimize side effects is probably a good idea.

But outlined here are the all grade cytokine release syndrome in the grade 3 or higher across the constructs as well as neurotoxicity. And probably the thing that jumps out the most is the neurotoxicity associated with YESCARTA® or Axi-cel is numerically higher than what we see with the other agents.



Outcomes with Standard of Care Axi-Cel

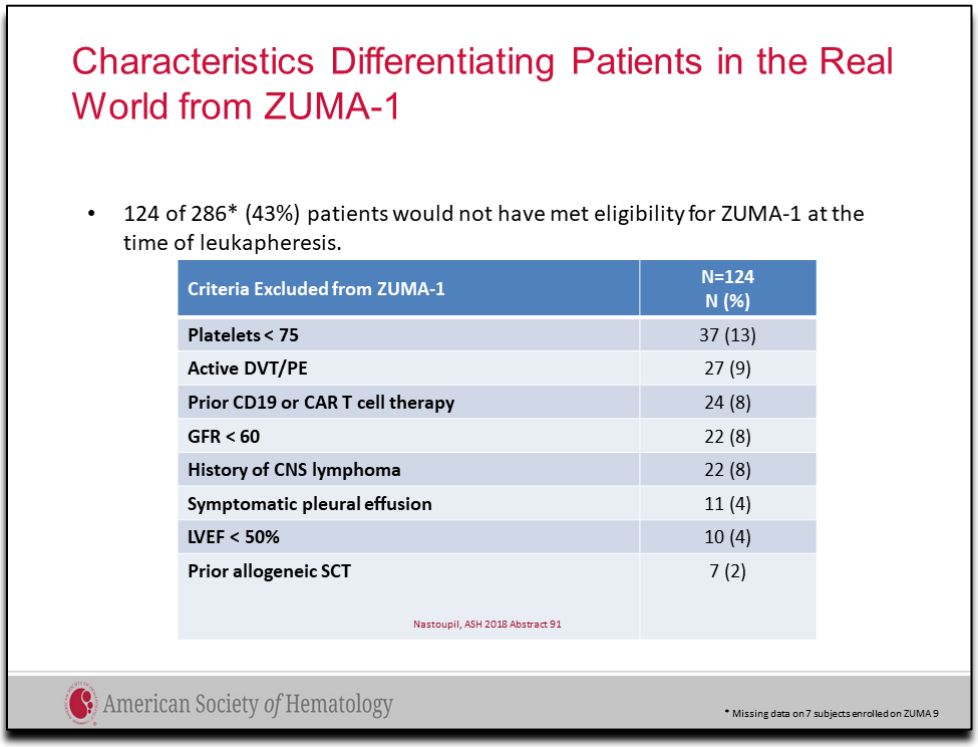
What about the outcomes of patients who now are being treated outside of the confines of the clinical trial?



Study Design: Outcomes with SOC Axi-Cel

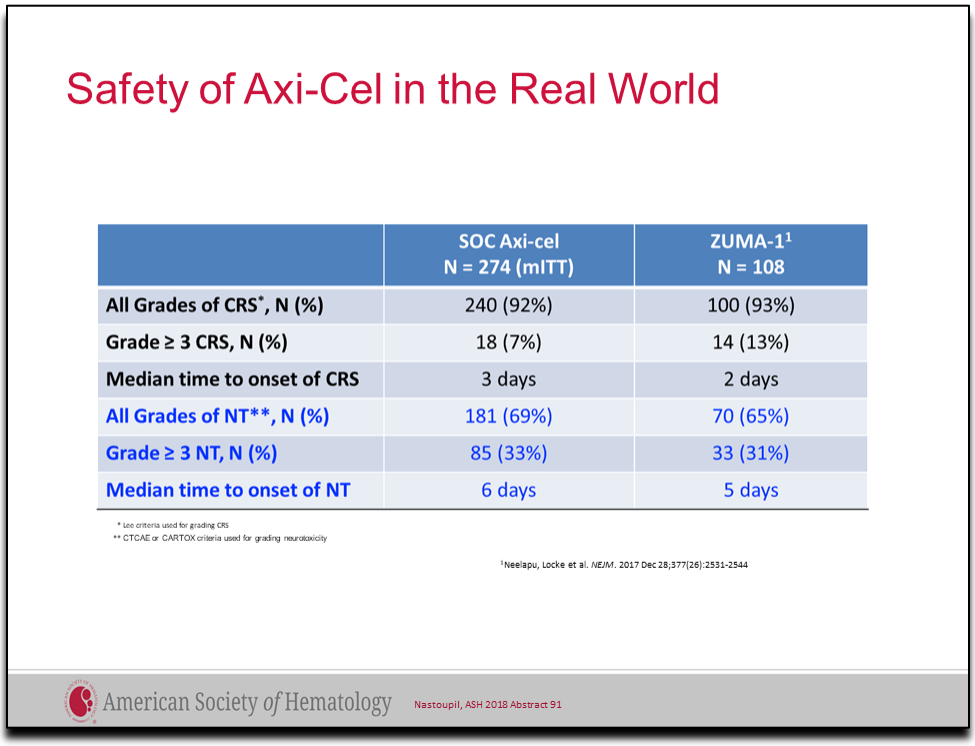
We presented this data at ASH (American Society of Hematology)[meeting] in December, looking at the number of patients that have been treated with standard of care Axi-cel since its approval in October of 2017 and where these patients were treated. So you can see, this was a collaboration of 17 centers. So not all patients who received CAR T-cell Therapy are treated in Houston, Texas, there are a number of patients treated across the country.

Now, there were differences in terms of quantity of standard of care CAR Ts across the centers but in general, we looked at all patients who underwent leukapheresis as of August 31, 2018, with the intent to manufacture standard of care CAR Ts.



Characteristics Differentiating Patients in the Real World from ZUMA-1

And it's not surprising that once we have a treatment that is no longer confined to a prospective clinical trial there will be some drift away from the eligibility criteria that are strictly applied in clinical trials. And what we highlight here are features that would have excluded patients from participation on the clinical trial that led to FDA approval of Axi-cel, including some notable things such as having a history of CNS lymphoma, having a low ejection fraction that suggests maybe a cardiomyopathy, having undergone a prior knowledge allogeneic stem cell transplant.

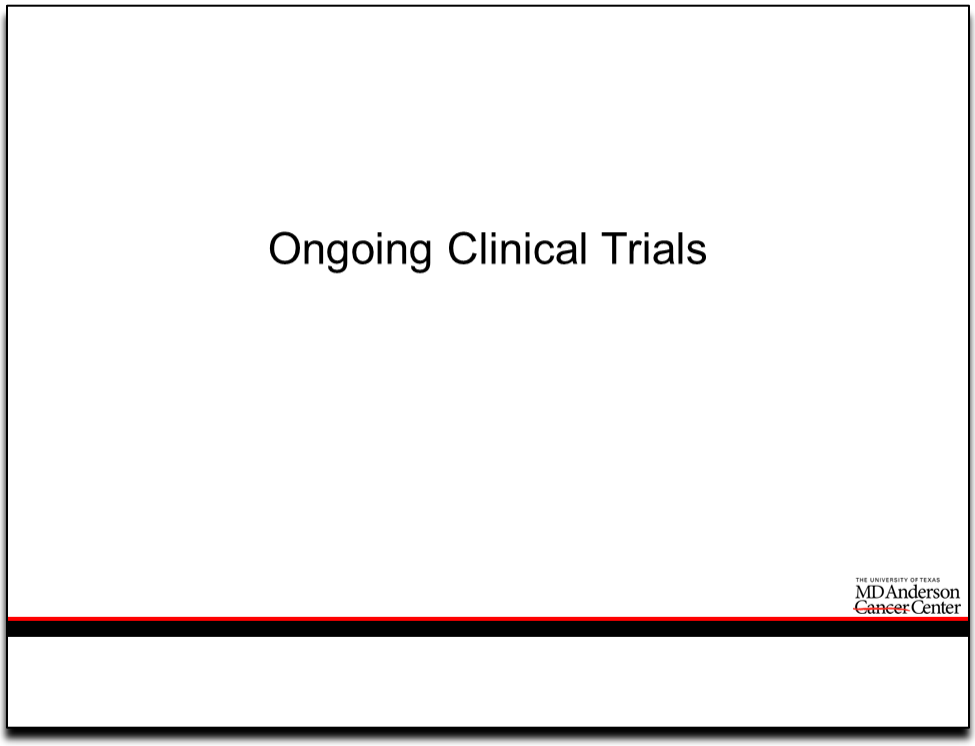


Safety of Axi-Cel in the Real World

Again, this is not surprising when we're restricted to the indication, which is just 2 prior lines of systemic therapy, and the question then becomes, how does this impact safety? So these were patients that all received standard of care Axi-cel, which is outlined here by the SOC column. And then we put up the safety of the ZUMA-1 just for comparison purposes, just for refreshment of the folks memory.

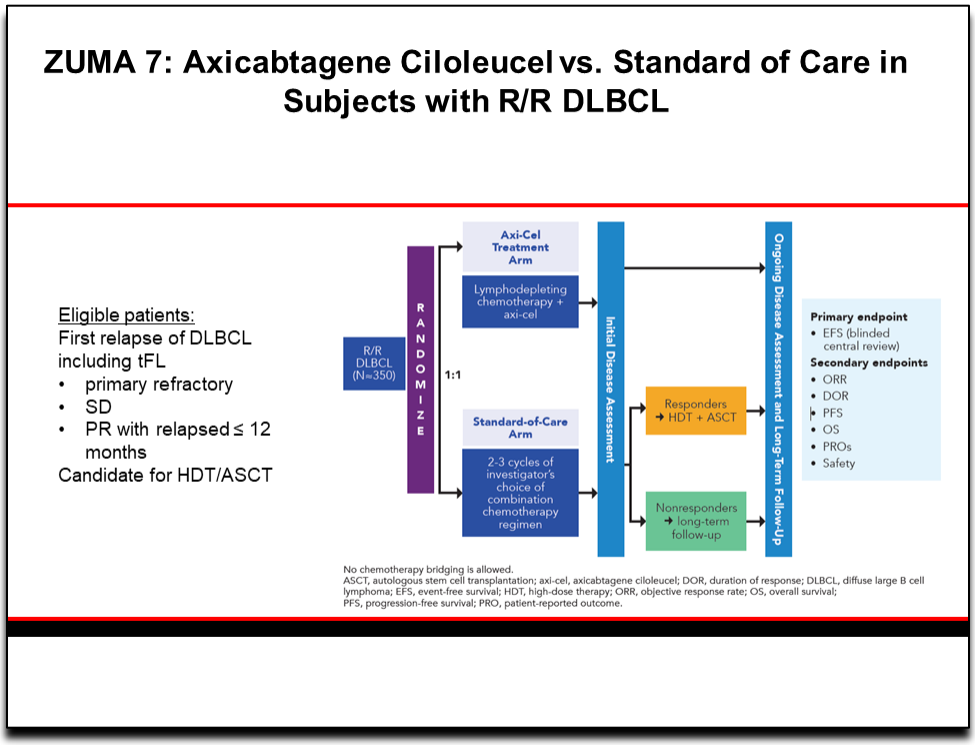
As you can see, again, the vast majority of patients had some form of cytokine release syndrome. The incidence of grade 3 or higher, which is severe cytokine release syndrome, was quite low. The time to onset of those symptoms was similar and the neurotoxicity, again, was quite similar.

So what this implies is though many patients did not meet the eligibility criteria of the ZUMA-1, which is 43% of this study population, and we had nearly 300 patients, which was about 3 times the size of ZUMA-1, our outcomes were very similar. So not only did we see those patients who achieved a complete remission remaining in a complete remission, but also the safety profile is very favorable, which suggests that we can reproduce the very favorable outcomes seen in the prospective study in the real world—which is quite encouraging.



Ongoing Clinical Trials

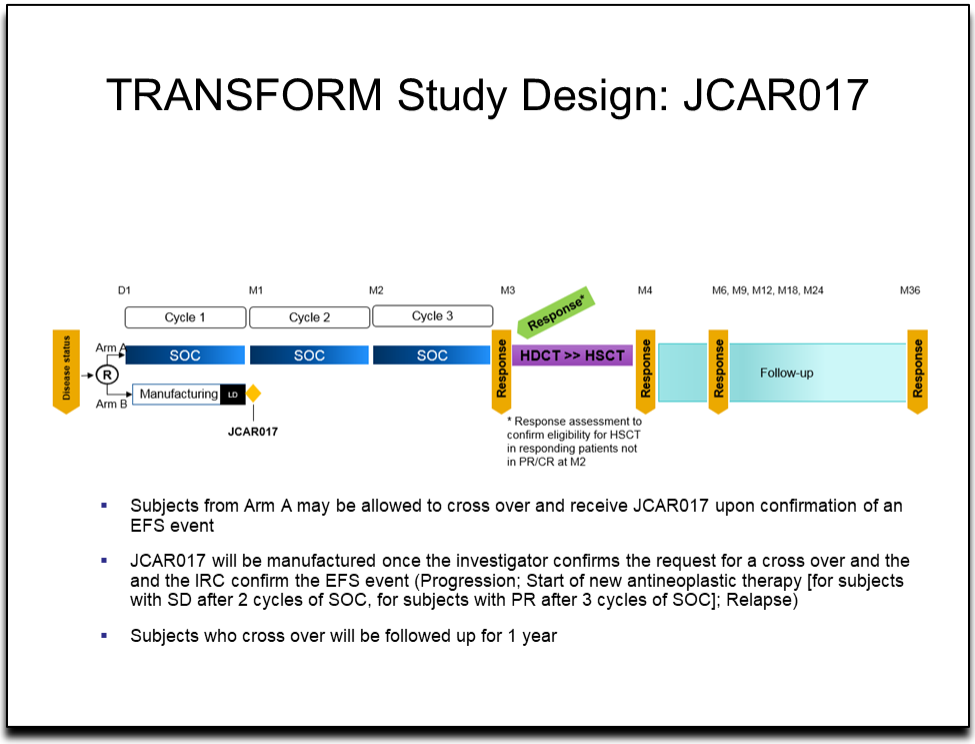
What are the future directions of this? You heard Dr. Rouce do a nice summary of where this can be applied, in additional tumors with additional targets. I will discuss some of the largest studies ongoing right now that are potentially practice changing.



ZUMA 7: Axicabtagene Ciloleucel vs. Standard of Care in Subjects with R/R DLBCL

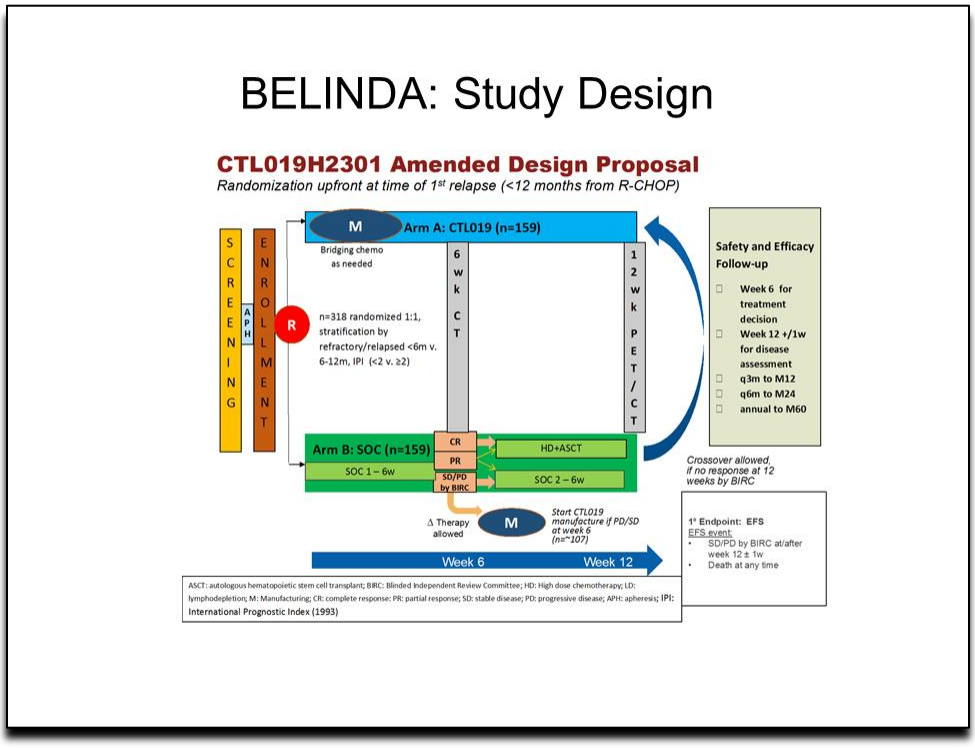
So this is a study called ZUMA-7, which is now exploring CAR T in the setting where salvage chemotherapy and autologous stem cell transplant is being used. Axi-cel or YESCARTA® is currently approved for patients who have failed 2 lines of therapy, which implies they are not transplant candidates or they have already failed a stem cell transplant. So this takes patients who relapse within 12 months of their front-line treatment and they get randomized to the standard arm, which is what's being done currently outside of this trial, which is salvage chemotherapy. And for those patients who respond to salvage chemotherapy as determined by PET, they go on to high-dose therapy autologous stem cell transplant. The other arm of the study is to go straight into CAR T-cell Therapy right now at their second treatment, which is not currently FDA approved.

So this study is nearing completion. We anticipate that the last patient will be enrolled this calendar year and then we'll have one of the first studies to read out as to whether CAR T should replace high-dose therapy/autologous stem cell transplant.



TRANSFORM Study Design: JCAR017

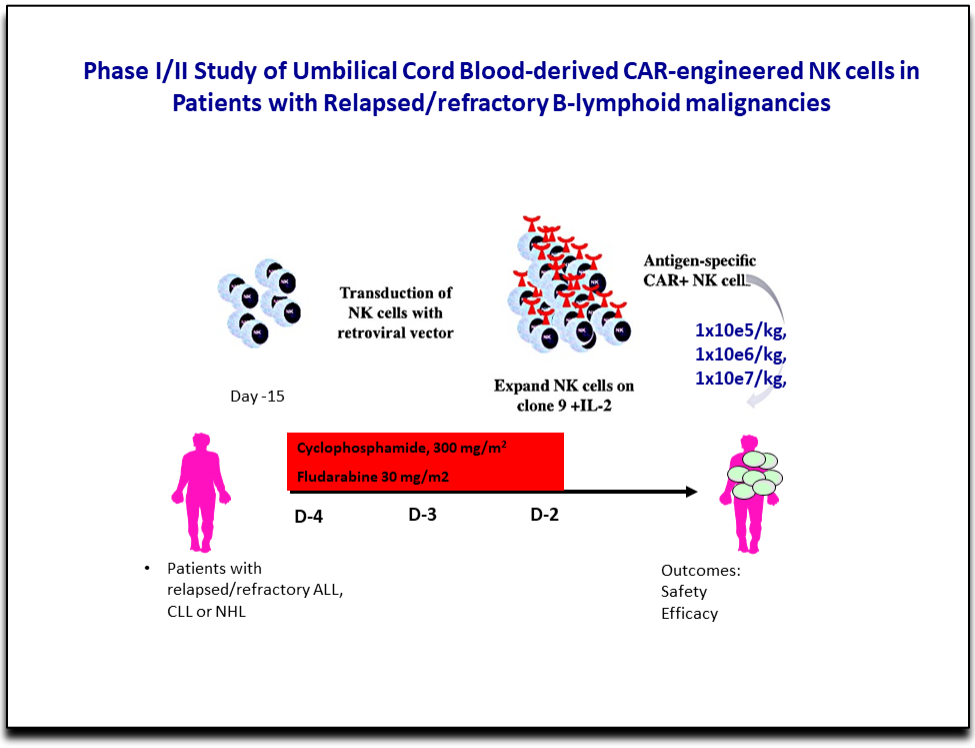
There are 2 other studies that are very similar in design. So, this is the TRANSFORM study, which uses the JCAR, which is not currently FDA approved. It has the 4-1BB costimulatory molecule, similar to KYMRIAH®, and with some of the preliminary data reported, it looks to be very similar in terms of safety and efficacy in comparison to KYMRIAH®. This looks like a very similar study design where patients are randomized at their first relapse to either salvage chemotherapy followed by high-dose therapy/autologous stem cell transplant or JCAR017. This study is just starting so it will likely be a number of years before we have the answer to this trial.



BELINDA: Study Design

And the BELINDA Study, which is also up and enrolling patients, is a randomized style looking at salvage chemo high-dose therapy/auto versus KYMRIAH®. A little bit different study design here in that patients start salvage chemotherapy and then they're randomized to the standard of care arm, as opposed to receiving straight out of the gate CAR T-cell Therapy.

These studies are important because it will answer the question, should you apply CAR T-cell Therapy in earlier lines of treatment failure?

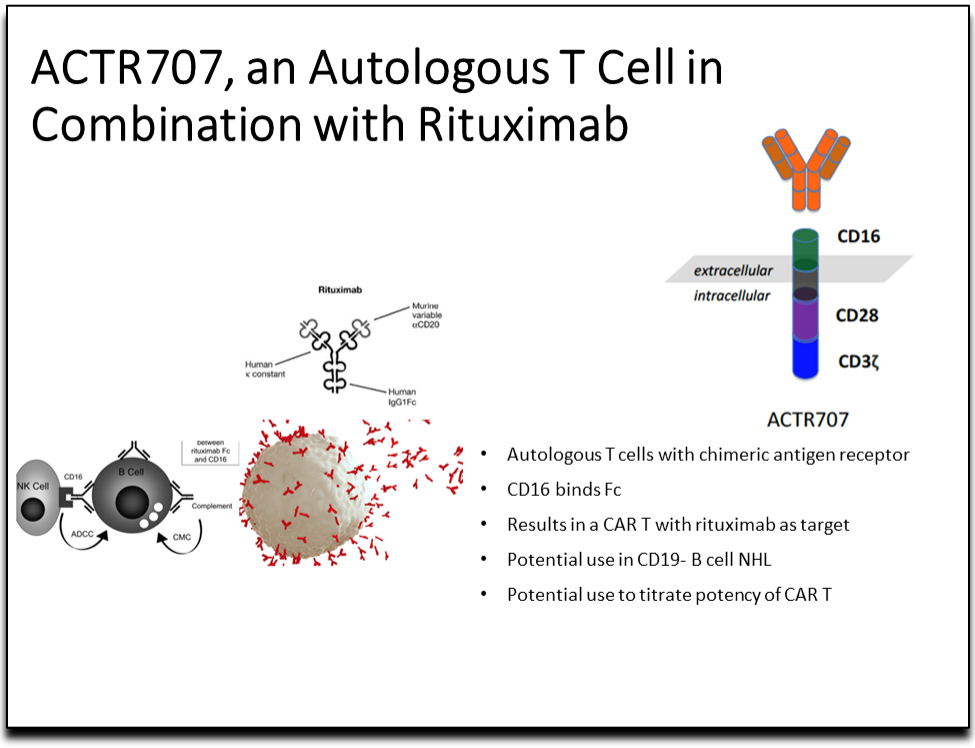


Phase I/II Study of Umbilical Cord Blood-derived CAR-engineered NK cells in Patients with Relapsed/refractory B-lymphoid malignancies

Another interesting area is looking at off-the-shelf CARs. So, this is a trial that's currently being conducted here at MD Anderson, where patients do not undergo leukapheresis. There are cord bloods that are sitting in a bank where those cord blood stem cells are taken, and they're differentiated into NK cells as opposed to T cells. And then they're genetically modified to express the surface receptor, which again, targets CD19, and they have costimulatory molecules as well.

They have some additional sort of unique features where there are enzymes that can be used to shut down the CAR as opposed to relying on steroids or antibodies that block receptors. So, it might be one way to mitigate some of the side effects, though the choice of the NK cell was also chosen to mitigate some of the side effects because you have less cytokine release syndrome with NK cells as opposed to T cells and we think they may be as effective at killing tumor cells as T cells.

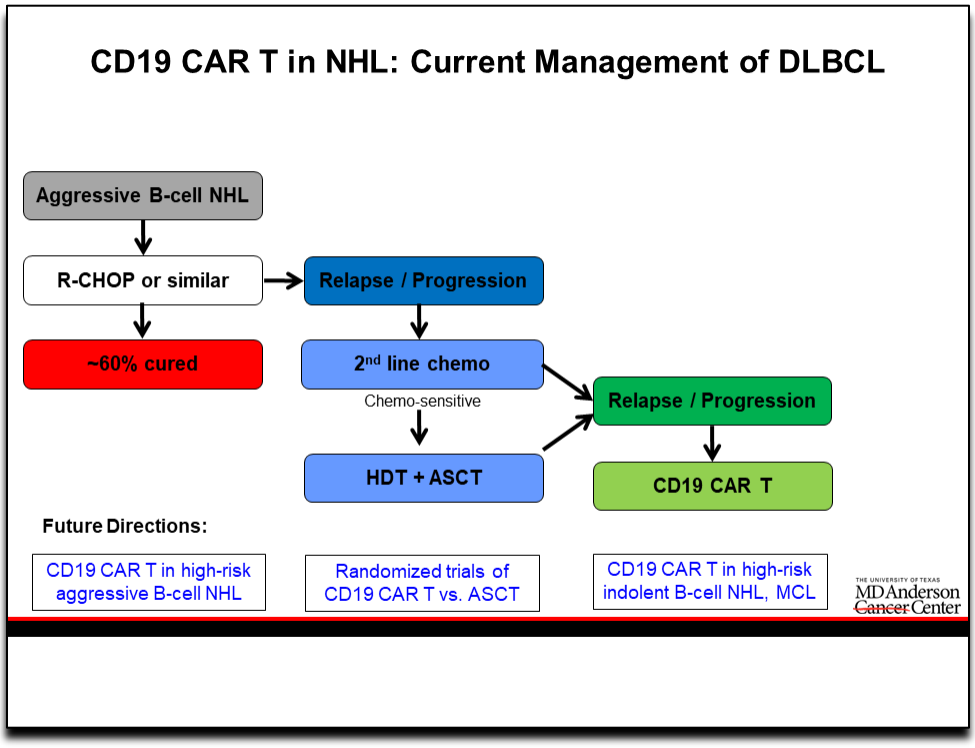
So the benefit of this is you don't have to pherese patients. Potentially, you can apply this to more patients because with one cord blood you can treat thousands of patients or hundreds of patients and again, the side effect profile may be more favorable.



ACTR707, an Autologous T Cell in Combination with Rituximab

The other thing I'll highlight is a unique spin on CAR T. So, this is a trial that's currently enrolling at MD Anderson. It's a phase 1 study so safety is currently the primary endpoint. But they have generated a CAR that will bind rituximab [Rituxan®]. And most patients with diffuse large B-cell lymphoma will be treated with rituximab [Rituxan®] at some point in the course of their disease, and though they may fail this, this is a unique way of using a CAR to target a protein that may not be on the surface of the tumor but may be a therapy that is appropriate for treatment.

So though targeting rituximab [Rituxan®] may not be the most exciting approach for diffuse large B-cell lymphoma, but then you could apply this more broadly to other cancers, such as targeting brentuximab vedotin [Adcetris®], which targets CD30. You could even potentially use this in solid tumors where you targeted things like Herceptin®. So the technology itself is quite intriguing where you could target potentially even more antigens.



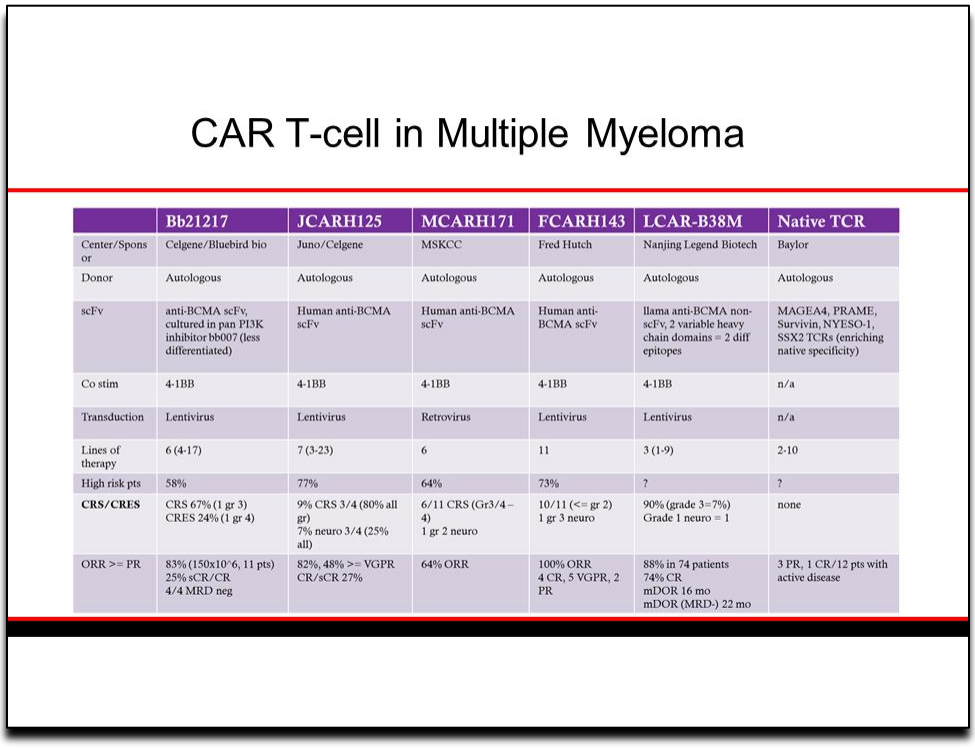
CD19 CAR T in NHL: Current Management of DLBCL

So to just close right now, the current approach to CD19-positive non-Hodgkin lymphoma in the U.S., we first approached this with R-CHOP and that cures at least 60% of patients. However, for those that currently relapse, outside of the clinical trials that are enrolling, the second-line approach is to pursue salvage chemotherapy and for patients who achieve a CR or have chemo-sensitive disease they currently go on to high-dose therapy/autologous stem cell transplant. For those that fail to respond to salvage chemotherapy or they fail following transplant, this is currently the patient population where CAR T-cell Therapy is FDA approved and you have 2 agents, KYMRIAH® and YESCARTA®.

And again, there are differences in terms of the patient population that were enrolled on study, differences in terms of manufacturing rates sometimes, and differences potentially in terms of toxicity. But there are 2; they're currently available.

What is currently being explored is looking at CAR T versus auto-transplant in that first relapse setting. CAR T is being moved up into earlier even potentially in front-line for patients who have very high-risk tumors that are demonstrating early treatment failure, even as early as 2 cycles of front-line chemotherapy and then again, in the relapse refractory setting, applying this to a broader patient population, including indolent lymphomas such as follicular and marginal zone lymphoma and mantle cell lymphoma.

So we're quite optimistic about what the future holds in terms of non-Hodgkin lymphoma and the number of studies that are currently enrolling that we hope will ultimately lead to additional approvals in the future.



CAR T-cell in Multiple Myeloma

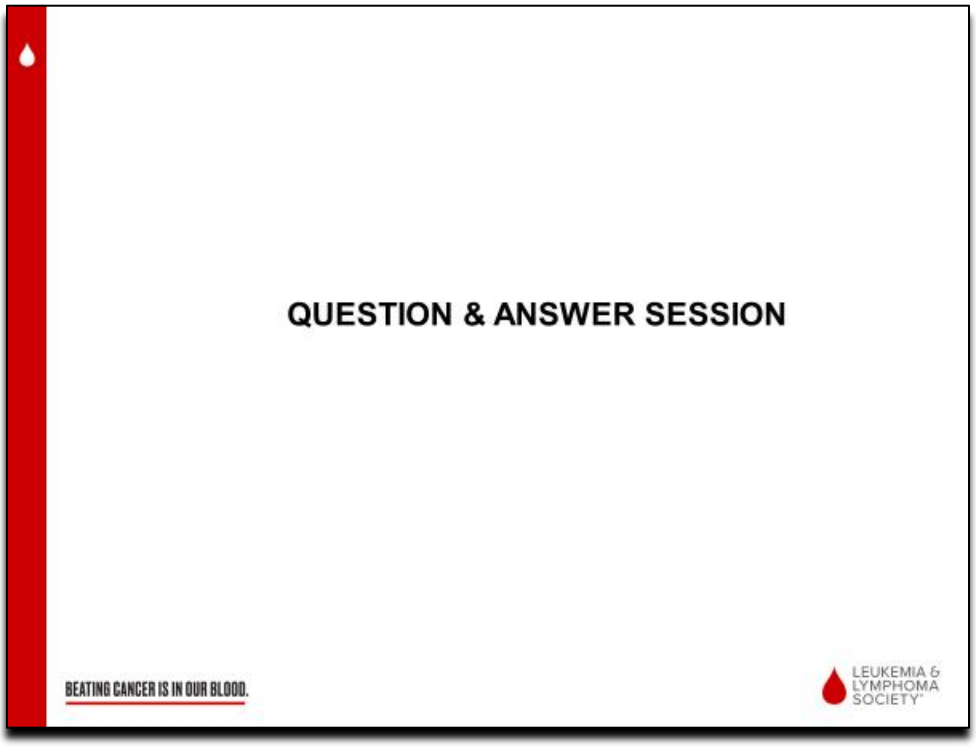
	Bb21217	JCARH125	MCARH171	FCARH143	LCAR-B38M	Native TCR
Center/Sponsor	Celgene/Bluebird bio	Juno/Celgene	MSKCC	Fred Hutch	Nanjing Legend Biotech	Baylor
Donor	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous
scFv	anti-BCMA scFv, cultured in pan PI3K inhibitor bb007 (less differentiated)	Human anti-BCMA scFv	Human anti-BCMA scFv	Human anti-BCMA scFv	llama anti-BCMA non-scFv, 2 variable heavy chain domains = 2 diff epitopes	MAGEA4, PRAME, Survivin, NYESO-1, SSX2 TCRs (enriching native specificity)
Co stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	n/a
Transduction	Lentivirus	Lentivirus	Retrovirus	Lentivirus	Lentivirus	n/a
Lines of therapy	6 (4-17)	7 (3-23)	6	11	3 (1-9)	2-10
High risk pts	58%	77%	64%	73%	?	?
CRS/CRES	CRS 67% (1 gr 3) CRES 24% (1 gr 4)	9% CRS 3/4 (80% all gr) 7% neuro 3/4 (25% all)	6/11 CRS (Gr3/4 – 4) 1 gr 2 neuro	10/11 (<= gr 2) 1 gr 3 neuro	90% (grade 3=7%) Grade 1 neuro = 1	none
ORR >= PR	83% (150x10^6, 11 pts) 25% sCR/CR 4/4 MRD neg	82%, 48% >= VGPR CR/sCR 27%	64% ORR	100% ORR 4 CR, 5 VGPR, 2 PR	88% in 74 patients 74% CR mDOR 16 mo mDOR (MRD-) 22 mo	3 PR, 1 CR/12 pts with active disease

CAR T-cell in Multiple Myeloma

And lastly, I'd like to discuss the role of CAR T-cell Therapy in multiple myeloma because there may be a number of you on the line that have multiple myeloma, which is also a B-cell problem. It's just a little bit different in terms of which point in the B-cell lineage the tumor arises. But this is a very busy slide. There are a number of studies that are currently enrolling, looking at CAR T-cell Therapy and multiple myeloma. The important thing is the target will be different in these for the majority of patients.

So there's been early reports of the Bb212 in multiple myeloma, which it targets anti-BCMA. There are others that are also currently under exploration. With a small number of patients and very early or preliminary findings, it looks to be very safe and potentially highly effective. So stay tuned as the studies continue to mature and read out.

And with that, I'd like to thank the LLS group for allowing us to have the opportunity today to present some of this interesting data. It's a whirlwind of information and at this point, I think we're very happy to answer any questions you might have.



Q&A

Ms. Lizette Figueroa-Rivera:
Thank you both, Dr. Nastoupil and Dr. Rouce, for your very informative presentations. It's now time for our question and answer portion of our program.

Ms. Lizette Figueroa-Rivera:
I know that there's a lot of different folks on the line, people are asking if CAR T-cell Therapy will be available for CLL, CML, mantle cell lymphoma, MDS, Waldenström's macroglobulinemia, follicular lymphoma? Could you just speak to maybe the future of CAR T cell?

Dr. Loretta Nastoupil:
Yes, this is Loretta. There are current studies underway looking at the role of CAR T-cell Therapy in mantle cell, in follicular lymphoma, and in marginal cell lymphoma. And these studies have—the mantle cell, they are more than one—have been ongoing for several months now. So I anticipate in the next 1 to 2 years we'll start to hear the findings from these studies, and if they're positive studies that may ultimately lead to approval in those lymphoma subtypes.

In regards to CLL, there's been a lot of work that has been done. There's a small number of patients and probably what's most intriguing right now is utilizing drugs like ibrutinib [Imbruvica®] up to the use of CAR T-cell Therapy to potentially select out more robust T cells. So those trials are underway and there's been some small case reports reported out that that might be an effective strategy. In CML, I'm unaware of any trials that are currently underway, but Dr. Rouce may know more than I do.

Dr. Rayne H. Rouce:
Hi. I will absolutely mirror your responses and there are currently not any trials underway for CML. And part of the reason is what Dr. Nastoupil so nicely discussed about CLL, for example, there are other mechanisms of treating these diseases and finding a target that's present on a CML cell and blast CARs

can be quite challenging. The same thing goes for MDS, if MDS transforms to AML there are certainly some CAR T cell options.

Ms. Lizette Figueroa-Rivera:
Thank you. And we'll take the next question from the telephone audience, please.

Operator:
Our first question comes from the line of Chris from New York. You are now live.

Question:
Hi. I'd like to find out if this can apply to someone with MDS, which is myelodysplastic syndrome?

Dr. Loretta Nastoupil:
This is Loretta. I'm unaware of any trials currently, though there have been some studies in AML, which MDS can sometimes progress to AML. Though I will have to follow-up on that one to see if there's any studies in the pipeline that are planned.

Ms. Lizette Figueroa-Rivera:
Thank you. And Dr. Rouce, Kelly is asking, "How long would a child have to wait before returning to school?"

Dr. Rayne H. Rouce:
Hi, Kelly. That's an excellent question. So one of the main differences with CAR T-cell Therapy and with our standard ways of targeting leukemia, such as chemotherapy, is that the therapy itself is not really designed to drop your blood count significantly. So, whereas when patients are receiving front-line chemotherapy for ALL, they typically are taken out of school until they get to the lighter portions of therapy, such as maintenance, with CAR T-cell Therapy, the initial period where you're most likely to have adverse events is typically within the first few weeks. It's rare that after 4 weeks after treatment you would develop something like cytokine release syndrome and neurotoxicity. And importantly, when people have low blood counts—specifically white blood cells and platelets—after CAR T-cell Therapy, it's often a contribution of both the lymphodepleting chemotherapy they received before and a little bit of the inflammation.

So most kids can probably return to school within a couple of months of receiving CAR T-cell Therapy, but again, it's really important to remember that this is on a case-by-case basis. So if it's a patient who had some other infectious complications, or anything else that came up, they might have to wait a bit longer. And a reminder that I don't think either one of us mentioned during our presentations: Because CD19 CAR T cells do attack CD19-expressing cells, they also will kill the normal B cells. So patients typically do require long-term intravenous immunoglobulin therapy. So it is case-to-case basis, but I have had some patients who've gone back to school within a few months of CAR T-cell Therapy.

Ms. Lizette Figueroa-Rivera:
Thank you, doctor. And Dr. Nastoupil, Hewitt, as well as many folks are asking if there is any age restriction for CAR T-cell Therapy?

Dr. Loretta Nastoupil:
That's a great question. And we actually presented some data at ASH that there should not be an age restriction. Some of the initial studies did have an age limit in terms of eligibility, though the larger studies that led to FDA approval did not. And so in ZUMA-1, there was about 25% of patients that were over the age of 65. What we set out to do was look at our own outcomes using the standard of care patients and then we utilize those patients of ours that were also enrolled on the prospective studies and looked at the patients that were over 65 versus those that were under 65 and wanted to know, was the toxicity different? Was the efficacy different? And we found there were no significant differences.

Now, that being said, the side effects of CAR T can be very cumbersome, the logistics of CAR T can be challenging, so just like we would with any treatment that we recommend to a patient, knowing their

functional capacity, how physically strong they are, independent of age is still important, but age alone should not be a factor.

Ms. Lizette Figueroa-Rivera:
Thank you. And we'll take the next question from the telephone audience, please.

Operator:
Our next question comes from the line of Corrin from New Jersey. You are now live.

Question:
Hi. I'm familiar with TIL, the tumor-infiltrating lymphocytes. It seems like it's a generic of CAR T, how do the two relate?

Dr. Loretta Nastoupil:
So primarily the CAR Ts are genetically modified so that we build in a receptor so that they'll bind a specific protein and whenever they target their protein, then those internal costimulatory molecules will pass the message on into the cell that "This is okay. Get rid of it." Whereas with the TIL, they may select out T cells that are better at recognizing proteins, generally speaking, they're not genetically modified to do so, there's just more of a selection process in beefing them up and then infusing them. Dr. Rouce, you can add on to that.

Dr. Rayne H. Rouce:
I absolutely echo that. One other important difference to point out is TILs are typically used in diseases that you're trying to get into the tumor microenvironment and the main difference is, as Dr. Nastoupil has stated, that they are not genetically modified cells.

Ms. Lizette Figueroa-Rivera:
Thank you. Is there any prior chemotherapy regimen that would make CAR T-cell Therapy ineffective?

Dr. Rayne H. Rouce:
I can start with that one. This is Dr. Rouce. So great question.

So while there's not therapy that's known to make it ineffective, there are specific chemotherapy agents that we know may make it more difficult to generate CAR T cells. So there are some chemotherapies

that will wipe out your T cell lymphocytes for longer than others and make them less functional. And even though we're removing them from the patient's body and manipulating them in the lab, these still can have an effect.

So from the commercial products, they typically have some guidelines that they'll share with you and your physician about agents that you should try to avoid within certain time periods before CAR T cells. But after the cells are collected in the bridging period that Dr. Nastoupil talked about, there aren't generally things that we try to avoid. But one thing that's really important is if you're waiting on CAR T cells to be manufactured, most physicians are trying to keep your cancer at bay as opposed to wiping it completely out, which could lead to long-term low blood counts and side effects before the CAR T-cell Therapy.

Dr. Loretta Nastoupil:
I absolutely echo that. I don't have any other comments.

Ms. Lizette Figueroa-Rivera:
Thank you. And Timothy is asking, "How intensive is the conditioning therapy necessary prior to receiving CAR T cell? Reason being many relapse or refractory patients can't withstand strong chemo again."

Dr. Rayne H. Rouce:

Great question. I can answer from a pediatric standpoint first.

The most common lymphodepletion or conditioning regimen is a combination of cyclophosphamide and fludarabine the doses of which are typically lower than what we use in upfront acute lymphoblastic leukemia therapy and also lower than what you would use in the conditioning regimens for someone prior to a bone marrow transplant—it's normally a few days.

There are times where if a patient had some underlying kidney disease or had a history of having a side effect from one of those medications where you could potentially modify the doses and there have been patients who've been treated with CAR T cells who did not necessarily get the full conditioning therapy prior to that still have had good outcomes.

Dr. Loretta Nastoupil:
Yes and in adults, there's been a lot of debate about what is the proper dose and regimen to use with conditioning chemotherapy, but most commonly we're using fludarabine and Cytoxan® (cyclophosphamide) and again, the doses may vary between KYMRIAH® and YESCARTA®. For instance, I think we still subscribe that you need conditioning chemotherapy and quibble a little bit less about exactly the dose and which regimen in adults.

Ms. Lizette Figueroa-Rivera:
Thank you. And our last question today, Galen asks, “I'm cancer-free 3 and a half years after receiving CAR T-cell Therapy. I was number 11 to submit to it and was told my response to it and recovery was unprecedented. I'm extremely thankful for this. And I was given just 3 months to live before receiving CAR T-cell Therapy. I'm curious about how treatment may have been adapted or improved since I went through it?”

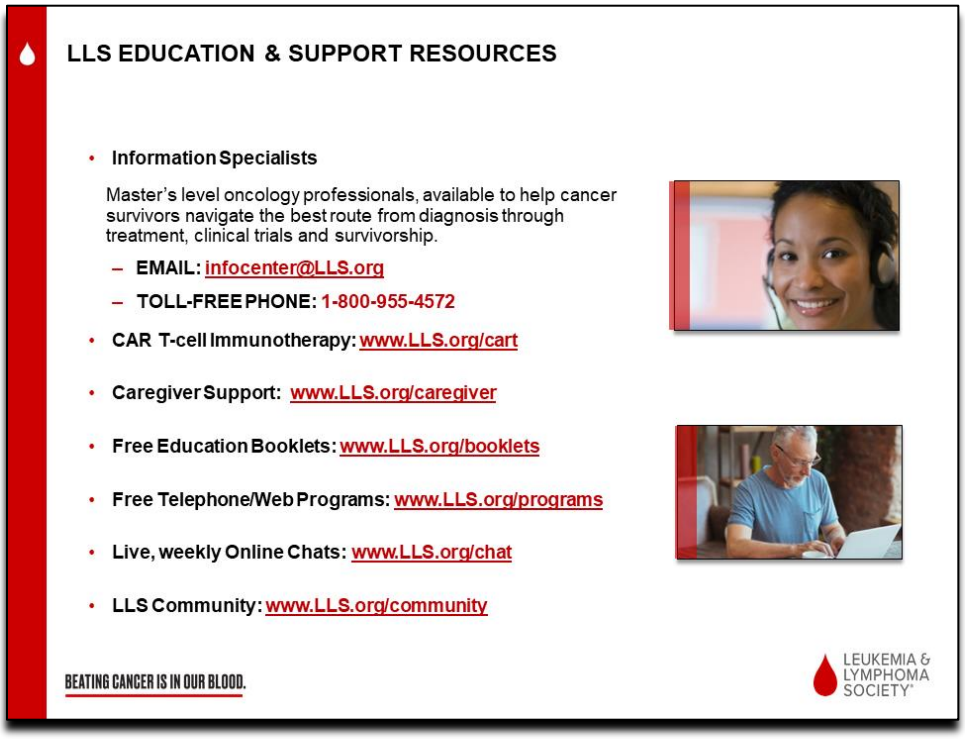
Dr. Loretta Nastoupil:
Well, in the adult world it's probably not much different with the exception that now we have standard of care options for more patients that may not have met the eligibility criteria of the prospective studies so we're more broadly applying it. And so far with limited follow up but a larger number of patients, that doesn't seem to impact how well it works. What has happened over time is that we've probably gotten better at managing the side effects in adult patients.

So as I showed in one of the slides, there's more use of steroids and tocilizumab , which initially when we were doing this in the phase 1 and early parts of the phase 2 study, we were very nervous about any steroids or any toci use and we've gotten a little bit more liberal with that, and at this point it does not appear to have impacted the outcomes. I think with anything, as you get more experience you just get a little bit better at managing it and potentially maybe a little bit more selective at which patients are better suited. We do know that we're probably curing about 40% of patients. And now we need to figure out why that number is not higher.

Dr. Rayne H. Rouce:
Great answer. I'll just add a little bit on there. That's amazing, first of all. It's wonderful to have you here on the line with us and have had this amazing response to this therapy.

One thing that I'll add is that a number of research groups, including ours, are still looking at how can we make these cells last longer? How can we make them impervious to things that may try to exhaust them or kill them? How can we make them last longer in all patients? And so there are a number of ongoing research efforts that are looking at these things as well as targeting additional antigens.

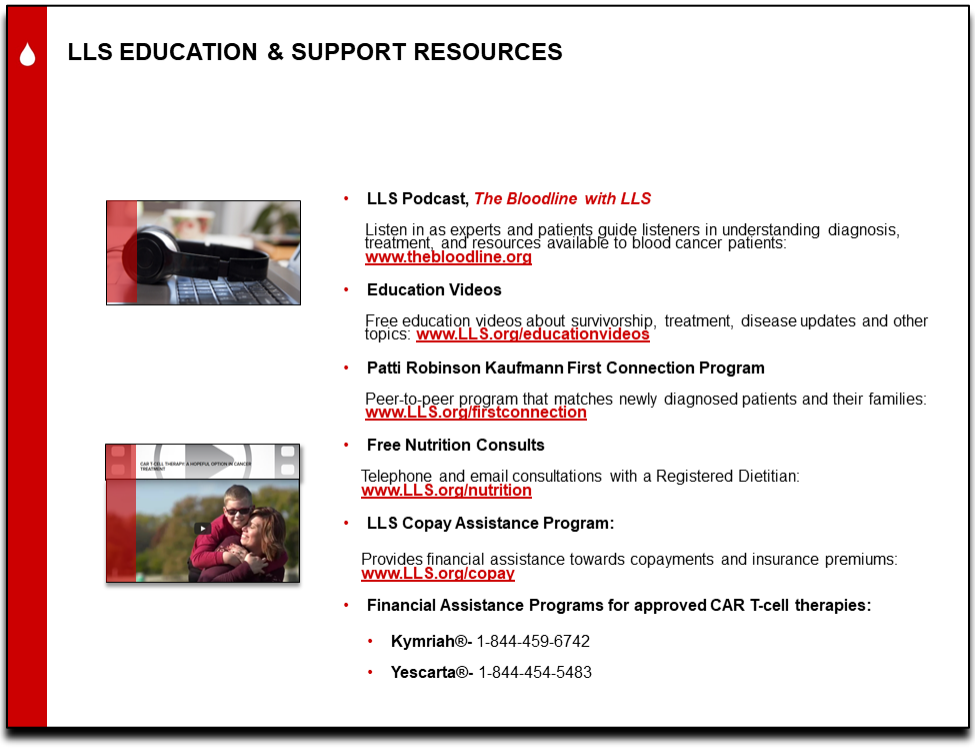
So for patients who have received one type of CAR T-cell Therapy, in the unfortunate event that they may relapse, it's always worth going back and looking at the trials and looking at the work that's available at the time because we're still answering questions and making great strides in the field.



LLS Education & Support Resources

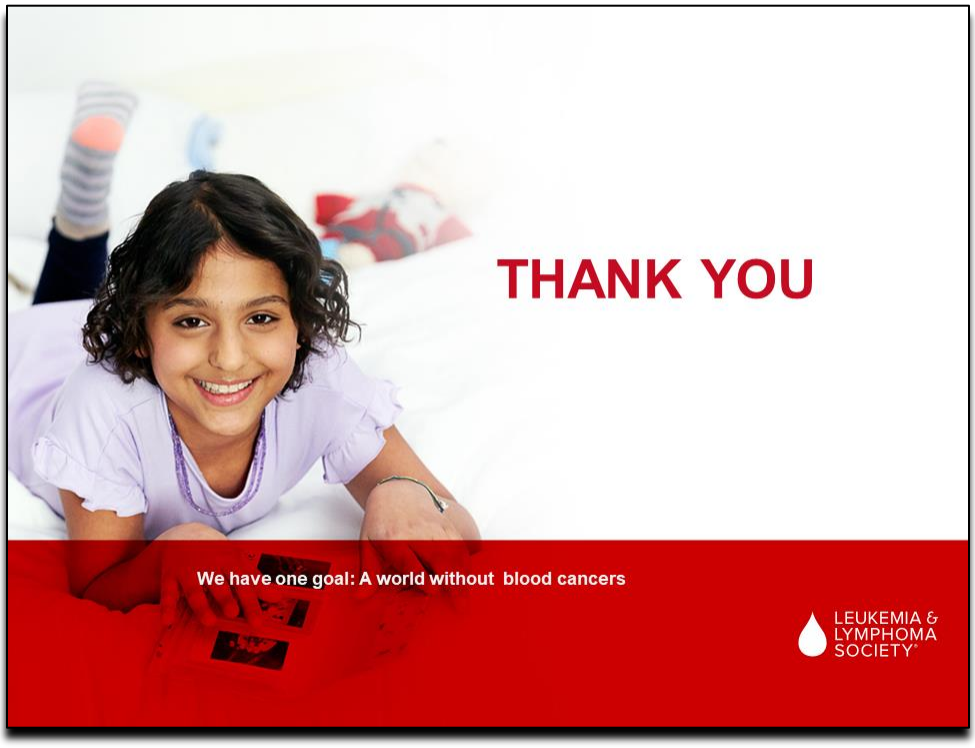
Ms. Lizette Figueroa-Rivera:
Well, thank you so much, Dr. Rouce and Dr. Nastoupil, for doing this type of research and for helping so many of our patients.

If we weren't able to get to your question today, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572, from 9 a.m. to 9 p.m. Eastern Time, or you can reach us by email at *infocenter@lls.org*.



LLS Education & Support Resources

I encourage you to contact us. We can guide you and provide you with more information. We also have a Clinical Trial Support Center (CTSC), as well as our Information Specialists, who can navigate you through the clinical trial process and assist in helping you navigate the website that Dr. Rouce mentioned, *clinicaltrials.gov*.



Thank You

Again, we would like to acknowledge and thank Celgene; Kite, a Gilead company; and Novartis for support of this program.

Again, Dr. Nastoupil and Dr. Rouce, thank you both for volunteering your time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program and we hope that you will join us in the future as we strive to keep you up-to-date on the latest advancements for all blood cancers. Thank you and take good care.