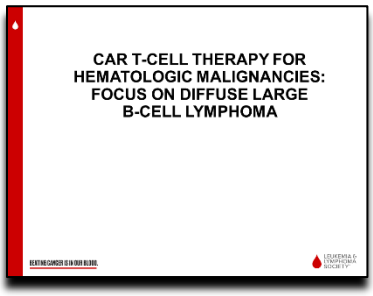
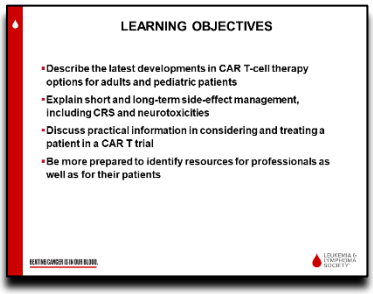
Transcript



Slide 1 – CAR T-Cell Therapy for Hematologic Malignancies: Focus on Diffuse Large B-Cell Lymphoma

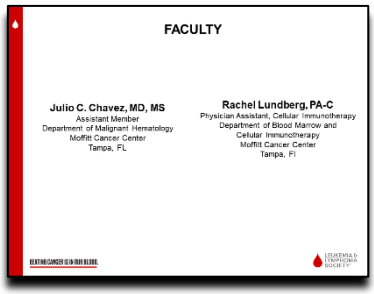
Lauren Berger: Hello, everyone. On behalf of The Leukemia & Lymphoma Society and Medical Learning Institute, Inc, thank you for sharing your time with us for this continuing education program on CAR T-cell Therapy for Hematologic Malignancies: Focus on Diffuse Large B-cell Lymphoma.



Slide 2 – Learning Objectives

The learning objectives for this program are listed on the slide:

- Describe the latest developments in CAR T-cell therapy options for adults and pediatric patients
- Explain short and long-term side-effect management, including CRS and neurotoxicities
- Discuss practical information in considering and treating a patient in a CAR T trial
- Be more prepared to identify resources for professionals as well as for their patients

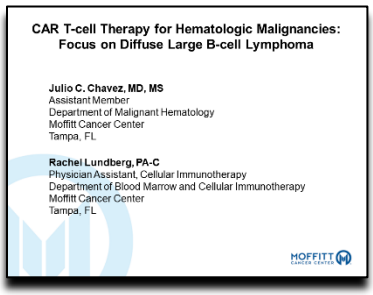


Slide 3 – Faculty

We 're fortunate to have as our presenters, Dr. Julio Chavez and physician assistant Rachel Lundberg, leading experts in CAR T-cell Therapy for blood cancer patients. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

Dr. Chavez is Assistant Member, Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida. Ms. Lundberg is Physician Assistant, Cellular Immunotherapy in the Department of Blood Marrow and Cellular Immunotherapy at Moffitt Cancer Center in Tampa, Florida

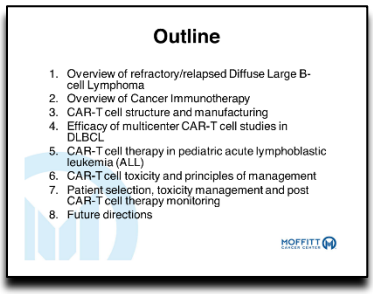
Our special thanks to Dr. Chavez and Ms. Lundberg for volunteering their time and expertise with us. Dr. Chavez, I am now privileged to turn the program over to you.



Slide 4 – CAR T-Cell Therapy for Hematologic Malignancies: Focus on Diffuse Large B-Cell Lymphoma

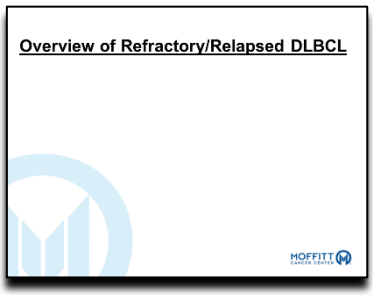
Julio C. Chavez, MD: Good afternoon, everyone. My name is Julio Chavez. I'm from the Department of Malignant Hematology at Moffitt Cancer Center. I'm here with Rachel Lundberg from the Department of Blood Marrow Transplantation at Moffitt Cancer Center. Today we're going to talk about the chimeric antigen receptor [T-cell therapy] for hematologic malignancies with focus on diffuse large B-cell lymphoma.

Transcript



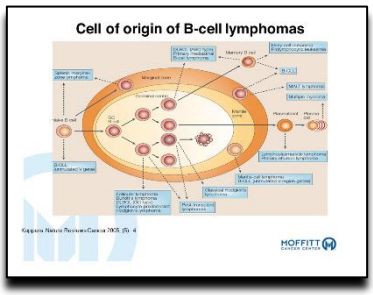
Slide 5 – Outline

This is the outline of, the present talk we're going to discuss about these points, an overview of refractory/relapsed-diffuse large B-cell lymphoma, an overview of cancer immunotherapy, CAR T-cell structure and manufacturing, efficacy of multicenter CAR T-cell studies in diffuse large B-cell lymphoma, CAR T-cell therapy in pediatric acute lymphoblastic leukemia. Then we're going to talk about the CAR T-cell toxicity and principal management, then patient selection toxicity management of post-CAR T-cell therapy monitoring, and we'll end it up with the future directions in this therapy.



Slide 6 – Overview of Refractory/Relapsed DLBCL

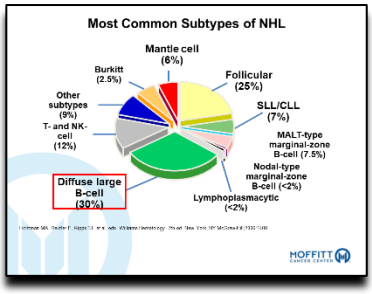
So, I'm going to talk a little about the overview of this disease.



Slide 7 – Cell of Origin of B-Cell Lymphomas

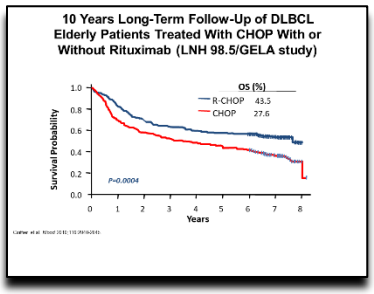
Diffuse large cell lymphoma is a B-cell malignancy. This cartoon here shows where diffuse large B-cell lymphoma originates. As I mentioned, diffuse large B-cell lymphoma is a B-cell malignancy that starts in the germinal center.

We have two main types. There is the ABC subtype (the primary mediastinal subtype) and the GCB or germinal center B-cell subtype. They have different prognostic outcomes with the standard therapy.



Slide 8 – Most Common Subtypes of NHL

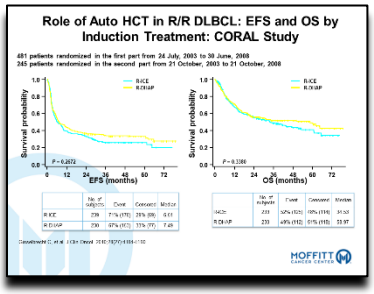
Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphoma. About 30% to 40% of lymphoid malignancies are consistent with diffuse large B-cell lymphoma.



Slide 9 – 10 Years Long-Term Follow-Up of DLBCL Elderly Patients Treated With CHOP With or Without Rituximab (LNH 98.5/GELA Study)

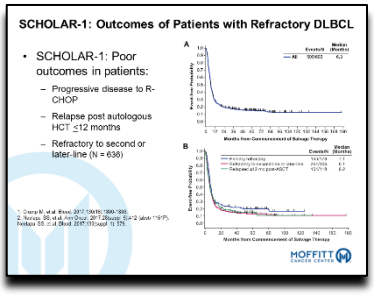
The standard treatment for diffuse large B-cell lymphoma in the frontline setting was defined by the GELA study in which the introduction of rituximab (Rituxan®) to the CHOP chemotherapy improved the overall survival by about 20%. However, despite this advance in the treatment of diffuse large B-cell lymphoma, there are still many patients who relapse.

This is the 10-year follow-up of the GELA study on patients who receive R-CHOP versus CHOP and about 40% to 50% of patients still relapse.



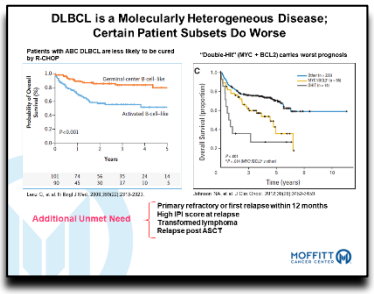
Slide 10 – Role of Auto HCT in R/R DLBCL: EFS and OS by Induction Treatment: CORAL Study

There are treatment options for patients who relapse. You know, the CORAL study demonstrated that salvage chemotherapy followed by autologous transplantation showed clinical benefit and also survival benefit. But still, this procedure cures about 50% of patients; 50% of patients still relapse, die from the disease, even with salvage chemotherapy and autologous transplantation.



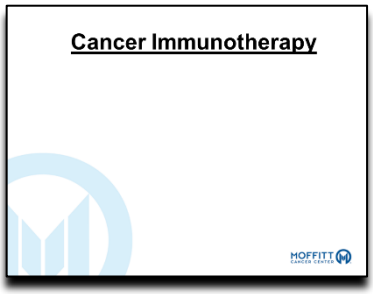
Slide 11 – SCHOLAR-1: Outcomes of Patients with Refractory DLBCL

However, who are the bad actors in diffuse large B-cell lymphoma in the refractory setting? There are good outcomes that we see, those are patients who had progressive disease through R-CHOP basically, patients who don't respond to R-CHOP at all, patients who relapse post-autologous transplant, especially within the first year of transplantation, and those patients who are refractory to a second-line therapy. The overall survival for those patients in average is about 6 to 7 months. Their response rates to the next therapy is about 25%.



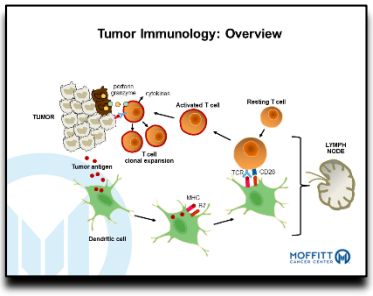
Slide 12 – DLBCL is a Molecularly Heterogeneous Disease; Certain Patient Subsets Do Worse

Diffuse large B-cell lymphoma is also a molecularly heterogeneous disease. It's clinically heterogeneous but also molecularly heterogeneous. So, there are certain types of diffuse large B-cell lymphoma that have an overall bad prognosis, especially the activated B-cell subtype has significantly bad prognosis in comparison to the GCB or the germinal center B-cell subtype and also the double-hit lymphoma, those who had overexpression of MYC and BCL-2 plus/minus BCL-6. They also have poor outcomes with the standard therapies.



Slide 13 – Cancer Immunotherapy

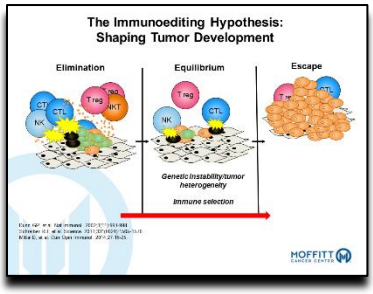
So now we're going to talk about a little bit of cancer immunotherapy and how these therapies consistent with CAR T-cell therapy have been developed.



Slide 14 – Tumor Immunology: Overview

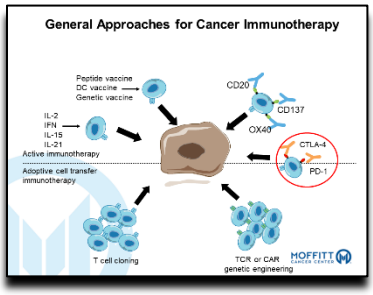
So, I'm going to give you a little bit of simple overview in this cartoon of the tumor immunology. Basically, when a patient develops a cancer, there are several tumor cells that display the tumor antigen. So, there are immune system cells or blood cells that actually capture these antigens. We call these cells the dendritic cells. Those cells actually present the antigen to immune system cells, that we call the T-cells. Those T-cells usually are in resting phase. However, when they're exposed to the antigens, they kind of get activated and then through several mechanisms, through cytokines or other chemokines, can actually destroy and kill cancer cells.

This antigen interaction, of course, is actually in the lymph nodes. So, however, this is something that happens initially with good efficacy in destroying cancer cells.



Slide 15 – The Immunoediting Hypothesis: Shaping Tumor Development

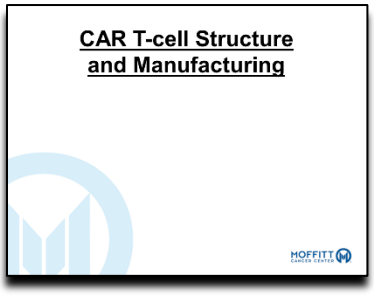
However, some cancer cells develop several mechanisms to avoid or escape this process. This escape causes an increase in T-regulatory cells which actually are kind of inactive and actually work against the normal immune system response. And that leads to tumor growth and refractoriness. So, basically, what occurs is some type of immune selection so cells that had mechanisms to escape the immune system, they survive, and they continue to grow.



Slide 16 – General Approaches for Cancer Immunotherapy

So, on the basis of that, CAR T-cell therapy has been developed. So, this cartoon shows the general approaches for cancer immunotherapies. In general, there are two types of cancer immunotherapies, the active immunotherapy and the adoptive cell transfer immunotherapy or ACT. The active immunotherapy, basically, we're giving active immune agents that can destroy cancer cells using different mechanisms. The most common one is the anti-CD20 monoclonal antibody which is rituximab. However, there are other antibodies that actually have effects on immune stimulation that can destroy cancer cells.

The other subtype, ACT, or adoptive cell transfer immunotherapy, is basically modifying CAR T in normal T-cells from the patient in order to produce a cytotoxic effect on the tumor. So, we're going to talk about what is the adoptive cell transfer immunotherapy, specifically chimeric antigen receptor T-cell therapy or CAR T-cell therapy.



Slide 17 – CAR T-Cell Structure and Manufacturing

So, we're going to talk a little bit of the CAR T-cell structure and manufacturing, just to kind of guide you through the process.

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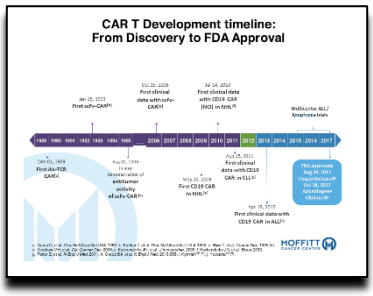
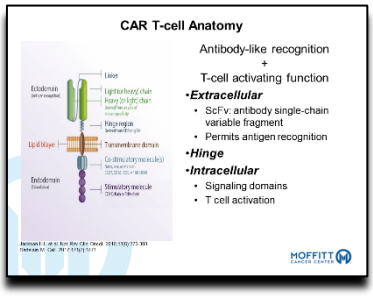


Slide 18 – CAR T-Cell Development Timeline

In this slide I would like to mention how CAR T-cells were developed over time. As you see CAR T-cell treatment or CAR T-cell therapy is not a new concept. Actually, it started in the late '80s with the first CAR T-cells that actually didn't have a costimulatory domain. However, over time, it's been learned that using, in order to improve a CAR T-cell efficacy and activity, there was a need of better receptor and also of better costimulatory domain.

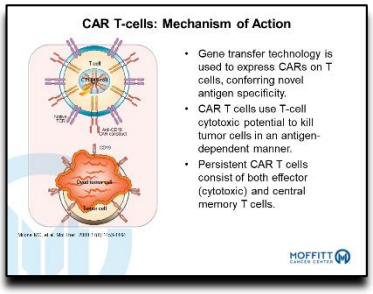
The first CAR T clinical data with efficacy was presented, in 2009 in the patients with refractory non-Hodgkin lymphoma, by the National Cancer Institute. So since then, the development has increased with new CAR T-cell concept until the approval of the first CAR T-cells for acute lymphoblastic leukemia in August 2017, and the first CAR T-cell therapy for, diffuse large cell lymphoma in October 2017.



Slide 19 – CAR T-Cell Anatomy

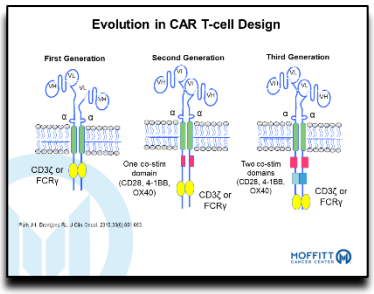
A little background of the CAR T-cell anatomy. The CAR T-cell molecule has three parts. You have the ectodomain, which is the outside part; the transmembrane domain; and the endodomain. The ectodomain is basically the one that kind of recognizes the antigen of the tumor. The transmembrane portion is just the one that keeps this stable; the recognition area, with the stimulatory area; and the endodomain, which basically consists in the costimulatory molecules and the stimulatory molecules.

So, the costimulatory molecule is basically that one that gives the higher potency to CAR T-cells to activate T-cells and have an appropriate cytotoxicity response.



Slide 20 – CAR T-Cell Mechanism of Action

So how CAR T-cells work. So CAR T-cells consist in a gene transfer technology that is used to express CAR, the molecule that I just presented in the previous slide, in order to confer antigen specificity and potency. CAR T-cell uses the normal T-cell cytotoxic potential to kill cancer cells in an antigen-dependent manner. There is a possibility that after CAR T-cell infusion, there's persistent CAR T-cells that still can have antitumor effects because most of these cells will become memory cells.



Slide 21 – Evolution in CAR T-Cell Design

So there has been an evolution of the CAR T-cell design, you remember the external portion, the transmembrane portion, and the costimulatory portion, the initial CAR T-cell, the first-generation CAR T-cells were developed with like a CD3 stimulatory molecule. However, these CAR T-cells actually had lower response rate and shorter responses, so they were not translated into the clinical use. However, the current CAR T-cell constructs or programs that we have available and have been approved are the second-generation CAR T-cells. That, in addition to the CD3 stimulatory molecule, has a costimulatory domain that actually increases the activation and potency of CAR T-cell therapy.

There are also third-generation, and later on I'll talk to you about the new construct in which there is a dual costimulatory domain. So just to kind of give you a background, the most common one that we have is the CD28 costimulatory domain. However, the 4-1 will be on the OX-40 are also costimulatory domains. There are differences in the type of costimulatory domains. Some have higher expansion and activation but less persistence. But the others have much more persistence for longer period of time. So, the future of CAR T-cells are actually including a new construct that has both constructs.

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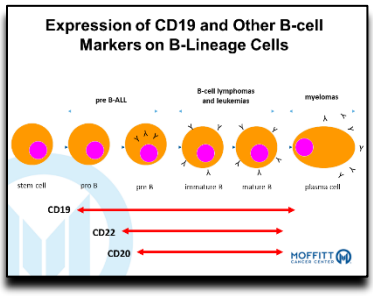
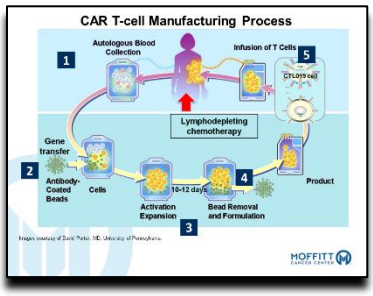


Slide 22 – Expression of CD19 and Other B-Cell Markers on B Lineage Cells

So why CD19? In order for a CAR T-cell to work, we have to have an appropriate reliable antigen to target. So CD19 is expressed on basically all B-cell malignancies, so except for the stem cells and also for late plasma cells.

So that's why it's an ideal target for CAR T-cell therapy. The CAR T-cell therapy is also for CD22 and CD20 antigens. However, given that CD19 is broadly expressed in B-cell metastatic disease, CD19 is the one that is the most commonly used.

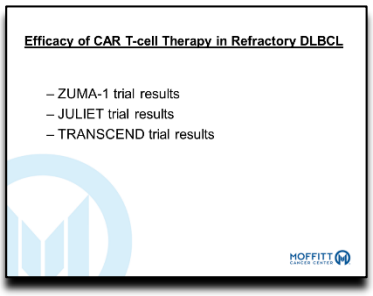


Slide 23 – CAR T-Cell Manufacturing Process

So, this is just to kind of give you a CAR T-cell manufacturing process. Basically, once the patient is selected to start CAR T-cells, they go for what we call autologous blood collection. Basically similar to what happens with autologous stem cell transplantation. Then after the collection, this is shipped to the pharmacological company that makes the CAR T-cells where gene transfer occurs, and basically introduced the CAR into the T-cells. Then, after there is activation and expansion of the CAR T-cells, then there is a bead removal or reformulation and then, at the end we have the final product that is infused to the patient.

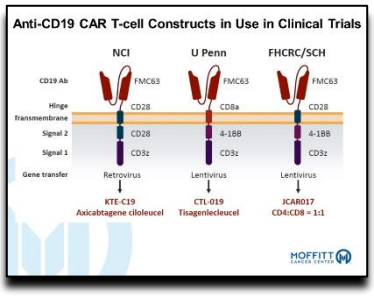
So, prior to infusion, patients are required to have lymphodepleting chemotherapy. There are several reasons why lymphodepleting chemotherapy is important for CAR T-cell therapy. The main reason is that it's going to decrease the T-regulatory cells that work against CAR T-cells and also activate cytokines that creates a better environment for CAR T-cells to work.

So, the process from the collection of the cells until the patient is infused is variable, depending of the type of the CAR T-cells and the company that makes the CAR T-cells. It goes anywhere from 14 to 17 days, but there are others that takes up to 23 days. So, on average it's like 2 to 4 weeks to get the CAR T-cells manufactured on these patients.



Slide 24 – Efficacy of CAR T-Cell Therapies in Refractory DLBCL

So, the next topic is about the efficacy of CAR T-cell therapy in refractory diffuse large B-cell lymphoma. And in this section, basically, we're going to talk about the three major multicenter clinical trials, the ZUMA-1, the JULIET, and the TRANSCEND.

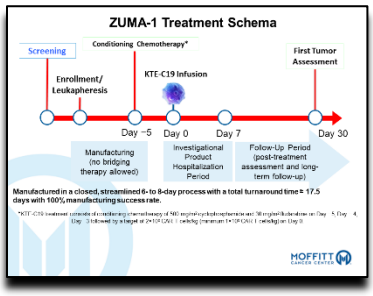


Slide 25 – Anti-CD19 CAR T-Cell Constructs in Use in Clinical Trials

Just to kind of go over again, in regard to the CAR T-cell construct targeting CD19 in B-cell malignancies. So, the first one that was approved for diffuse large B-cell lymphoma was the axicabtagene ciloleucel (Yescarta®) that was initially developed in the National Cancer Institute. It targets CD19, has a costimulatory signal of CD28, and the gene transfer is made by a retrovirus.

The one from the University of Pennsylvania uses a costimulatory signal called 4-1BB used as gene transfer using a lentivirus, and this is CTL-019, the Novartis product, tisagenlecleucel (Kymriah®).

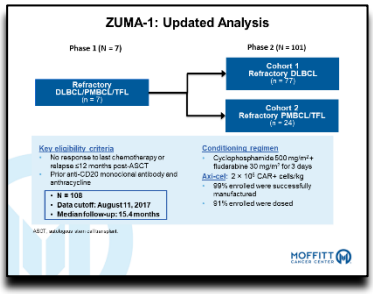
And the third one, developed by the Fred Hutchinson Cancer Center, is also 4-1BB using a lentivirus for transfer, genetic transfer, and the name is JCAR17 - 017. The particular property of the JCAR017 is that it has 1:1 selection, 1:1 ratio that allows a better T-cell, subsets for CAR T-cell manufacturing and also for anti-lymphoma activity.



Slide 26 – ZUMA-1: Treatment Schema

So, I'm going to talk about ZUMA-1, a clinical trial. The ZUMA-1 clinical trial was CAR T-cell, anti-CD19, the axicabtagene ciloleucel (Yescarta®) for refractory patients with diffuse large B cell lymphoma. Just to kind of give you an idea about the treatment schema, basically patients went to a screening. They were enrolled, and once they met criteria, they basically had leukapheresis. It took like about 14 days to have the CAR T-cells manufactured. The patients underwent conditioning chemotherapy, and CAR T-cells was infused on Day 0. So, and the patients were followed with the first assessment at day 30.

So, the total turnaround time for the CAR T-cell was about 17 days, two weeks, 14 to 17 days. And then it was reported 100% manufacturing success rate.

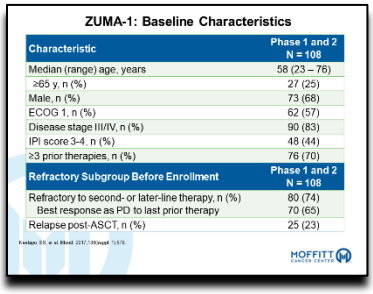


Slide 27 – ZUMA-1: Updated Analysis

So, what I'm going to present is the updated analysis. ZUMA-1 was divided in 2 phases – the phase 1 portion that included 7 patients, and the phase 2 portion that included the expansion portion that included 101 patients.

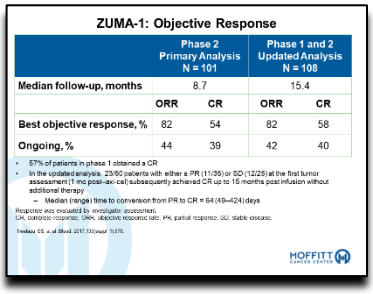
The eligibility, basically, patients with refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed lymphoma from follicular lymphoma.

The median follow-up of this study was 15.4 months. So, basically, key eligibility criteria, patients with no response to the last chemotherapy or relapse within 12 months post-transplantation. The conditioning regimen was cyclophosphamide-fludarabine, which is the one we use after their approval.



Slide 28 – ZUMA-1: Baseline Characteristics

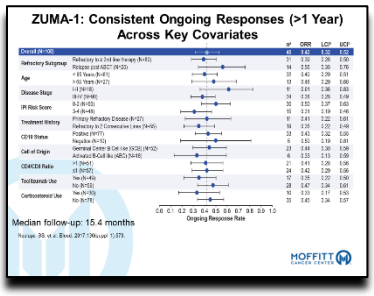
So just to kind of give you an idea of the baseline characteristics. Fifty-eight years old median age. About 35% of patients were older than 65. Majority of the patients had a stage III or IV. Majority of the patients had an IPI score of 3 and 4. They have several lines of therapy, 70% of patients had more than three lines of therapy, and 70% of patients were refractory to the last-line therapy. And about 23% of patients were refractory to or were relapse post-transplantation. So, basically, a very poor prognostic patient in which the expected survival was about 6 months with more chemotherapy.



Slide 29 – ZUMA-1: Objective Response

And just to show like the primary analysis and updated analysis of responses, the objective response, which was the primary endpoint of the study, was 82%, the best response. At the last follow-up was 58% with complete remission of 40%.

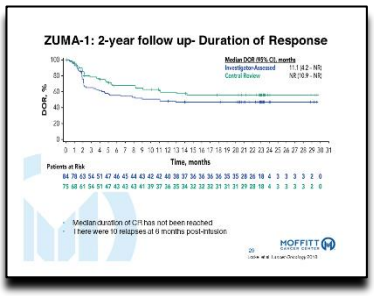
Just to kind of mention in the updated analysis, about 23 patients with PR and stable disease at the first tumor assessment at day 30, they actually converted into CR up to 15 months post-infusion without additional therapy. So even patients who had stable disease, or had partial remission, they eventually achieve a complete remission later on.



Slide 30 – ZUMA-1: Consistent Ongoing Responses (>1 Year) Across Key Covariates

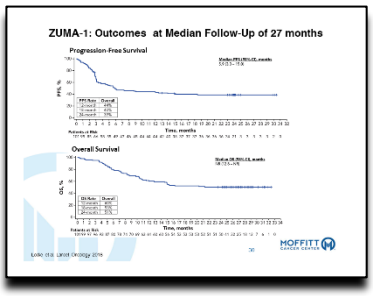
The responses in the ZUMA-1 were consistent with several covariates, like there was no differences whether the patient was refractory or relapsed post-transplant, whether patients were younger or older than 65, whether they had a high or low IPI score. There was no difference in the treatment history, like the number of lines of therapies. CD19 status again, you know, there were a few patients who were CD19-negative, but they also responded. There were concerns also about the use of steroids to treat the toxicity; however, there was no difference in terms of response.

So pretty consistent with the key variables and key factors in patients with refractory diffuse large B-cell lymphoma.



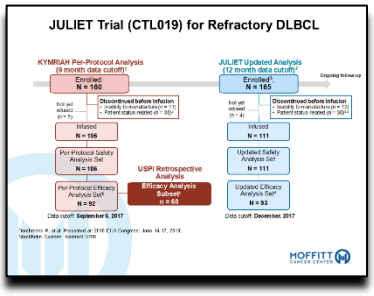
Slide 31 – ZUMA-1: 2-year follow up- Duration of Response

In this slide I'm showing the two-year follow-up of the ZUMA-1, clinical trial. The median follow-up was about 27 months. And as we see, is there is a median duration of response on these patients' high-risk patients were about 11.1 months. The median duration of patients who achieved CR has not been reached actually. However, there were ten relapses after six months post infusions of CAR T-cell.



Slide 32 – ZUMA-1 Outcomes at Median Follow-Up of 27 months

In this slide I'm showing the progression-free survival and overall survival. The PFS was about 5.9 months with a 24-month PFS of 39%. And the overall survival was not reached with a 24-month overall survival of 51%.

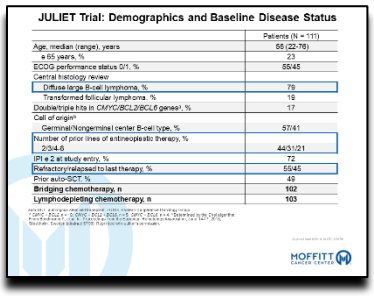


Slide 33 – JULIET Trial (CTL019) for Refractory DLBCL

So, the JULIET clinical trial, the CTL019, is the Novartis trial developed with the University of Pennsylvania, also recently presented their results updated results at the European Hematology Association meeting in 2018. There is also an updated analysis and per-protocol analysis. There were some key differences between the JULIET and the ZUMA-1.

What I'm going to present here is the efficacy analysis based on the patients that had evaluation prior to CAR T-cell infusion. So, I'm going to explain.

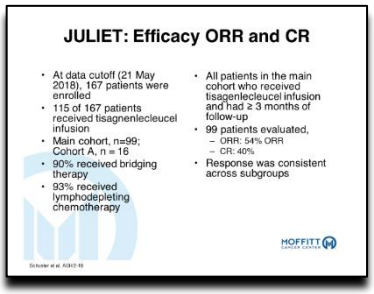
So, the JULIET trial allowed patients to receive bridging chemotherapy because of the time that it took to manufacture the CAR T-cells, a little bit over 3 weeks. So, bridging chemotherapy was allowed in this study. In order to get approval by the FDA, the FDA requested the subset of patients to be analyzed, the 68 patients who had imaging evaluation post-bridging chemotherapy and prior to the combination chemotherapy and CAR T-cell infusion. So, these subset analyses include the 68 patients who had proven disease recurrence prior to CAR T-cell infusion.



Slide 34 – JULIET Trial: Demographics and Baseline Disease Status

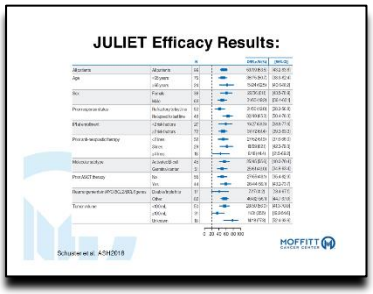
So, for the total patients, they're pretty much similar. Median age, 56 years. Majority of the patients had diffuse large B-cell lymphoma, but transformed follicular lymphoma were included too. There no patients with primary mediastinal large B-cell lymphoma. About 17% of patients were double-hit lymphoma. Patients who had bridging chemotherapy, 102. And patients who had lymphodepleting chemotherapy, 103.

This trial didn't mandate for bridging chemotherapy. It was basically depending on the absolute lymphocyte count that the patient had, but the majority of the patients ended up having lymphodepleting chemotherapy.



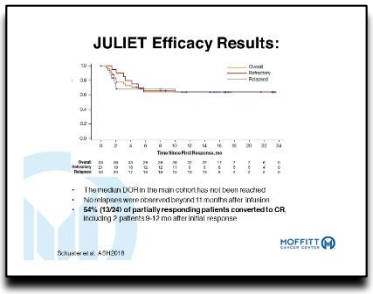
Slide 35 – JULIET: Efficacy ORR and CR

In this slide, I'm showing the efficacy in regards of overall response rate on CR of the JULIET study, last presented in ASCO 2018. The date cutoff of May 2018, 167 patients were enrolled already. 115 of those 167 patients received CAR T-cell infusion, 90% received bridging therapy and 93% received lymphodepleting chemotherapy. There were 99 patients who were evaluable by the time this study was presented, and the overall response rate was 54%, CR rate 40%. And response was consistent across subgroups.



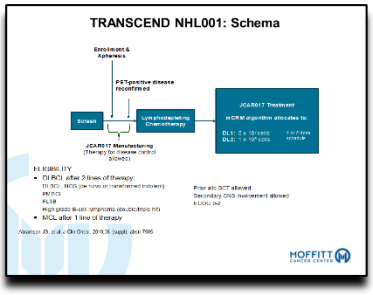
Slide 36 – JULIET: Efficacy Results

In this slide I'm showing the covariates of the JULIET study in regards of CAR T-cell response. And as you see there was no difference in terms of response in regards of age, gender, of prior response studies whether a patient have refractory disease or relapse with last line therapy, IPS score at the time of enrollment and molecular subtype whether a patient have ABC or GCV subtypes or whether the patient has prior autologous stem cell transplantation.



Slide 37 – JULIET: Efficacy Results

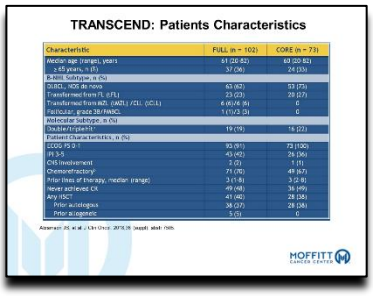
In this slide, I am showing the median duration of response of the JULIET study that was not reached in the main cohort of patients who were evaluable. There was no difference whether the patient had refractory disease or lymphoma or relapsed disease. As mentioned before, about 50% of patients who had a PR they later converted into complete response, and about two patients achieved CR after 9 to 12 months from initial response assessment. There were no relapses observed beyond 11 months after infusion.



Slide 38 – TRANSCEND NHL001: Schema

This is the last trial I'm going to talk about is the TRANSCEND NHL001, which is a JCAR017, 4-1BB with 1:1 CD4, CD8 selection. So, this was a clinical trial also focusing on diffuse large B-cell lymphoma after at least 2 lines of therapy, including transformed from indolent lymphoma or de novo, included primary mediastinal large B-cell lymphoma, included high grade B-cell lymphoma, double-hit lymphoma, and even included also mantle cell lymphoma after 1 line of therapy.

So, the initial trial actually included 2 dose levels, dose number 1 and dose number 2, and there was a subset of patients, a subset cohort that had 2 doses, actually.

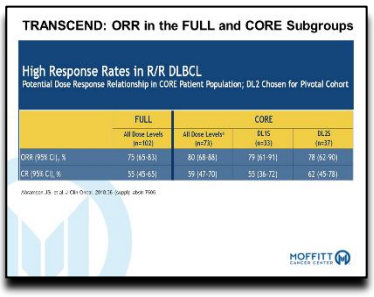


Slide 39 – TRANSCEND: Patient Characteristics

So, what I'm going to focus basically is the CORE subgroup. The CORE subgroup includes patients with diffuse large B-cell lymphoma and transformed follicular lymphoma. The FULL subgroup includes all the other subtypes, all the other types of transformed lymphomas from other indolent lymphomas. But the CORE subgroup included, basically, the target patient, the diffuse large B-cell lymphoma and transformed from follicular lymphoma.

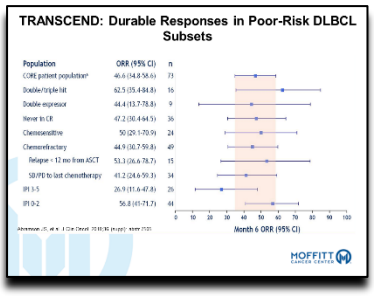
The median age was 60 years old. Thirty percent of patients were older than 65. About 22% of patients had double-/triple-hit lymphoma, and the IPI score was high, 3 to 5 in 36% of patients.

A few patients had a history of CNS involvement. 67% of patients were chemorefractory, so no response to that treatment. The medium number of prior lines of therapy was three. Patients who had primary refractory disease were 49%. Patients who had prior autologous transplant were about 40% of cases.



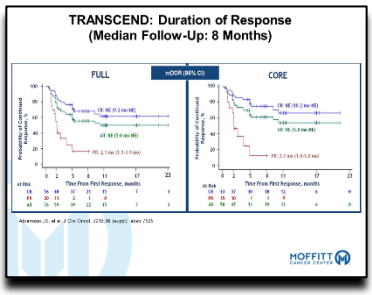
Slide 40 – TRANSCEND: ORR in the FULL and CORE Subgroups

So high response rate, the best overall response at all dose levels was 80% with CR rates at 59, with a median follow-up of about 8 months.



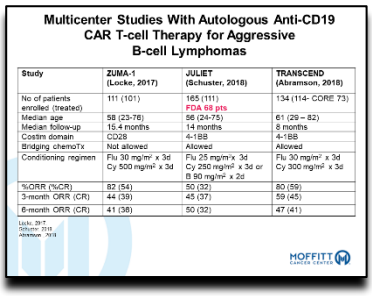
Slide 41 – TRANSCEND: Durable Responses in Poor-Risk DLBCL Subsets

Again, just to show the durable responses independent of covariates similar responses in patients that had double-hit or triple-hit lymphomas, double expressor lymphomas, patients who never had or primary refractory disease, patients who had transplants or, regardless of the IPI score, there was similar responses in these population of patients.



Slide 42 – TRANSCEND: Duration of Response (Median Follow-Up: 8 Months)

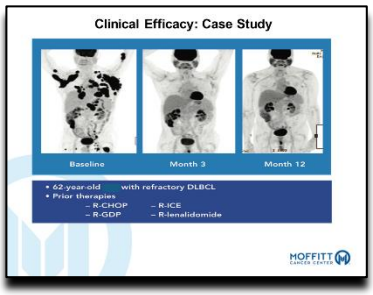
The duration of response, again, in patients who had CR, was not reached. In patients who had PR, the main duration of response was about 2 months. So, again, patients that had CR, had better outcomes in this study.



Slide 43 – Multicenter Studies With Autologous Anti-CD19 CAR T-Cell Therapy for Aggressive B-Cell Lymphomas

So, this is just to summarize all the studies. Basically, similar median age. A little longer follow-up with the ZUMA-1 than the other studies. The costimulatory, we talked about the differences within costimulators. Bridging chemotherapy, only ZUMA-1 didn't allow bridging chemotherapy. JULIET and TRANSCEND, they allowed bridging chemotherapy.

Conditioning chemotherapy was similar across the study with the lowest modifications in the doses. The overall response rate, the key thing here is the 6-month overall response rate. And there's always the question, which one is more efficacious than the other one? They're not comparable. I think they're all efficacious. They all have some differences in terms of patient population and whether patients have autotransplant or CNS involvement. So, it's going to be difficult to conclude that one probably is better than the other, and at the end, what matters is the experience of the physician of the cancer center in order to decide which product we have to choose.



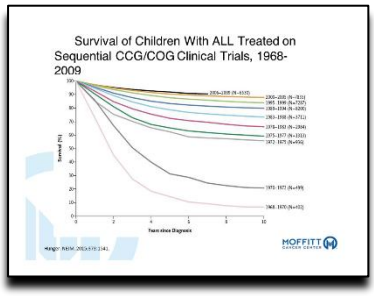
Slide 44 – Clinical Efficacy: Case Study

Just to kind of show you like a case study, here's actually one of our patients, as you see on the left-hand side, disseminated disease with even bone disease, diffuse large B-cell lymphoma patient that's 62 years old. A male patient, the typical patient who was in the study. He had R-CHOP, was refractory to R-CHOP, then went into R-ICE, no response. R-GDP, no response, and he was on a fourth-line therapy, lenalidomide.

As we said, in these patients, the chance of response to the next therapy is probably about 20% and survival was 6 months. However, you know, at month 12 still the patient is showing ongoing response.

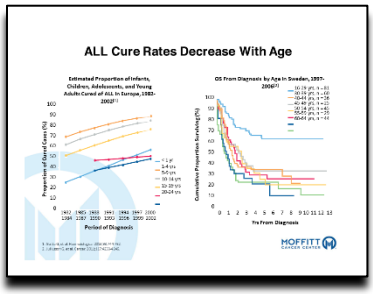
Slide 45 – CAR T-cell therapy in pediatric B-ALL

Now we're going to talk a little bit about CAR T-cell therapy in pediatric, B-cell acute lymphoblastic leukemia.



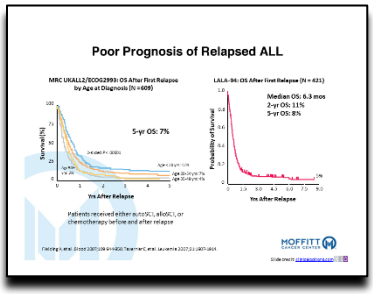
Slide 46 – Survival of Children With ALL Treated on Sequential CCG/COG Clinical Trials, 1968-2009

This shows the survival of children treated with several protocols from the Children's Oncology Group, from the late '60s until late 2000. And basically, as the figure shows there has been an, improvement in survival in the last four years in patients with acute lymphoblastic, leukemia as now majority of patients are being cured, with the current regimens as opposed of the early treatment regimens.



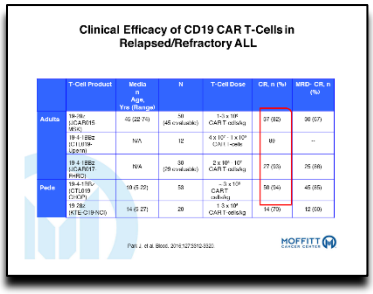
Slide 47 – ALL Cure Rates Decrease With Age

In this slide, basically on the left-hand side, we see that majority of patients with ALL occurs in children, adolescents, and young adults. However, it can also occur in older patients as we see in a better prognosis, we see in the pediatric population than in all those elderly patients.



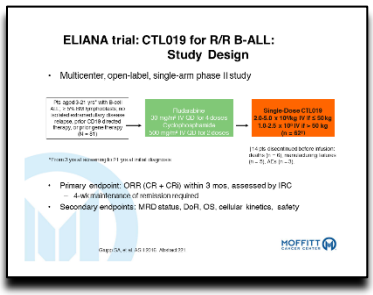
Slide 48 – Poor Prognosis of Relapsed ALL

Despite improvement in the treatment of ALL in pediatric patients, there is still relapses. And unfortunately, these patients who relapse have a poor prognosis with a five-years overall survival of 7% or 8% depending of the protocol used. And, therefore, there is an unmet need in pediatric patients with ALL that relapse after frontline chemotherapy.



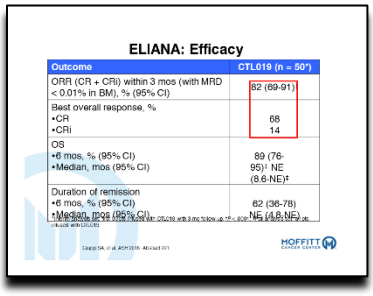
Slide 49 – Clinical Efficacy of CD19 CAR T-Cells in Relapsed/Refractory ALL

In the clinical efficacy of anti-CD19, CAR T-cell has been studied in refractory/relapsed ALL and in this table, I show several studies done in all those in pediatric patients. And as you see the responses have been remarkable with CR rates within 70% to 94%, including an MRD negative study from patients who were evaluable. Some patients who had up to 80% of MRD negativity three months from this step.



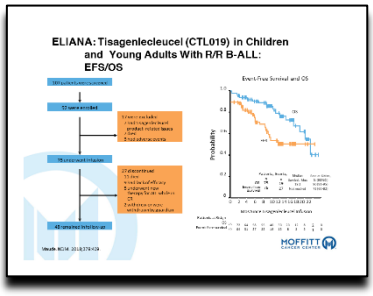
Slide 50 – ELIANA trial: CTL019 for R/R B-ALL: Study Design

ELIANA trial. Given the promising results of the CAR T-cell therapy in early studies in ALL the ELIANA trial was conducted. The ELIANA trial is a Phase II large study, multicenter, open label that includes patients from 3 to 21 years old with B-cell acute lymphoblastic leukemia. They had to have at least 5% of bone marrow lymphoblast, no extramedullary disease, and no prior CD19-directed therapy. So patients received conditioning chemotherapy with fludarabine and cyclophosphamide and received a single dose of CTL CD19 and the CAR T-cell from the University of Pennsylvania about 2 billion cells per kilogram in less than 50kg of weight and 1 to 2.5 million, IV on patients who had more than 50 kilos of weight. The primary endpoint of the study was overall response rate, CR rates. And within three months, secondary endpoint was MRD status, duration of response overall survival, and safety.



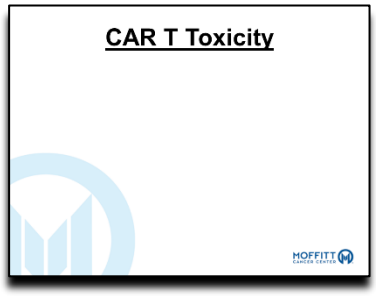
Slide 51 – ELIANA: Efficacy

ELIANA trial efficacy. The results were remarkable as in the initial report presented at ASH 2016. In the first 50 patients in the study, there was an overall response rate of 82% within three months from infusion, including MRD negative status in these patients. The overall survival at six months was 89% and the duration of remission the six-month duration of remission was 52%.



Slide 52 – ELIANA: Tisagenlecleucel (CTL019) in Children and Young Adults With R/R B-ALL: EFS/OS

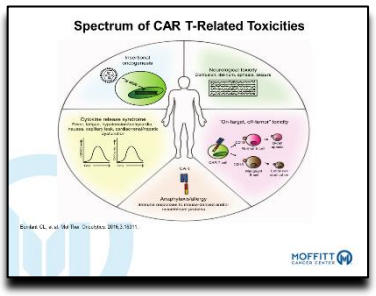
Here we show the long-term follow-up of patients in the ELIANA trial. At the time of that this study was published, 92 patients were already enrolled, and 75 patients underwent infusion and about 48 patients remained in long-term follow-up just to show that the overall survival was 19.1 months and the estimated, event-free survival was not reached. The six-month overall survival was 90% and the six-month EFS was 73%.



Slide 53 – CAR T Toxicity

Now we're going to move on into the CAR T-cell therapy, and Ms. Lundberg is going to talk about this.

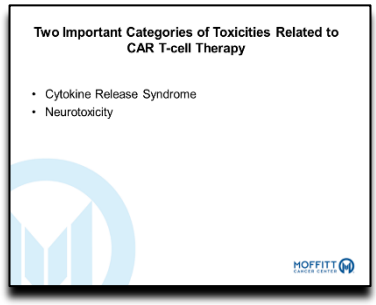
Rachel Lundberg, PA: So, while we've seen that the CAR T-cell therapy is offering really promising results in terms of options for these high-risk populations, it doesn't come without its own serious risk of side effects and morbidity and mortality, which I'll touch upon here.



Slide 54 – Spectrum of CAR T–Related Toxicities

The spectrum of CAR T–related toxicity ranges from what we see almost immediately with infusion in terms of anaphylaxis or allergy to the mouse-derived proteins within the CAR T-cell itself, to things that happen shortly afterwards, including cytokine release syndrome, which is a clinical syndrome where the CAR T-cells themselves interact with the tumor cells and release inflammatory proteins that cause fever, fatigue, hypotension, and tachycardia, as well as another clinical spectrum of disease.

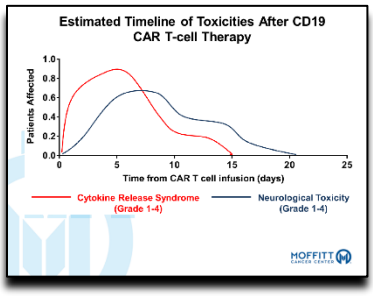
Neurologic toxicities are also very common and range from confusion, delirium, aphasia, and seizure. Later on, in the course of CAR T-cell therapy, we see off-tumor targeted toxicities where these CAR T-cells do attack cells with the CD19 antigen, which can be normal B-cells and lead to B-cell aplasia, which increases the risk of infection, as well as an additional oncogenesis leading to the risk of secondary malignancy.



Slide 55 – Two Important Categories of Toxicities Related to CAR T-Cell Therapy

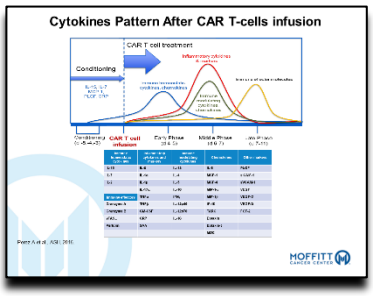
The two most common seen most readily are the cytokine release syndrome and neurotoxicity.

Transcript



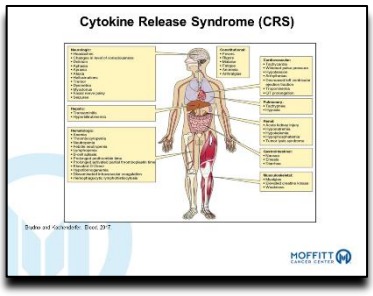
Slide 56 – Estimated Timeline of Toxicities After CD19 CAR T-Cell Therapy

When we correlate the timing of these syndromes, cytokine release syndrome typically happens within the first 24 to 48 hours of CAR T-cell infusion and can last anywhere from the two weeks. Neurologic toxicity tends to occur a little bit later and lasts really within the first 30 days of cell therapy, although it can be seen even later than that.



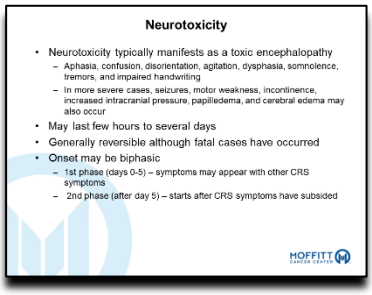
Slide 57 – Cytokines: Pattern After CAR-T Cell Infusion

These syndromes correlate very closely to inflammatory cytokines and markers that are released into this system with CAR T-cell therapy, specifically, these inflammatory cytokines such as IL-6, IL-1A. And those peaks, like we saw in the slide before, around day 5 or 6 after cell therapy.



Slide 58 – Cytokine Release Syndrome (CRS)

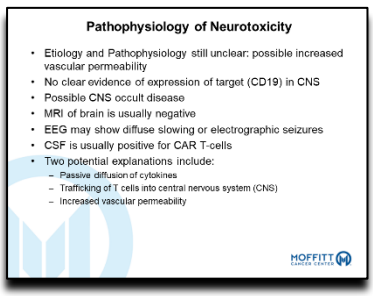
So, again, cytokine release syndrome, what we typically see clinically are high fevers, low blood pressure, tachycardia, and rigors. But it can include hepatic dysfunction, cardiac dysfunction, pulmonary dysfunction.



Slide 59 – Neurotoxicity

The neurologic toxicity typically clinically manifests as encephalopathy. We see any clinical syndromes from something as mild as a tremor to word-finding difficulty. In most severe cases we have seen patients with coma, cerebral edema, and increase in intracranial pressure. This can last several hours, and in our worst cases have lasted a few months. And, unfortunately, there have been irreversible cases with fatalities involved.

Initially, this can be related to cytokine release syndrome itself, but there seems to be a biphasic occurrence where it is seen after the symptoms of CRS have resolved by a different pathway.

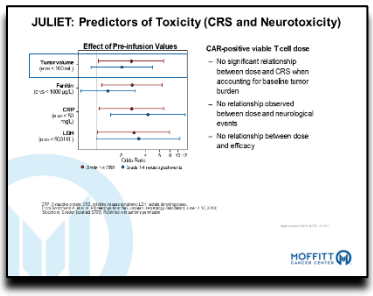


Slide 60 – Pathophysiology of Neurotoxicity

The pathophysiology of neurotoxicity is not as well understood as that of CRS. There are two main hypotheses, whether this is, the passive diffusion is cytokine or actually trafficking of those T-cells into the central nervous system. When we get MRIs of the brain, it is usually negative, although we do sometimes see an autoimmune encephalitis picture.

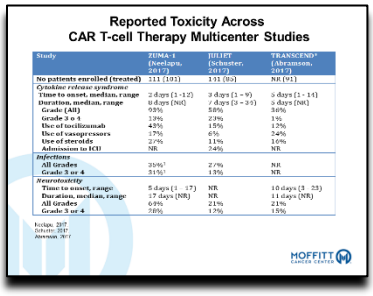
EEG shows diffuse slowing or may show evidence of seizures. And CSF is usually positive for CAR T-cells. In severe instances, the pressure of CSF is elevated, indicating cerebral edema.

Transcript



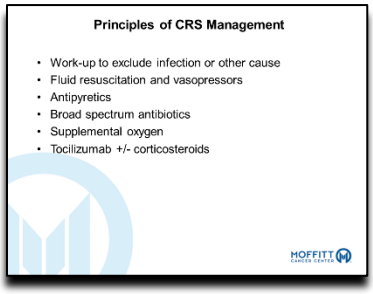
Slide 61 – JULIET: Predictors of Toxicity (CRS and Neurotoxicity)

In clinical trials, when you looked at what were the predictors of toxicity for both the neurotoxicity, what predisposes patients almost across the board is the amount of tumor volume to the amount of lymphoma a patient has coming in. And their general inflammatory state, which we measure by ferritin, CRP, and LDH, are strong predictors of their chances of CRS and neurotoxicity. Interestingly, the dose of CAR T-cell therapy was not at all correlated with the incidence of CRS or neurotoxicity.



Slide 62 – Reported Toxicity Across CAR T-Cell Therapy Multicenter Studies

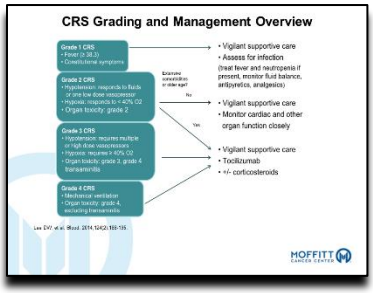
When we looked across the board at the major trials ZUMA-1, JULIET, and TRANSCEND, the trials that led to the products we just mentioned, there were some differences in grades and incidence of CRS, as well as neurotoxicity. Although what's important to remember here is that each clinical trial has a different reporting system, and so it is difficult to say if there's going to be one product that is more likely to cause these syndromes than other.



Slide 63 – Principles of CRS Management

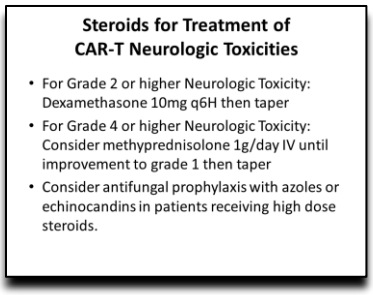
When a patient develops CRS, it's important to exclude infection. Typically, we do treat these patients for neutropenic fever and treat with fluid resuscitation, antipyretics, and broad-spectrum antibiotics.

Tocilizumab (Actemra®) is an IL-6 receptor antagonist which can shut down the process of CRS, and it's indicated for grades 3 to 4 CRS. And in those instances, we also consider high-dose steroids.



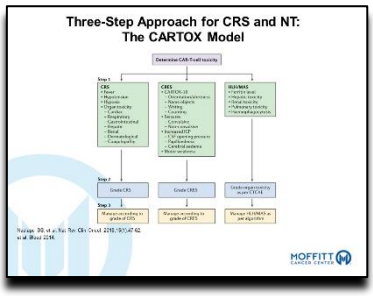
Slide 64 – CRS Grading and Management Overview

It's important to grade these because it determines our clinical management. Anything that is responsive to antipyretics and fluid is graded as a 1 or a 2. But after those measures are no longer successful, we consider tocilizumab



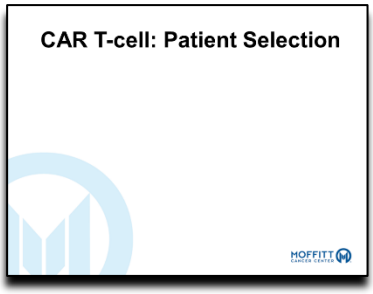
Slide 65 – Steroids for Treatment of CAR-T Neurologic Toxicities

And steroids because those are automatically grade 3 or grade 4 toxicities.



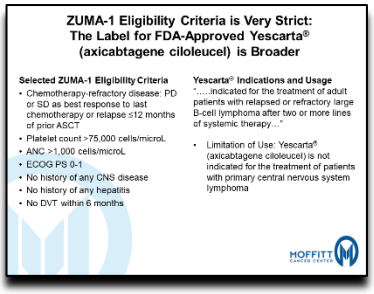
Slide 66 – Three-Step Approach for CRS and NT: The CARTOX Model

And this is another algorithm that can help us kind of determine how to manage both CRS and neuroepileptic toxicity.



Slide 67 – CAR T-Cell: Patient Selection

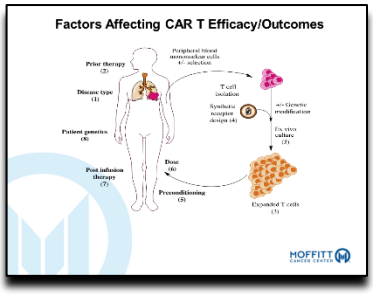
Given those risks for severe side effects and morbidity and mortality, one of the most important processes in our practice is determining which patients are going to benefit from this therapy the most and not be subject to any adverse events.



Slide 68 – ZUMA-1 Eligibility Criteria Is Very Strict; The Label for FDA-Approved Yescarta® (axicabtagene ciloleucel) Is Broader

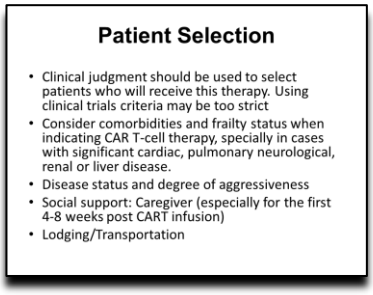
The ZUMA-1 clinical trial gave us pretty strict criteria in trying to decipher this. Patients had to have chemotherapy-refractory disease. They had to have adequate bone marrow functioning, adequate end-organ disease, and no evidence of CNS disease.

When Yescarta® (axicabtagene ciloleucel) was approved, based on the ZUMA-1 criteria, the eligibility was then not nearly as strict and left the door a little bit open for interpretation. Essentially, the only indication for Yescarta® (axicabtagene ciloleucel) is that a patient must have diffuse large B-cell lymphoma and be refractory to two or more lines of systemic therapy without evidence of CNS disease.



Slide 69 – Factors Affecting CAR-T Efficacy/Outcomes

So, when we were trying to decide who this therapy is best for, there's a lot of factors that go into determining both the efficacy and the outcomes, as well as some of the side effects of the therapy. Of course, the patient's genetics, disease type, and prior therapy and many factors kind of outside of their control related to the T-cell genetic modification and the expansion of those T-cells and the preconditioning, the dose of the T-cells, and the therapy they receive afterwards.

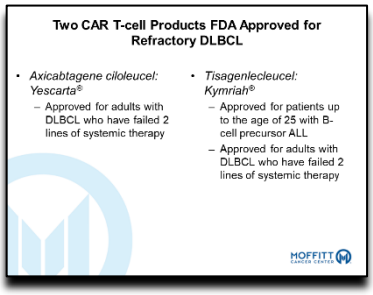


Slide 70 – Patient Selection

Taking all of this into consideration, it really just comes down to clinical judgment in terms of which patients are going to receive this therapy and benefit the most from it. Our clinical trial criteria at this point might be a little too strict in terms of looking at patients who might benefit from this therapy.

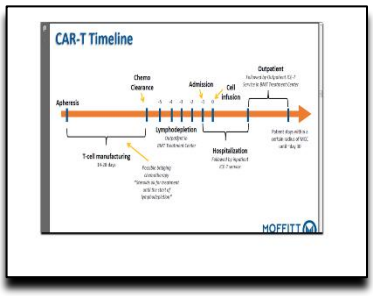
One thing that we do consider very important because of the intensity of this procedure is that patients have good social support, that they have a caregiver who's available to stay with them for the first 4 to 8 weeks after CAR T-cell infusion, and that they're able to stay within a local radius of our institution. Our

social workers work with each patient to help organize local lodging and transportation so that they have access to our facility.



Slide 71 – Two CAR T-Cell Products FDA-Approved for Refractory DLBCL

There are currently two CAR T-cell products that are FDA-approved for refractory diffuse large B-cell lymphoma and B-cell precursor ALL. Axicabtagene ciloleucel or Yescarta® was approved in the fall of 2017 and was based on the ZUMA-1 trial. This is approved for adults with diffuse large B-cell lymphoma who have failed two systemic lines of therapy, again, without evidence of CNS disease. Tisagenlecleucel or Kymriah® was approved the spring of 2018, and it has two indications, for diffuse large B-cell lymphoma but also for patients up to the age of 25 with ALL.

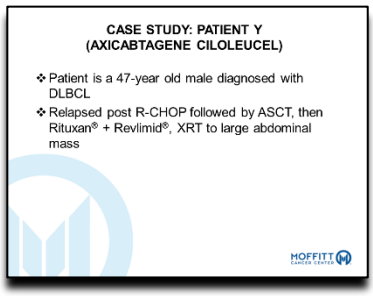


Slide 72 – CAR T Timeline

In terms of the patient timeline, a patient will come to us and undergo T-cell collection by a process of apheresis. Those T-cells then go to a lab and are manufactured for an average of 14 to 28 days. Our average here at Moffitt is 17 days until T-cell manufacturing.

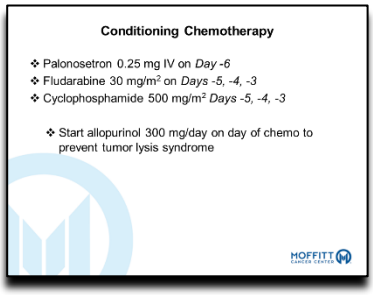
During that time, we often treat patients with bridging chemotherapy in order to stabilize their disease right before they come forward for their therapy. They then receive outpatient lymphodepleting chemotherapy, usually fludarabine and cyclophosphamide for 3 days, and then are admitted on the day prior to their cell infusion.

The hospitalization averages about 2 weeks, and then we do ask our patients to stay for 2 weeks following infusion for frequent outpatient follow-up to monitor labs as patients frequently stay pancytopenic up to and sometimes past day 30.



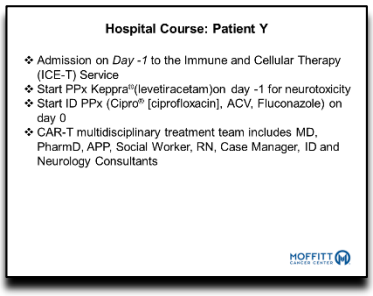
Slide 73 – Case Study: Patient Y (axicabtagene ciloleucel)

This is a brief case study of one of our first patients to receive commercial Yescarta® or axicabtagene ciloleucel. He is a 47-year-old man with diffuse large B-cell lymphoma that had been refractory to prior lines of therapy. He was treated with upfront R-CHOP, followed by consolidated stem cell transplant, then with rituximab (Rituxan®) and Revlimid® (lenalidomide) and radiation to a large abdominal mass.



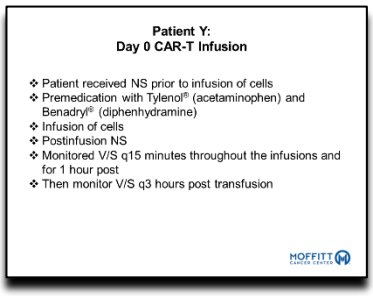
Slide 74 – Conditioning Chemotherapy

He received standard chemo, conditioning chemotherapy with fludarabine and cyclophosphamide. We also treat with a long-acting antiemetic and allopurinol to prevent tumor lysis syndrome.



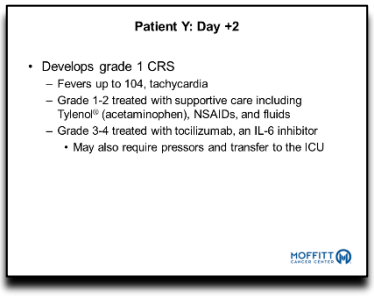
Slide 75 – Hospital Course: Patient Y

He was admitted on day -1 to our inpatient ICE-T service and was started on prophylactic Keppra® (levetiracetam) and prophylactic anti-infective, including Cipro® (ciprofloxacin), acyclovir (Zovirax®), and fluconazole (Diflucan®).



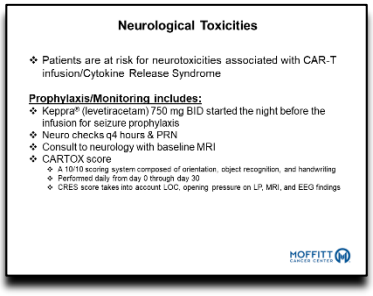
Slide 76 – Patient Y: Day 0 CAR T Infusion

On day 0, he received his genetically modified CAR T-cells. We premedicate with Tylenol® (acetaminophen) and Benadryl® (diphenhydramine) as well as saline and monitor frequently during and after the infusion.



Slide 77 – Patient Y: Day +2

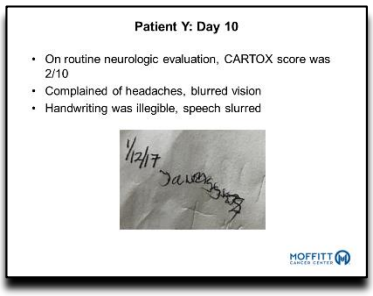
On day +2, he did develop grade 1 cytokine release syndrome with fevers up to 104, tachycardia up to 150. He was treated with alternating Tylenol® (acetaminophen) and NSAIDs every 4 hours and normal saline.



Slide 78 – Neurologic Toxicities

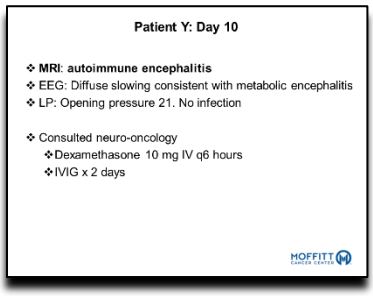
Because patients are at such high risk for neurologic toxicities, we do start everyone on a prophylactic Keppra® (levetiracetam) the night before their infusion. And throughout the course of their hospitalization, have neuro checks every 4 hours.

We also follow a CARTOX score, which is a 10 out of 10 scoring system based on orientation, object recognition, and daily handwriting. This is performed daily from day 0 to day 30. We also have a CRES score that takes into account opening pressure on LP, MRI, and EEG findings.



Slide 79 – Patient Y: Day 10

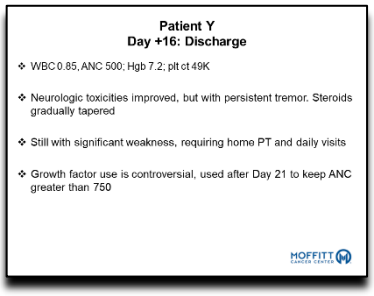
On day 10 our patient did experience significant neurologic toxicity. His CARTOX score was 2 out of 10. He only was oriented to person and place. He complains of headache and blurred vision, and his handwriting was illegible. His intent, he had said, was to say, "I hope today is a better day."



Slide 80 – Patient Y: Day 10

His MRI did show what our radiologist read here as autoimmune encephalitis, and his EEG showed diffuse slowing consistent with metabolic encephalitis. He had an LP, which showed no evidence of infection, but his opening pressure was 21.

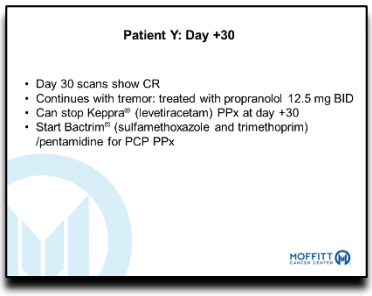
We consulted neuro-oncology and started dexamethasone 10 milligrams IV q6 hours and IVIG for 2 days for this autoimmune component of the encephalitis.



Slide 81 – Patient Y: Day +16 – Discharge

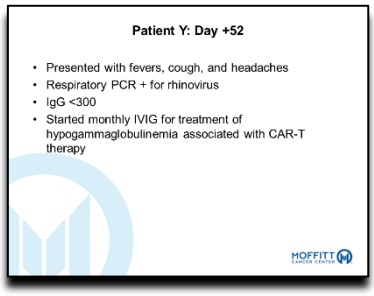
By day 16, his neurologic toxicity had nearly resolved. He had a mild tremor on exam, but his CARTOX score was 10 out of 10, and his handwriting had completely recovered.

He remained pancytopenic, still with significant weakness. But as his ANC was 500, we discharged him to our outpatient program and followed him with daily visits. Growth factor use is controversial. So, at our practice, we typically wait until day 21. And afterwards, aim to keep the ANC greater than 750.



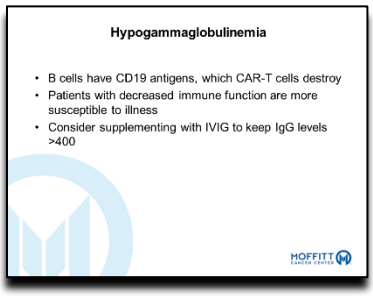
Slide 82 – Patient Y: Day +30

On day 30 the patient returned, and his PET scan showed a CR. He did continue with the mild tremor, which we treated with low-dose propranolol. We stopped his Keppra® (levetiracetam) prophylaxis at day 30, and we start either Bactrim™ (sulfamethoxazole and trimethoprim) or pentamidine (Nebupent®) for PCP prophylaxis for 6 months following therapy.



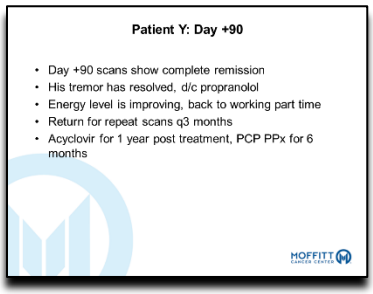
Slide 83 – Patient Y: Day +52

On day 52 the patient returned with fevers, cough, and headaches, and was found to have rhinovirus. We checked his immunoglobulins, and his IgG was less than 300. So, at this point we started him on monthly IVIG for treatment of hypogammaglobulinemia associated with his CAR T therapy.



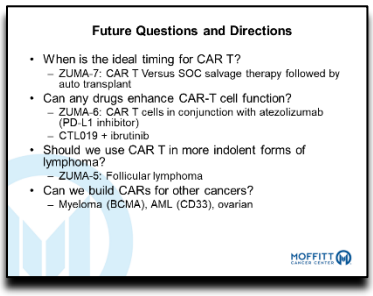
Slide 84 – Hypogammaglobulinemia

As B-cells have CD19 antigen, CAR T-cells can also destroy these and leave patients with decreased immune functions and, that they become more susceptible to illness. So, for these patients, we follow their immunoglobulins and consider supplementing to keep IgG levels greater than 400.



Slide 85 – Patient Y: Day +90

On day 90, or 3 months from therapy, the patient returns for repeat staging, and thankfully his disease is in complete remission. His tremor resolved and he returned to work part time. We keep these patients on acyclovir for 1 year post-therapy and on PCP prophylaxis for 6 months.



Slide 86 – Future Questions and Directions

Dr. Chavez: Thank you, Rachel, for your explanation about CAR T-cell toxicity management. We're glad here at Moffitt Cancer Center that our advanced practitioners have extensive experience with CAR T-cell management and thank you, again, for your input.

So, what are our future questions and directions in regards of CAR T-cell therapy? There are many, so I'll try to summarize this in the simplest slide, but it may not be complete, you know, a question or reactions that may happen in the future years.

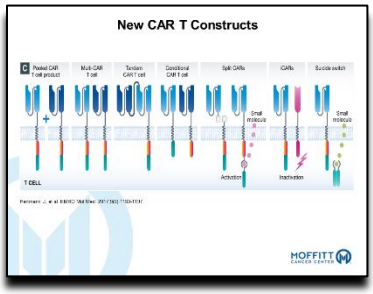
One question is, when what is the ideal timing for CAR T-cell therapy? So far, we know that it's approved for after two lines of therapy. However, are there any benefits on doing it in earlier situations such as when the patient is primary refractory to frontline therapy, whether CAR T-cell therapy is better than the standard of care, autologous transplant.

So, we have trials that are looking at that. One of those is the ZUMA-7, who is comparing CAR T-cell versus stem cell transplantation.

Is there any chance that CAR T-cell function can be enhanced by medications? ZUMA-6 is trying to answer these questions by giving CAR T-cell therapy in conjunction with atezolizumab (Tecentriq®), which is a PD-L1 inhibitor to decrease the T-regulatory cells' effect and also enhance T-cell cytotoxicity. CTL019, Novartis is studying the efficacy of ibrutinib in combination with CAR T-cell therapy.

The next question is, should we use CAR T in other types of lymphomas? As I said, so far, it's approved for aggressive lymphoma. It's not approved for other type of lymphomas like follicular lymphoma or mantle cell lymphoma or marginal zone lymphoma. The ZUMA-5 is trying to answer the question with follicular lymphoma. There are trials for marginal zone lymphomas and also mantle cell lymphoma.

Can we build CAR T-cells for other cancers? And the answer is, there are trials ongoing for multiple myeloma, acute myeloid leukemia, and ovarian cancer as sponsored studies and also investigator-initiated trials.



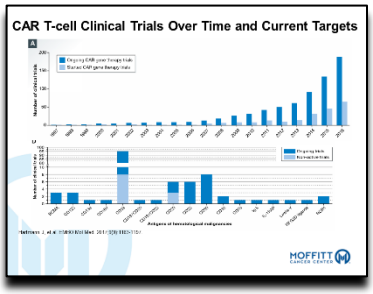
Slide 87 – New CAR T Constructs

So just to kind of give you a little overview of the new CAR constructs. So, if you remember, the anatomy of the CAR T-cell. These are a little bit different. There are pooled CAR T-cells in which basically patients are treated with two types of CAR T-cells with different targets in the same tumor. There is are the multi CAR T-cell that has a different costimulatory domain. The tandem CAR T-cell is, or we call the bispecific CAR T-cell, basically it's just one CAR T-cell that targets two antigens, which seems to be efficacious at least in the clinical data and a small subset of patients.

The conditional CAR T-cell in which basically one will be shut off if the other doesn't work. The split CAR T-cells that has an activator molecule that activates CAR T-cells as soon as they are actually exposed or attached to the target antigen.

The iCARs or basically the idea is to shut down CAR T-cells when there is excessive toxicity. CAR T-cell is not an easy treatment. There is significant toxicity, and if the hospital or the cancer center doesn't have experience, probably not a good idea to start doing CAR T-cells. There has to be knowledge in treating severe CRS and severe neurotoxicity.

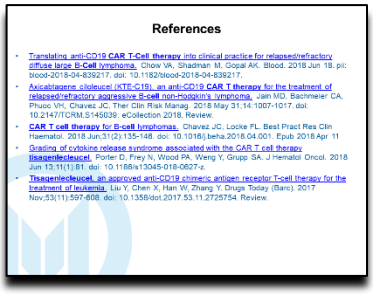
So, these new CAR T-cells are being developed. They either have a switch or gene that will actually shut down or shut off the CAR T-cells that we call the suicide genes.



Slide 88 – CAR T-Cell Clinical Trials Over Time and Current Targets

Since the development of the initial CAR T-cells, there has been an explosion of CAR T-cell trials. There were very few clinical trials in the late '90s and early 2000s. However, this is increasing, concentrating the last few years. There's so much and still ongoing trials and so much in new trials.

Majority of the CAR T-cells are starting to focus on CD19 with combinations and different constructs. However, there are other targets like a BCMA for AML, also for multiple myeloma, CD123 for AML, CD22, CD20 for lymphoma, CD30 for CD30-positive and lymphomas such as Hodgkin and T-cell lymphomas and so on.

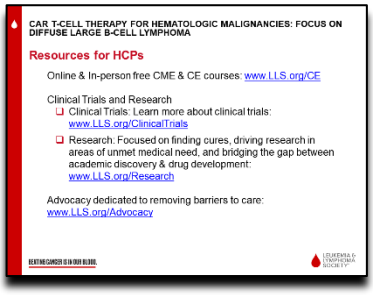


Slide 89 – References

So, these are some of the references we used to develop this slide deck for The Leukemia & Lymphoma Society. Thank you very much.

Slide 90 – Thank You

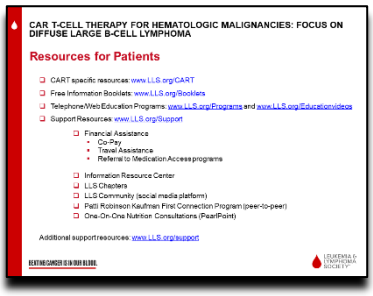
Lauren Berger: Thank you, Dr. Chavez and Ms. Lundberg, for your very clear and informative presentations.



Slide 91 – Resources for HCPs

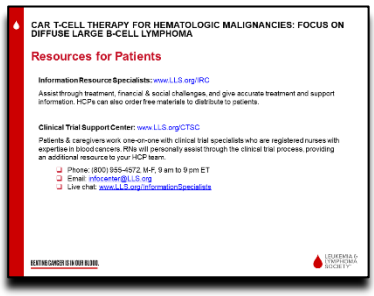
I am now pleased to share resources for healthcare professionals and patients from The Leukemia & Lymphoma Society. Please visit our website to access web based and in-person programs offering free CME and CE credit, Fact Sheets on CAR T-cell Therapy, treatment and support information, research, and other information on blood cancers. To date The Leukemia & Lymphoma Society has invested more than 1.2 billion dollars in cutting edge research. Funding nearly all of today's most promising advances, including CAR T-cell therapy. All these bringing us closer to cures.

Transcript



Slide 92 – Resources for Patients

Resources for patients are listed on this slide and include webinars, videos, and booklets on CAR T-cell Therapy and other treatments for blood cancers, financial assistance, and more.



Slide 93 – Resources for Patients

We encourage you to refer your patients to The Leukemia & Lymphoma Society Information Resource Center to link them with services to supplement the information that you provide. Staffed by Masters Level social workers, nurses, and health educators, they assist patients through cancer treatment, financial and social challenges, and give accurate up-to-date disease, treatment, and support information. Referral to Information Specialist helps patients develop the confidence to ask questions and seek support and information. They can also send quantities of disease treatment and support booklets to your office at no charge or send them directly to your patient.

Slide 94 – Guides, booklets, and Fact sheets

We know that most patients know little about clinical trials and we believe that all patients should learn about all of their options for treatment. LLS Clinal Trial Specialists, who are registered nurses with expertise in blood cancers, provide a personalized service for patients seeking treatment in a clinical trial. They speak with patients to understand their goals, help them decide if a clinical trial is right for the person, search for trials, and provide information to bring to their healthcare team to discuss. These services are complementary to the support you and your team provide. We hope that you will reach out to The Leukemia & Lymphoma Society for these resources and that they are helpful for you.