



Slide 1: Advances in CAR T-Cell Therapy

Lizette Figueroa-Rivera:


Hello everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you. For this program, we would like to acknowledge and thank Bristol Myers Squibb, CRISPR Therapeutics, Kite, a Gilead Company, and Novartis for support of this program.

LLS has played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies, such as CAR T-cell therapy, that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Today, I'm pleased to introduce Dr. Iris Isufi from the Yale Cancer Center/Smilow Cancer Hospital and Yale University School of Medicine in New Haven, Connecticut, who will provide us with an overview of CAR T-cell therapy and discuss which blood cancer indications are utilizing this treatment. Dr. Isufi, I'm privileged to turn the program over to you.


Dr. Iris Isufi:

Thank you very much, Lizette, and thank you to LLS for giving me this opportunity. As Lizette mentioned, I will be speaking to you about advances in CAR T-cell therapy in hematologic malignancies.

 **DISCLOSURES**
Advances in CAR T-cell Therapy

Iris Isufi, MD, has affiliations with Astra Zeneca, Celgene, Kite Pharmaceuticals and Novartis (*Consultant*).

BEATING CANCER IS IN OUR BLOOD.

 LEUKEMIA &
LYMPHOMA
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Slide 2: Disclosures

Dr. Iris Isufi:

I do have some disclosures as outlined in this slide.

Objectives

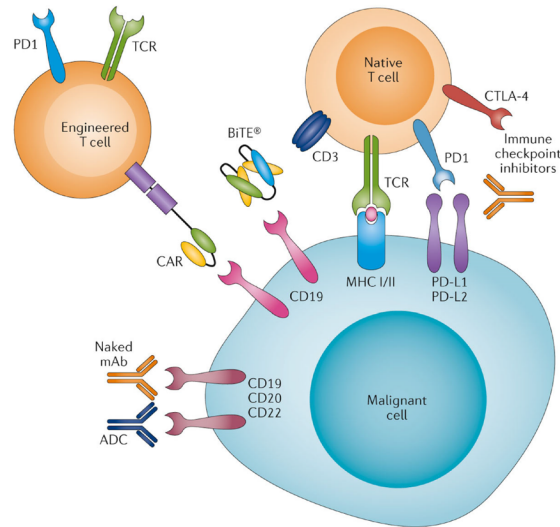
- Why CAR T-cell (chimeric antigen receptor T-cell) therapy shows promise for blood cancers
- Approved and emerging CAR T-cell therapies
- Side effects of CAR T-cell therapy: what to expect
- The future of CAR T-cell therapy for blood cancer patients

Slide 3: Objectives

The objectives of my talk for today are to outline for you how promising CAR T-cell therapy is for blood cancers, to discuss some of the approved therapies for different hematologic malignancies, and some of the exciting emerging new data with novel CAR T-cell therapies. I will also discuss the side effects and what patients and caregivers can expect, as well as what the future holds and the promise of CAR T-cell therapy for blood cancer patients.

Multiple Mechanisms of Modulating Immune System to Treat Cancer

- Monoclonal antibodies or antibody drug conjugates
- Dual antigen re-targeting proteins
- Immune checkpoint antibodies
- Chimeric antigen receptor T cells



Batlevi, C. L. et al, Nat. Rev. Clin. Oncol, 2015

Nature Reviews | Clinical Oncology

Slide 4: Multiple Mechanisms of Modulating Immune System to Treat Cancer

As you know, there are multiple mechanisms of modulating a patient's immune system to treat cancer, and I've outlined here just a few for you. They include antibodies, as shown here which, for example, like CD20 antibodies that directly bind to the cancer cell. Here in blue, I've represented a malignant cell and this can be any type of blood cancer cell, lymphoma, chronic lymphocytic leukemia, ALL, which is acute lymphoblastic leukemia. So, we have monoclonal antibodies that recognize proteins on the surface of the cell and target the cell, the cancer cell, directly.

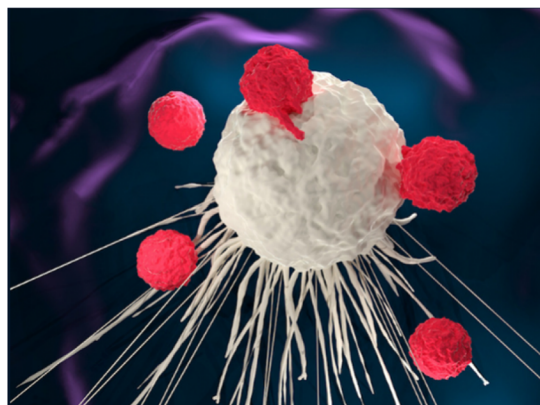
We also have these antibodies here in dark pink that are called dual antigen BiTE® antibodies, because they recognize the protein on the surface of the malignant cell, but they also bind it to a T cell, which is a cell of an immune system, and engage this T cell to come in close contact with a cancer cell and destroy it.

And then in addition to that, we have these drugs called immune checkpoint inhibitors that unleash the patient's own immune system basically. They block these signals that typically inhibit T cells from acting, and they unleash the immune system to target cancer.

However, sometimes T cells, despite all our best efforts, don't recognize the cancer cells or cannot fully destroy them in the body. And in order for us to improve the cancer-killing ability of the T cells, the next step is to genetically alter them. And here is the representation of a genetically altered T cell, and basically these are cells that are generated in a special laboratory. They have special receptors on their surface that are able to recognize the cancer cell and kill it. And these are called chimeric antigen receptor cells. They are cells that are better able to recognize cancer, they become activated, they multiply in large numbers, and they kill the cancer.

What is CAR T-cell therapy?

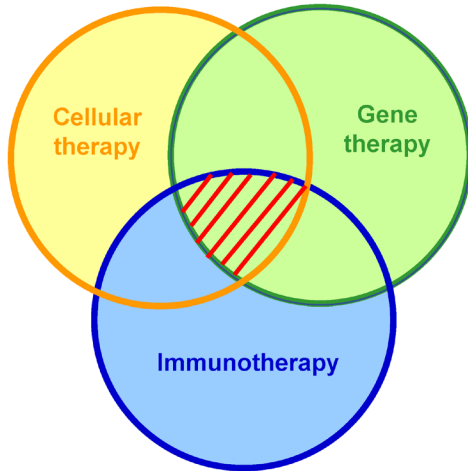
CAR T-cell therapy is a type of cancer therapy that uses a patient's own modified white blood cells to kill cancer cells.



Slide 5: What is CAR T-cell therapy?

So, this is a cancer cell here in white and these are the T cells that are surrounding it, and the type of therapy we're talking about today is basically using a patient's own T cells. We're taking them out of the patient's body and we're modifying them to target the cancer cell.

CAR T-Cells are at The Intersection of Three Innovative Technologies



Cellular therapy

Using the patient's own T- cells as therapy

Gene therapy

Insertion of genes into a patient's cells, thereby causing these cells to produce a new therapeutic protein (CAR)

Immunotherapy

Harnessing the patient's own immune system (T- cells) to treat his/her disease

Slide 6: CAR T-Cells are at The Intersection of Three Innovative Technologies

So, this is a very novel type of therapy and it's actually at the intersection of 3 very innovative technologies. So, we're using cellular therapy, we're using the patient's own T cells to target cancer, we're using gene therapy, we're inserting genes into the patient's T cells, and we're causing these T cells to have a protein on their surface, that's a new therapeutic protein, and that's called the CAR. And then immunotherapy.

Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy

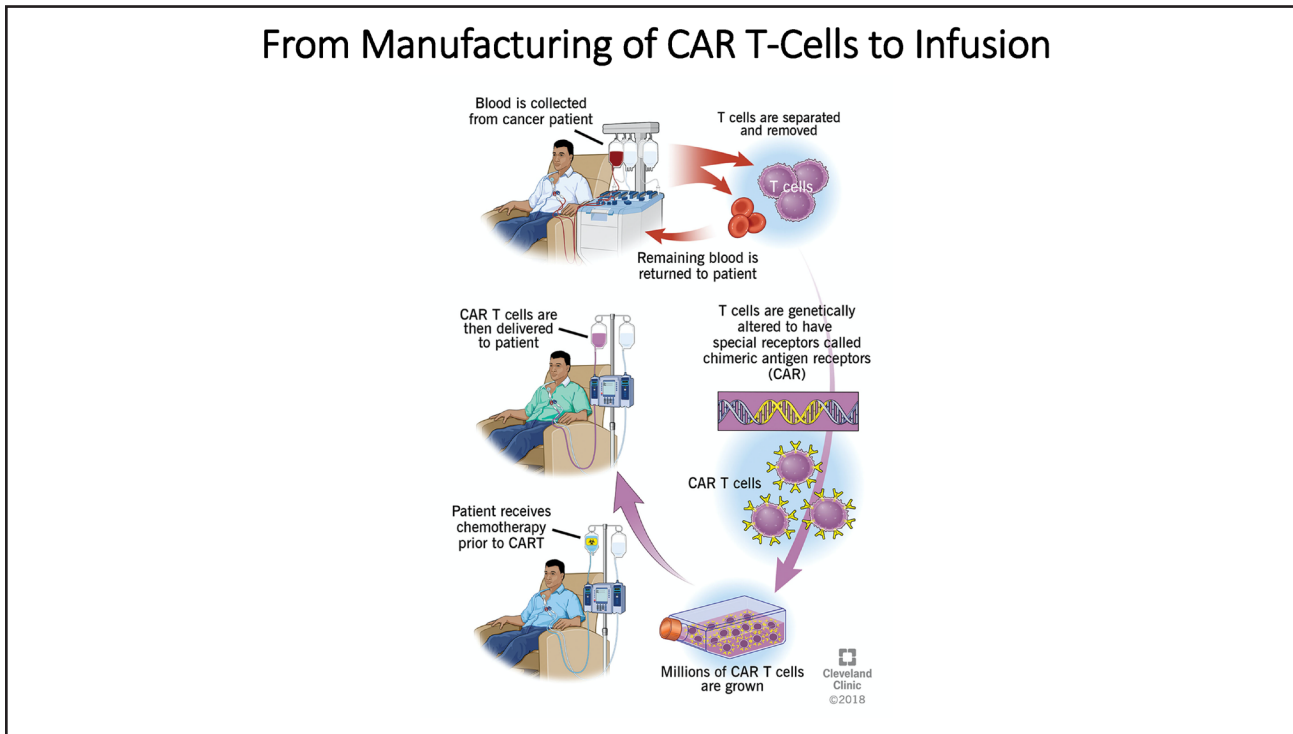
The emergence of CAR-T therapy, like most scientific advances, reflects the incremental insights of hundreds of scientists over decades. Indeed, the story of CAR-T therapy says as much about the methodical nature of scientific progress as it does about the passions that sustain it.

Lisa Rosenbaum, M.D.

N Engl J Med 377;14 nejm.org October 5, 2017

Slide 7: Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy

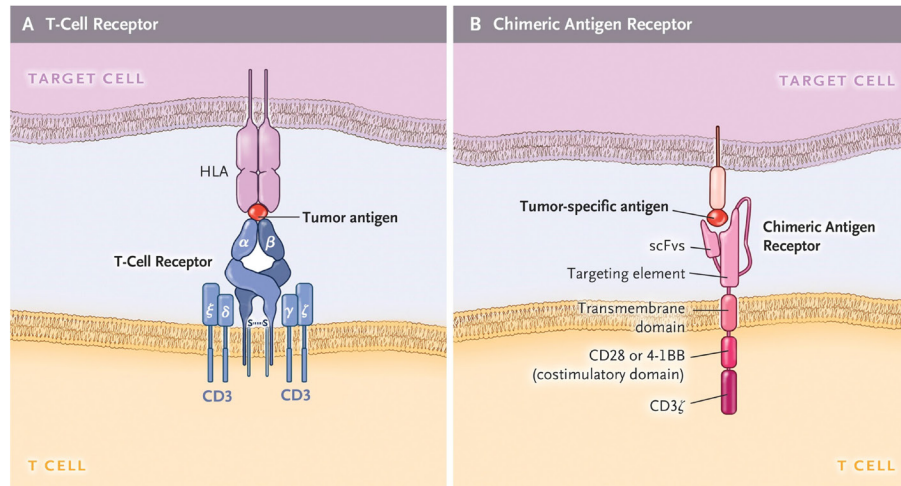
We're harnessing the patient's own immune system basically, the T cells, to treat his or her disease, where under normal circumstances the patient's own immune system was not able to recognize the tumor cell and kill it.



Slide 8: From Manufacturing of CAR T-Cells to Infusion

So how do we do this? So, we collect the blood from the patient with cancer. During this process, the T cells are separated, they're removed from the blood, and the remaining blood is returned to the body. This procedure is called leukapheresis or apheresis is the other term you may have heard, and it's basically very similar to the process of giving certain types of blood donations. And T cells, which are a type of the white blood cell of the immune system, are the body's primary killing cells. And they protect the body by destroying cancer cells. So those are the cells that we're trying to isolate. They get modified in the lab and then in a few weeks' time, they get sent back to us. We give the patient some chemotherapy and that's called the conditioning chemotherapy, to allow enough room for the new T cells to come in and multiply. After this chemotherapy, which typically goes on for about 3 days or so, we put the CAR T cells back into the patient, and then we monitor.

Structure of T-Cell Receptors and CAR Modified T-cells



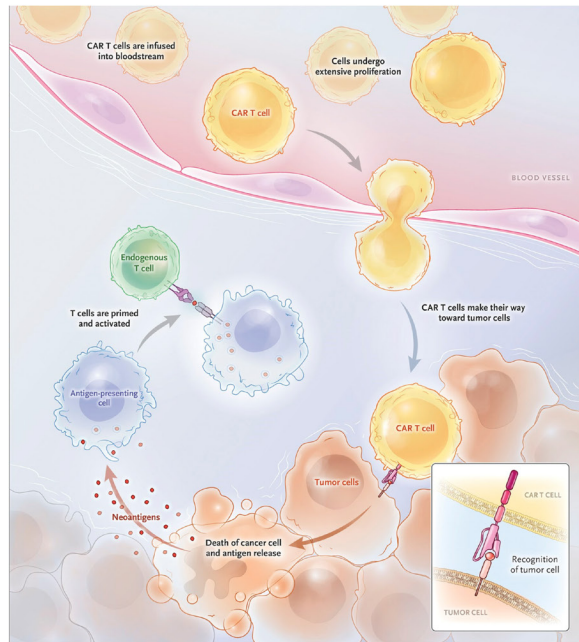
June CH, Sadelain M. N Engl J Med 2018;379:64-73

Slide 9: Structure of T-Cell Receptors and CAR Modified T-cells?

So, on the next slide I want to show you what the structure of these CAR T cells looks like and how they are different from the regular T cell receptors that are on the surface of the cell. So here on the left you have a target cell in purple, which is the cancer cell, the lymphoma or leukemia cell, and then here in yellow there's a T cell, typically a cancer cell will have something in the surface that the immune system, a protein on the surface, that's called an antigen, and that's a tumor antigen, that the T cell receptor on the surface of the T cell is able to recognize and kill the target cell.

However, in order for our own immune system to recognize the tumor antigen, the cancer cell has a protein on the surface called HLA molecule, that presents this antigen, the tumor antigen, to the T cell. And without this HLA molecule the T cell is not able to recognize the antigen. But, cancers are very smart and sometimes they hide this HLA molecule from the surface, so they're not presenting the tumor antigen for the T cells to see. And what this novel technology, CAR T-cell therapy technology has done, is that the chimeric antigen receptor, the CAR that's on the surface of the T cell, is able to recognize this antigen, this tumor-specific protein on the surface of the target cell, even without this HLA protein.

CAR T Cells Traffic to Tumor and Proliferate Extensively after Infusion



June CH, Sadelain M. N Engl J Med 2018;379:64-73

Slide 10: CAR T Cells Traffic to Tumor and Proliferate Extensively after Infusion

And so, what happens in the body is that once these CAR T cells get collected, the patients get chemo, and the CAR T cells get infused. They are to traffic from the bloodstream here, they go out of the blood cell, they go into the tissues, they get confronted with a tumor cell, and they basically get very activated and they start proliferating in large numbers, and they kill the tumor cell. The tumor cell now dies and it releases many of these proteins that the CAR T cells now are able to recognize because they're free and they've come out, they've been released from the tumor cell, and this also activates the body's own T cells that have not been genetically modified, to kill even more cells. And this process is actually called priming. So, these T cells make the chimeric antigen receptor cells proliferate and they also activate the patient's own T cells, which have now been genetically modified to kill even more cancer cells.

Ideal CAR Target

- Tumor specific antigen (Ag)
 - Required for tumor pathogenicity (ability to cause disease)
 - Critical for survival, such that loss of that Ag comes at really high cost for the cancer
- Highly expressed on all tumor cells (cancer stem cells?)
 - Cell surface molecule
- Absent from normal tissue (or where normal tissue is dispensable)
- Absent from T cells (to avoid self killing)

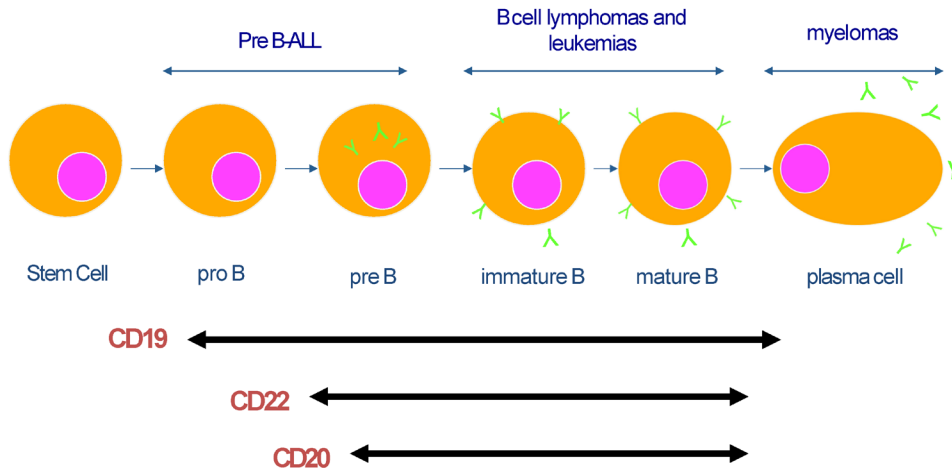
Slide 11: Ideal CAR Target

So, what is an ideal target for this CAR T-cell therapy? Well, ideally we want this antigen, this protein, to be specific to the tumor. And, we have to choose a target that is required basically for the tumor to cause disease, and that is critical for the survival of the cancer cell, so that if we target that antigen, that that really comes at a very high cost for the cancer.

We also want it to be expressed on all tumor cells, going all the way back to stem cells if we can. Ideally, it has to be a molecule that's on the surface of the cancer cell, so that the CAR protein is able to recognize it. And also, if at all possible, it should be absent from normal tissues because we don't want this therapy to be very toxic in parts of the body where we don't intend it to be.

And, we also want this target for the CAR T cells to be absent from our normal T cells, so that the CAR T cells do not kill our own T cells of our own immune system, that are also important to kill cancer, and also to provide immunity.

CD19 as a Target of B-Cell Malignancies

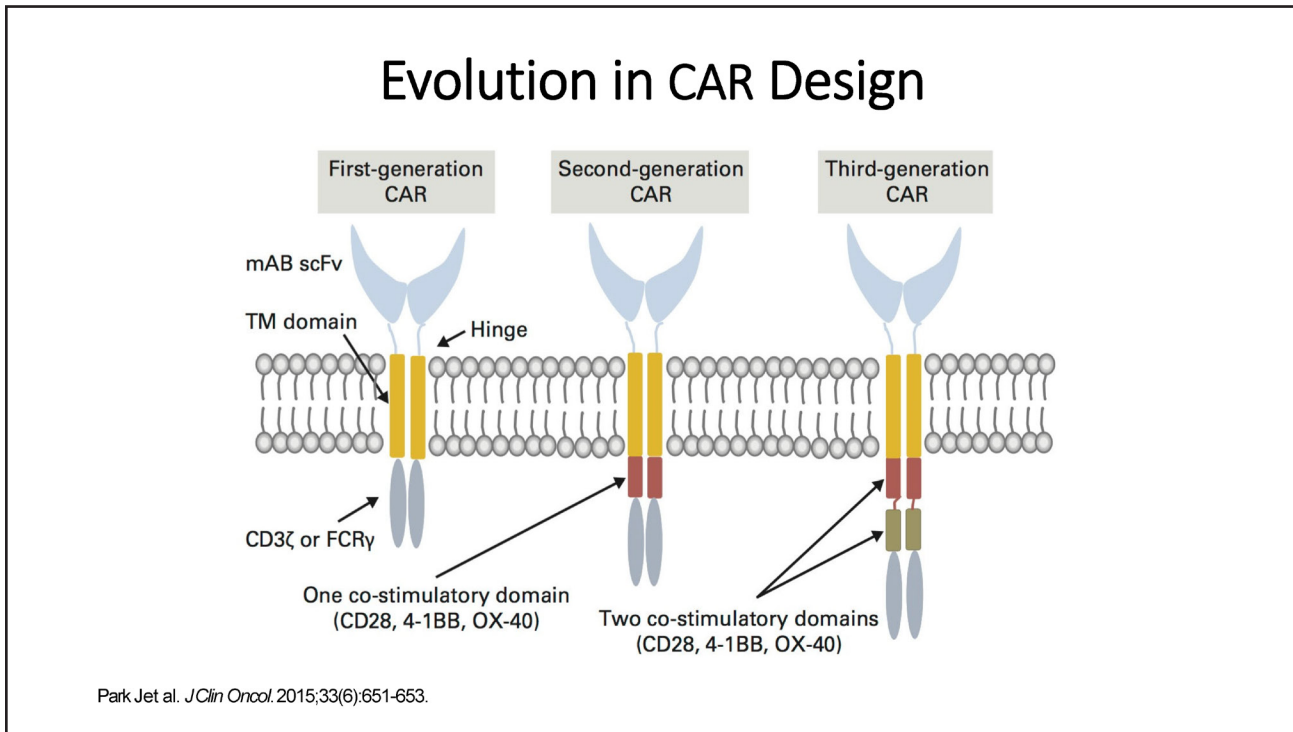


CD19 expression is generally restricted to B cells and B-cell precursors and, importantly, is expressed by most B-cell malignancies, and represents a rational target for therapy

Slide 12: CD19 as a Target of B-Cell Malignancies

The very first target for this CAR T-cell therapy was this protein expressed on the surface of leukemia cells, called CD19. And, the reason this was chosen as a target is that it is an antigen that is expressed through all of the phases of the development and maturation of the B cell, going all the way from an early stem cell to a very mature plasma cell in multiple myeloma. So, it was a target that could be used in B-cell acute lymphoblastic leukemia, in all of the B-cell lymphomas and leukemias, as well as in myeloma.

And, the other important part is that CD19 is actually not expressed in tissues outside of these blood cells that I mentioned. So that, it was a very rational target for therapy because it was not expected to cause a lot of toxicity outside of the B cells.

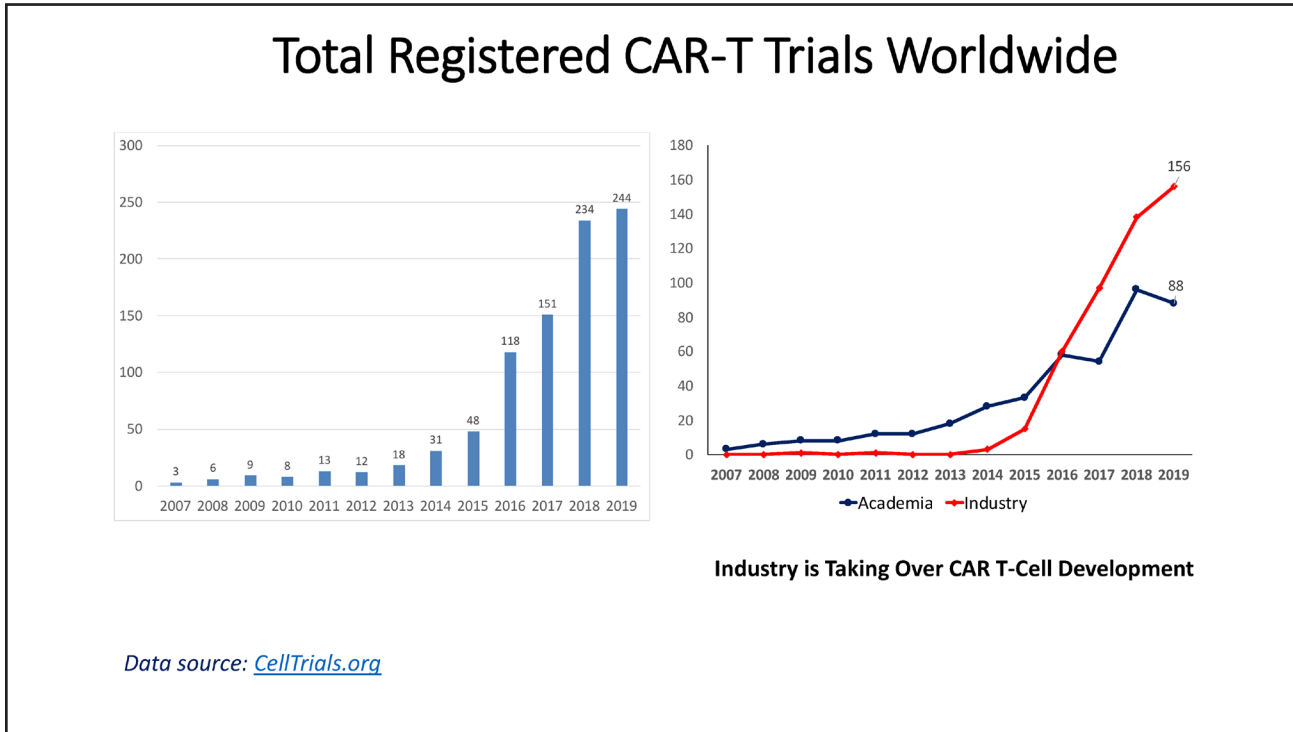


Slide 13: Evolution in CAR Design

So, this is what the cells, the CAR T cells, look like. There are several generations now from the first time they were developed. They have this portion that recognizes the antigen, the cancer antigen, and then they have a portion here that's fixed in the membrane of the T cell, and then an internal portion that is called CD3 zeta that's important for signaling, so that once the outside domain is bound to the cancer cell, it's able to transmit the signal inside the cell so the cell can proliferate.

However, initially the first-generation CARs were not very long-lasting. And since then, second- and third-generation CARs have been developed where these molecules called co-stimulatory domains, have been added, that give these second- and third-generation CAR cells the ability to proliferate and expand very rapidly and to persist in the body for a longer period of time.

The second-generation CARs are actually what is on the market right now and what is approved to treat cancer.



Slide 14: Total Registered CAR-T Trials Worldwide

It's important to note that first trials of CAR T-cell therapy started at academic institutions. However, due to the manufacturing costs and complexities of implementing these trials at very large scale, industry has since then taken over the administration of CAR T trials worldwide. And you can see here, the data goes up to the end of 2019, where there were 244 CAR T trials worldwide, and now there are more. And in red here, it shows that since 2015-16, basically, industry has taken over production of these CAR T cells by academic institutions. And, that is not to say that the academic institutions are not continuing to do research, they are, but when it comes to dealing with the large costs and manufacturing them at large scale, I think it's important to collaborate with the pharmaceutical industry.

Selected Approved or Late-Stage CAR T Therapies

Drug name	Company	Indication	Target
<i>Marketed</i>			
Tisagenlecleucel (CTL-019)	Novartis	Childhood B-cell ALL (≤ 25) Adult DLBCL, transformed FL (tFL)	CD19
Axicabtagene ciloleucel (KTE-C19)	Gilead Sciences (Kite Pharma)	DLBCL, tFL and PMBCL	CD19
Brexucabtagene autoleucel (KTE-X19)	Gilead Sciences (Kite Pharma)		
<i>Phase III</i>			
Lisocabtagene maraleucel (JCAR 017)	Celgene (Juno Therapeutics)	B-NHL	CD19
Idecabtagene vicleucel (bb2121)	Bluebird bio/Celgene	Multiple myeloma	BCMA

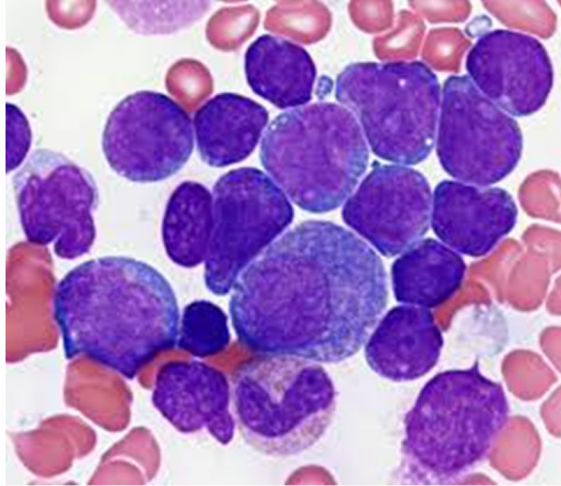
Slide 15: Selected Approved or Late-Stage CAR T Therapies

So, these are selected approved and late-stage CAR T-cell therapies that I will focus on today. So, we have tisagenlecleucel that is currently approved in childhood B-cell acute lymphoblastic leukemia, up and including age of 25. It is also approved for adult diffuse large B-cell lymphoma and transformed follicular lymphoma. The target is CD19. We have axicabtagen ciloleucel that is currently approved for diffuse large B-cell lymphoma, transformed follicular lymphoma, and primary mediastinal lymphoma, also targeting CD19. We have brexucabtagene autoleucel and this was just recently approved for mantle cell lymphoma, also targeted CD19.

There are at least 2 Phase III trials, large Phase III trials, that have published data, but are not yet approved, and that is lisocabtagene maraleucel, that is pending approval for B-cell non-Hodgkin lymphoma, and then idecabtagene vicleucel, that has a different target called BCMA for multiple myeloma.

So, those are the nearest ones.

CAR T- Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)



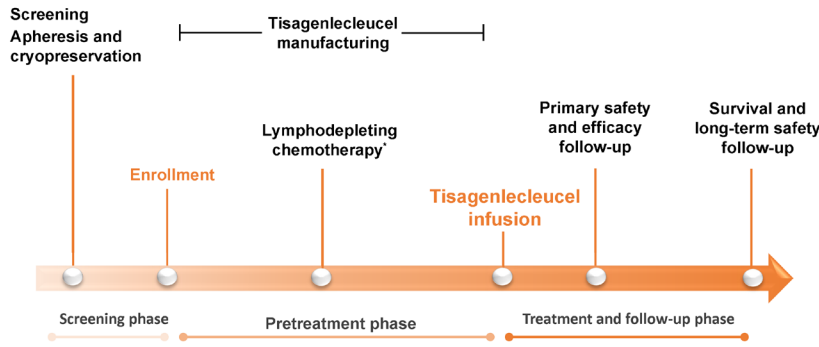
Atlas of Genetics and Cytogenetics in Oncology and Hematology

Slide 16: CAR T- Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)

So, I will start with CAR T-cell therapy in B-cell acute lymphoblastic leukemia because that's how the first approval came about.

Pediatric Relapsed/Refractory (R/R) B-ALL: ELIANA Study Design

- ELIANA (NCT02435849) is a phase 2, open-label, single-arm study in pediatric and young adult patients with r/r B-cell ALL¹⁻²



B-cell ALL, B cell acute lymphoblastic leukemia.

*To be completed 2 to 14 days prior to Tisagenlecleucel infusion.

1. Buechner J, et al. *Haematologica*. 2017;102(suppl 2) [abstract S476];
2. Maude SL, et al. *N Engl J Med*. 2018;378:439-448;

Slide 17: Pediatric Relapsed/Refractory (R/R) B-ALL: ELIANA Study Design

And this is a study that you may be familiar with. It was done in children who had relapsed and refractory B-cell acute lymphoblastic leukemia. And, this is called the ELIANA study. And, this was started at the University of Pennsylvania. This was a Phase II study and it had young adult patients up to the age of 25. So, the T cells were collected through this process of apheresis. The patients were enrolled, they received the lympho-depleting chemotherapy, and then they received the infusion of tisagenlecleucel. And you can see that there was about a 3 to 4 week time here for tisagenlecleucel manufacturing. And so, once the cells came back, they were infused into the patients, and the patients were followed for safety first and foremost, and then for efficacy.

ELIANA Study in B-ALL

- Single arm, open-label, multi-center, global phase 2 study
 - 107 pts screened, 88 enrolled, 68 treated
- Dose of Tisagenlecleucel: $2-5 \times 10^6$ CAR-T cells/kg
 - Conditioning chemo: Flu 30 mg/m² x 4days + Cy 500 mg/m² x 2 days
- Response rates: Complete Remission/Complete Remission with incomplete hematologic recovery **CR/CRi: 81%** (CR 60% + CRi 21%)
- **Tisagenlecleucel approved for treatment of patients up to age 25 with B-ALL that is refractory or in 2nd or later relapse**

1. Buechner J, et al. *Haematologica*. 2017;102(suppl 2) [abstract S476];
2. Maude SL, et al. *N Engl J Med*. 2018;378:439-448;

Slide 18: ELIANA Study in B-ALL

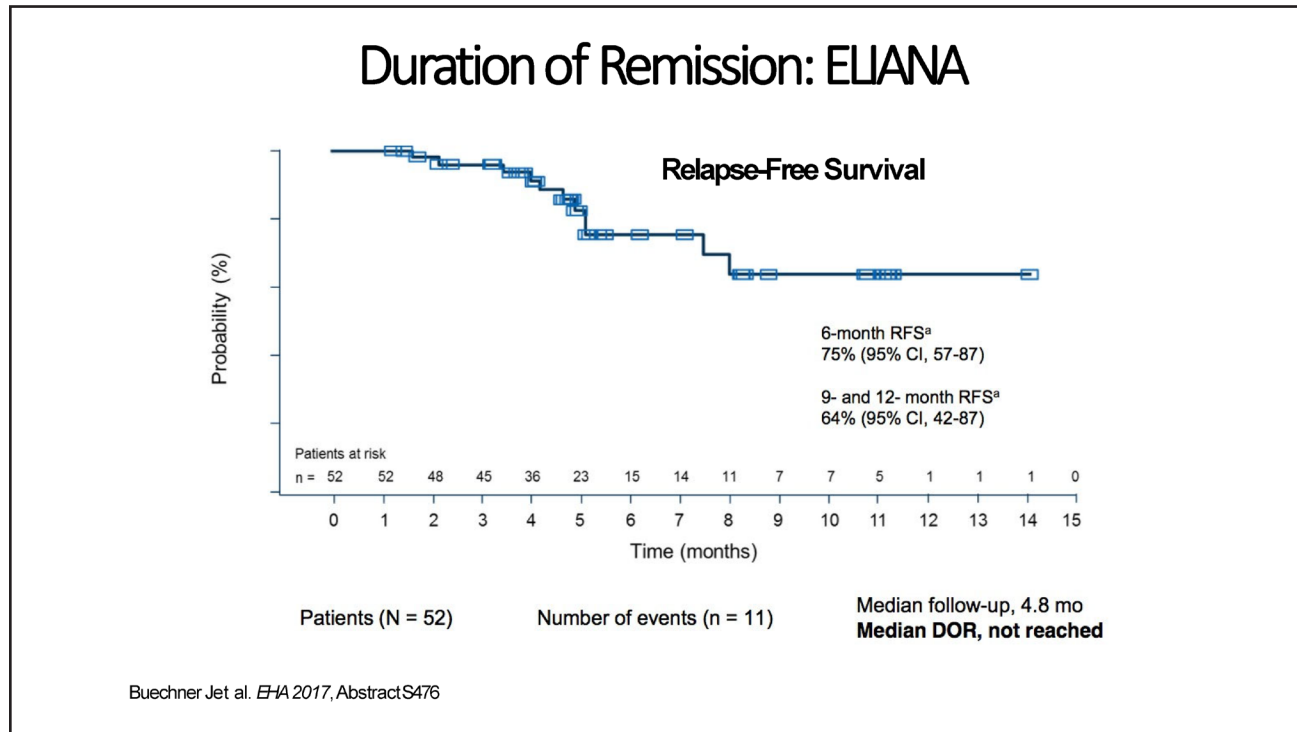
And the response rates were remarkable. These were patients who had had several lines of therapy, and 107 in total, 68 of whom were treated. The complete remission rates were in the order of 80%. And based on this data, this was approved for B-cell ALL that is refractory or that is in second or later relapse.

ELIANA: Patient Demographics and Baseline Clinical Characteristics

Characteristics	Patients (N = 75)
Age, median (range), years	11 (3-23)
Prior stem cell transplant, n (%)	46 (61)
Previous line of therapies, median (range), n	3 (1-8)
Disease status, n (%)	
Primary refractory	6 (8)
Chemo-refractory or relapsed	69 (92)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)

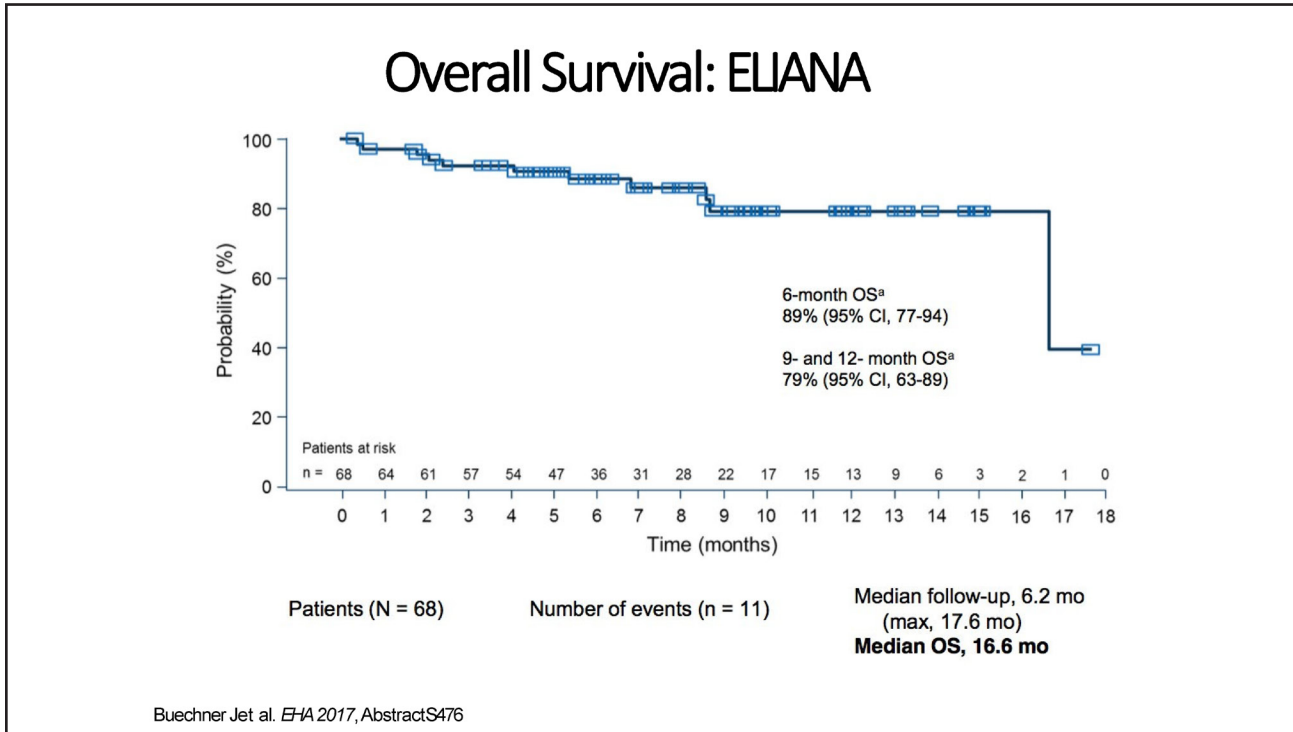
Slide 19: ELIANA: Patient Demographics and Baseline Clinical Characteristics

So, these were some of the demographics and characteristics of the patients. You can see that 92% were refractory to chemotherapy and many of them had very high leukemia burden in their bone marrow.



Slide 20: Duration of Remission: ELIANA

So really, this was very unexpected, but the duration was extremely remarkable, where at the first 6 months 75% of the patients were without relapse, and even if you followed them for a year, still about two-thirds of the patients maintained their disease remission.



Slide 21: Overall Survival: ELIANA

And, this is again the overall survival. At one year, 80% of the patients were alive.

ELIANA: Overall safety of Tisagenlecleucel

Event	Any Time (N = 75)	≤8 Wk after Infusion (N = 75)	>8 Wk to 1 Yr after Infusion (N = 70)
		<i>number of patients (percent)</i>	
Adverse event of any grade	75 (100)	74 (99)	65 (93)
Suspected to be related to tisagenlecleucel	71 (95)	69 (92)	30 (43)
Grade 3 or 4 adverse event	66 (88)	62 (83)	31 (44)
Suspected to be related to tisagenlecleucel	55 (73)	52 (69)	12 (17)

Maude SL, et al. *N Engl J Med.* 2018;378:439-448

Slide 22: ELIANA: Overall safety of Tisagenlecleucel

Adverse events were monitored very closely, and it became evident that the majority of them, about 70%, that were related to tisagenlecleucel, occurred within the first 8 weeks of the infusion. And, that it was extremely rare to see side effects that were new and developed after the first 2 months of therapy.

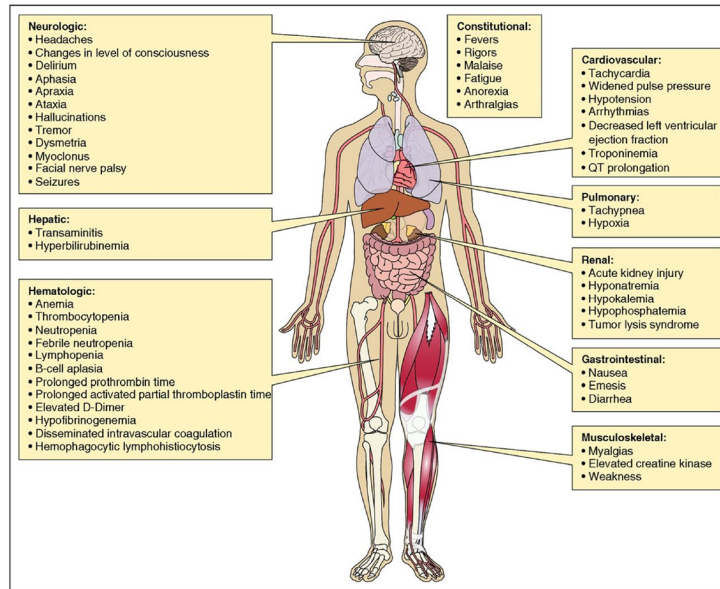
Outcomes with CART19 Therapy in Children and Adults with Relapsed/Refractory B-ALL

Reference	CAR	Population	Response
Maude et al. NEJM 2018	PENN 4-1BB	ALL (peds/adults) N=71	CR: 81% 6mo EFS & OS: 73% & 90% 12mo EFS & OS: 59% & 76% 11% proceeded to alloHSCT after CAR T cells
Park J et al. ASCO 2017, Abstract 7008	MSKCC CD28	ALL (adults) N=53	CR: 84.6% MRD-CR rate: 66.6% 39% proceeded to alloHSCT after CAR T cells.
Turtle et al. JCI 2016	Seattle 4-1BB Defined CD4/CD8 composition	ALL (adults) N=30	CR=93% MRD-CR rate: 86% 1 pt proceeded to alloHSCT after CAR T cells
Lee et al. Lancet 2015	NCI CD28	ALL (peds/adults) N=21	CR=67%

Slide 23: Outcomes with CART19 Therapy in Children and Adults with Relapsed/Refractory B-ALL

Similar studies were done in ALL in the adult population, and you will see here the complete response rates were very high in the adult population as well, in the order of 80 to 90%. While this has not yet been approved for adults, it is a very effective type of therapy and will in the future be approved as well.

CAR-T 19 Associated Toxicities



Professional illustration by Patrick Lane, ScEYence Studios

Slide 24: CAR-T 19 Associated Toxicities

So, what are these toxicities that we expect to see from CAR T-cell therapy? You can see in this slide that they can involve different parts, different organs, different parts of the body. So, there can be neurologic effects with headaches, changes in the level of consciousness, inability to move, tremors. There could be what we call constitutional effects, such as fever or shaking or rigors, malaise, people feel like they have the flu. There could be some effects on the heart. There could be effects on the lungs. Patients can have a difficult time breathing, and even sometimes require intubation. There could be effects on the kidneys and liver. And, there could be effects in the blood counts that can last for some time.

CAR-T 19 Associated Toxicities

- Cytokine Release syndrome (CRS)
 - Fevers, flu-like syndrome, low blood pressure, difficulty breathing
- Neurologic changes (NT, CRES, ICANS)
 - Headaches, tremors, mental status changes, difficulty speaking, rarely seizures (normal MRI)
- Organ toxicity (liver, kidneys)
- Off tumor/On target: B cell aplasia
 - Prolonged; Cases requiring IVIG repletion
- Toxicities are usually manageable and reversible

Slide 25: CAR-T 19 Associated Toxicities

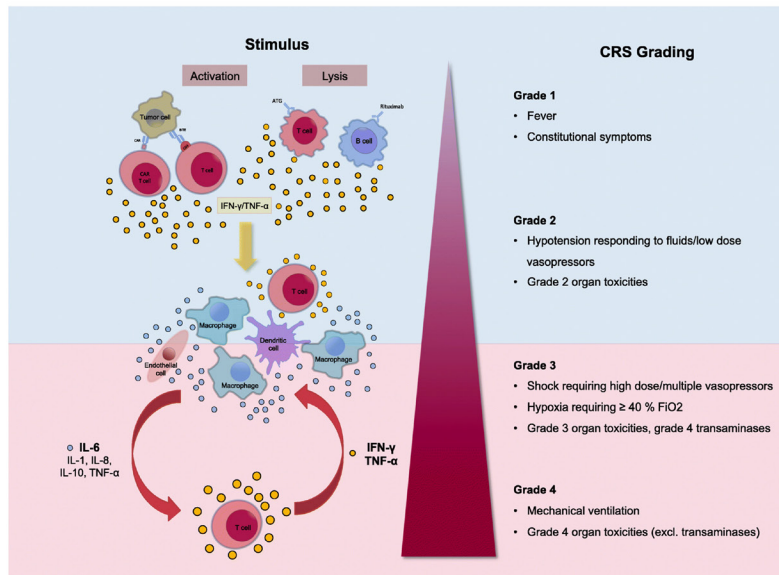
So, the main ones that we worry about are what's called cytokine release syndrome, that you may be familiar with, and that is a flu-like syndrome that presents with fevers, and then patients can develop difficulty breathing and low blood pressure. And, these cytokines are a large group of proteins that are made by cells of your immune system, they're released by the T cells and other cells, and normally they give signals that regulate the amount of inflammation in the body as well as immunity. But after CAR T-cell therapy, these cytokines can be released in large numbers and they can cause the patients to get sick, and this is an unintended side effect with this therapy.

There can be neurologic changes, starting with something like a headache or tremors in the hands, but patients can become very confused and sometimes they lose the ability to speak. It is very rare that patients can have seizures as well.

The main unintended organ toxicity with this type of therapy is actually the normal B cells. So, it tends to wipe out the B cells for some time. This can last in the order of a few months to a couple of years, and the B cells are the cells, the normal B cells are the cells that produce antibodies. So, patients can be at risk of developing infection.

It is very important to note that while these side effects are scary to the patient, the family, and the physicians and nurses treating the patient, the toxicities are manageable and reversible in the majority of patients.

Mechanism of Cytokine Release Syndrome (CRS)

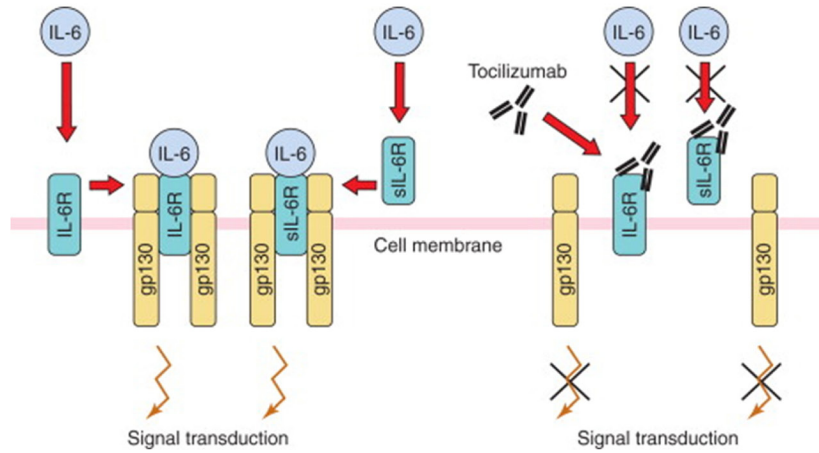


Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M. *et al.* Cytokine release syndrome. *j. immunotherapy cancer* 6, 56 (2018)

Slide 26: Mechanism of Cytokine Release Syndrome (CRS)

So, this is how the process starts. This is the mechanism. Like I showed you, it starts with a fever, and then all these cytokines are released and they cause raging fevers in the patients and sometimes a drop in the blood pressure and trouble breathing.

Inhibitory Action of Tocilizumab in IL-6 Signaling



Norihiro Nishimoto, Toru Mima, in *Rheumatoid Arthritis*, 2009

Slide 27: Inhibitory Action of Tocilizumab in IL-6 Signaling

So, what can we do to treat this cytokine release syndrome? We recognize that one of the most important cytokines or proteins that are secreted by the immune system after the T cells go in, is the cytokine called IL-6. And, we actually do have a drug called tocilizumab that was used in rheumatoid arthritis, that can block this IL-6 signaling and shut down this strong immune response and release of cytokines. So, we do give this to the patients for several doses if they develop CRS.

Neurologic Toxicity with CAR T-Cells

- Symptoms and signs: headaches, tremors, somnolence, speech difficulty, confusion, paralysis of limbs, rarely seizures, etc.
 - 1st phase (Days 0-5) – symptoms may appear with other CRS symptoms
 - 2nd phase (After day 5) – starts after CRS symptoms have subsided
- Neurotoxicity typically lasts 2-4 days but may vary in duration from few hours to few weeks. **It is generally reversible.**
 - **Corticosteroids** treatment of choice in managing neurotoxicity.
 - **Seizure prophylaxis** is recommended with levetiracetam (750 mg oral/IV q 12 hrs) from day 0 to day 30.

Neelapu, SS, et al. *Nature Reviews Clinical Oncology*, 15(1), 47-62.

Slide 28: Neurologic Toxicity with CAR T-Cells

What about neurologic toxicity? As I mentioned, patients can develop different symptoms. They can occur even with or without cytokine release syndrome. They typically last for a few days, although in some patients they can last for a few weeks. And, they're generally reversible. Steroids are the main treatment in managing neurologic toxicity, and we also put the patients on seizure prophylaxis to prevent seizure activity.

Mechanism of Neurotoxicity

- Pathophysiology remains unclear:
 - Diffusion of cytokines into central nervous system
 - Trafficking of T cells into central nervous system
- CSF is usually positive for CAR T cells
- MRI of brain is usually negative
 - Reversible white matter changes and cerebral edema have been rarely observed
- EEG is either non-focal with generalized slowing or might show non-convulsive seizure pattern

Maude et al. NEJM 2014; Davila et al. SciTrMed 2014; Lee et al. The Lancet 2015; Turtle et al. JCI 2016; Kochenderfer et al. JCO 2015; Turtle et al. JCI 2016; Gust et al. Cancer Disc. 2017

Slide 29: Mechanism of Neurotoxicity

The mechanism of neurotoxicity is less known compared to cytokine release syndrome. We think that the cytokines get into the central nervous system, and we also know that the T cells get into the central nervous system. MRIs are often normal and electroencephalograms of the brain in most patients do not show seizure activity.

Tools for Grading Neurotoxicity

Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [12]	ICE
<ul style="list-style-type: none"> • Orientation: orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points • Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points • Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • Attention: ability to count backwards from 100 by 10: 1 point 	<ul style="list-style-type: none"> • Orientation: orientation to year, month, city, hospital: 4 points • Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points • Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • Attention: ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.

Scoring: 10, no impairment;

7-9, grade 1 ICANS;

3-6, grade 2 ICANS;

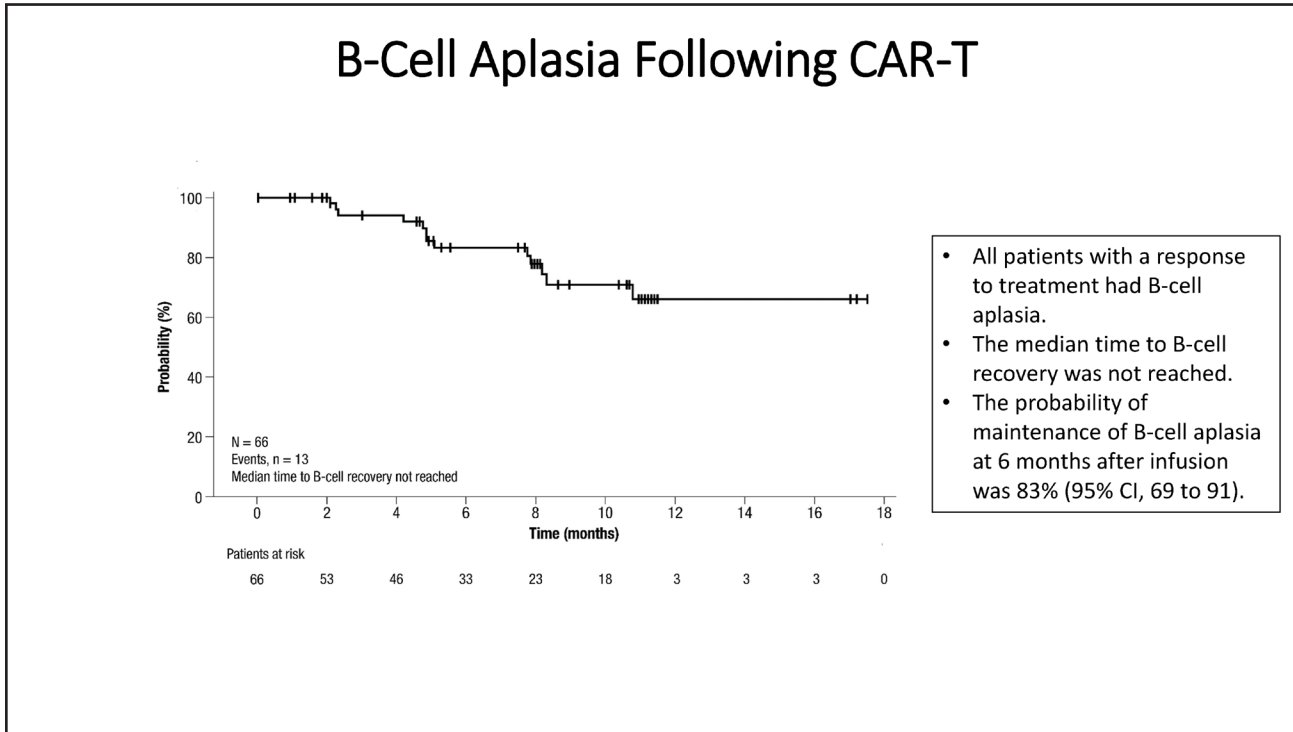
0-2, grade 3 ICANS;

0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

Lee DW, et al. (2018, December 19). ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation*. doi: <https://doi.org/10.1016/j.bbmt.2018.12.758>

Slide 30: Tools for Grading Neurotoxicity

We do have a way of scoring neurotoxicity and grading it, and this is where families are very helpful in monitoring the patient for side effects after they go home. We ask the family to monitor the patient for orientation to year, month, and place; the ability for the patient to name objects like point to a clock or pen or button; the ability to write a sentence; and the attention span, the ability to count backwards from 100 by 10. And, all of these things are given points. And, patients who are treated for example, have been unable after their CAR T-cell therapy, they develop neurologic toxicity, they're unable to write a sentence clearly, the handwriting becomes very small, or they can see and understand us, but they're not able to speak to us and tell us how they feel. And, that is expected and it is completely reversible.

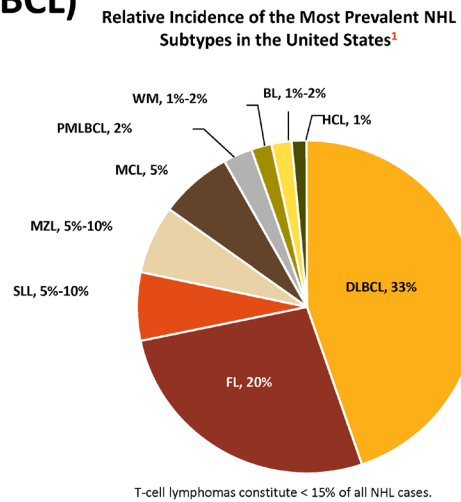


Slide 31: B-Cell Aplasia Following CAR-T

This is a slide showing what's called B-cell aplasia. So, the absence of the B cells, the normal B cells from the bloodstream, that can go on for several months. And, even beyond 6 months after infusion, and sometimes we have to give intravenous immunoglobulin antibodies to patients to prevent infections.

CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- **Diffuse Large B-Cell Lymphoma (DLBCL)**
- Mantle Cell Lymphoma (MCL)
- Follicular Lymphoma
- Marginal Zone Lymphoma



Slide 32: CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

So, from ALL I will change my focus now to B-cell non-Hodgkin lymphomas. I will discuss diffuse large B-cell lymphoma, mantle cell, and follicular.

Diffuse large B-cell lymphoma represents actually the majority of cases of B-cell non-Hodgkin lymphoma, about 30%, and that's followed by follicular, 20%, and then mantle cell lymphoma, and the rest are less common. So, that's why the efforts with CAR T-cell therapy focused on this patient population because it is more common.

Treatment of Aggressive DLBCL

1. First Line: Chemotherapy (R-CHOP or R-EPOCH) + Anti-CD20 monoclonal antibody (Rituximab)
2. Common 2nd line regimens if disease comes back: R-ICE, R-DHAP, R-GemOx*

***These regimens may induce remission but response is generally short-lived due to lymphoma stem cells that are resistant to “standard doses” of chemotherapy**

3. Autologous stem cell transplant (ASCT)

Slide 33: Treatment of Aggressive DLBCL

So, how do we treat aggressive diffuse large B-cell lymphoma? We typically first line stick with chemotherapy and a monoclonal antibody, for example, the R-CHOP regimen, you may be familiar with. And then, if the disease comes back, we give what's called the salvage chemotherapy regimen, like R-ICE or R-DHAP or R-GemOx.

However, even though these regimens can result in remission, the response is short-lived. And, we really need to consolidate the response to this chemotherapy with an autologous stem cell transplant.

Autologous Stem Cell Transplant (ASCT)

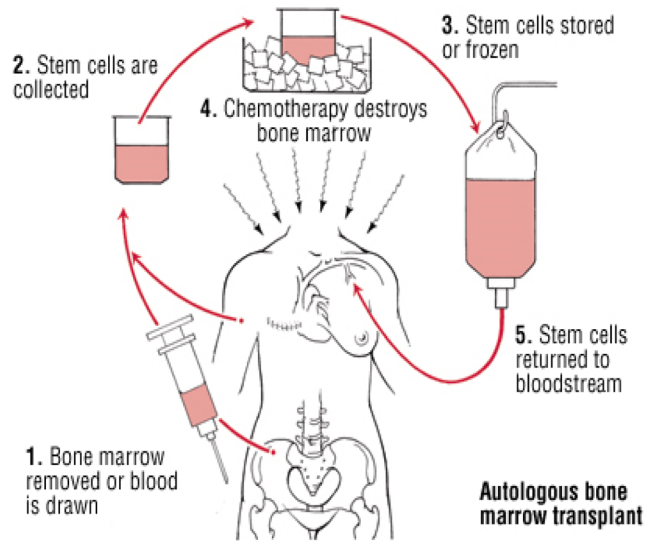
- If a patient's lymphoma goes into remission with 2nd line treatment, ASCT is used to **maintain** the remission.
- During 2nd line treatment, a patient's healthy blood-producing cells are obtained and frozen.
- After completing 2nd line chemotherapy, patient receives a "high dose chemotherapy" regimen, followed by infusion of their own healthy blood-producing cells.
 - This helps prevent toxicity of the "high dose chemotherapy."

Slide 34: Autologous Stem Cell Transplant (ASCT)

And, most of you probably already know how a stem cell transplant is done in order to maintain remission, that we collect the blood-producing cells, we freeze them, the patients receive high-dose therapy, and then they receive the stem cells back, and this is actually the process.

Autologous Stem Cell Transplant

- Must be in remission
- Stem cells derived from patient
- High dose chemotherapy
- Stem cell infusion
- Bone marrow recovers in 1.5-3 weeks
- Adverse effects in ~ 3-7%



Slide 35: Autologous Stem Cell Transplant

But, in order for an autologous stem cell transplant to work for diffuse large B-cell lymphoma, patients must be in remission. Typically, after the high-dose therapy and the stem cell infusion, it takes the bone marrow about 10 days to recover.

There are adverse events with this type of therapy as well, such as mouth sores, diarrhea, fevers, infections, and low blood counts.

Treatment Challenges

- What if lymphoma comes back after an autologous stem cell transplant?
- What if lymphoma will not go into remission in order to proceed to an autologous stem cell transplant?

Slide 36: Treatment Challenges

But, what can we do if the lymphoma comes back after an autologous transplant or what if it doesn't go into remission, for example, with one of those salvage regimens and patients are not able to proceed to an autologous stem cell transplant?

Three Large Multicenter CAR T Studies for DLBCL

- Zuma-1 (Kite/Gilead) Axicabtagene Ciloleucel -> First FDA approval October 2017
 - Treatment of adult patients with **relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy**, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (transformed follicular lymphoma, or tFL).
- Juliet (Novartis) Tisagenlecleucel -> FDA approval May 2018
 - Treatment of adult patients with **relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy** including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- Transcend NHL 001 (Juno/Celgene) Lisocabtagene maraleucel

Neelapu SS, et al. N Engl J Med. Volume 377(26):2531-2544. December 28, 2017
Schuster et al. N Engl J Med. Volume 377(26):2545-2554. December 28, 2017
Abramson, Palomba et al. ICML 2017

Slide 37: Three Large Multicenter CAR T Studies for DLBCL

Well, that's exactly where CAR T-cell therapy comes into play. There have been 3 large multicenter CAR T studies for diffuse large B-cell lymphoma. Those were led by Kite and Novartis and Juno. And, they led to the first FDA approval in October of 2017 for axicabtagen ciloleucel in patients who had relapsed after 2 lines of therapy. And then, tisagenlecleucel also approved now in addition to B-cell ALL, for diffuse large B-cell lymphomas as of May of 2018, after 2 or more lines of therapy. The third one, the TRANSCEND study of lisocabtagene maraleucel, was performed and published, but has not yet received FDA approval.

Three Major Anti-CD19 CAR T-cell Products for Lymphoid Malignancies

	Axicabtagene Ciloleucel- ZUMA-1	Tisagenlecleucel JULIET	Lisocabtagene Maraleucel TRANSCEND NHL- 001
Construct	antiCD19- CD28 -CD3z	antiCD19- 41BB -CD3z	antiCD19- 41BB -CD3z
T-cell Manufacturing	Retroviral vector Bulk T-cells	Lentiviral Vector Bulk T-cells	Lentiviral Vector CD4:CD8 1:1 ratio
Dose	2 x 10 ⁶ /kg (max 2 x 10 ⁸)	0.6 to 6.0 x 10 ⁸	DL1: 0.5 x 10 ⁷ , DL2: 1.0 x 10 ⁸
Bridging Therapy	None allowed in pivotal trial but often used in standard practice	93%	72%
Lymphodepletion	Flu/Cy 500/30 x 3d	Flu/Cy 250/25 x 3d, or BR	Flu/Cy 300/30 x 3d
Treatment Locale	Inpatient Only	Inpatient and Outpatient*	Inpatient and Outpatient*
Approval Status	FDA approved for DLBCL, high-grade B-cell lymphoma, transformed FL, primary mediastinal B-cell lymphoma	FDA approved for pediatric ALL, DLBCL, high-grade B-cell lymphoma, transformed FL	Not yet FDA approved

* Outpatient therapy requires careful patient selection and is center dependent based on outpatient resources

1. Schuster SJ, et al. NEJM 2018; 2. Neelapu SS, et al. NEJM 2017; 3. Abramson JS, et al. ASCO 2019

Slide 38: Three Major Anti-CD19 CAR T-cell Products for Lymphoid Malignancies

So, this slide puts the 3 products next to each other and I did that to show that they've never been compared head-to-head because this therapy is so new. But, there are significant differences between them. For example, the construct of the CAR T is different. The type of the stimulatory molecule here is CD20, for example, in these other products is 41BB. The types of viruses that were used to genetically modify the cells were different. The chemotherapy that was given differed slightly. Some of them were administered in the hospital only and some had the potential to be administered in the clinic. So, they're not comparable to each other.

CART 19 Therapy Outcomes in R/R LBCL

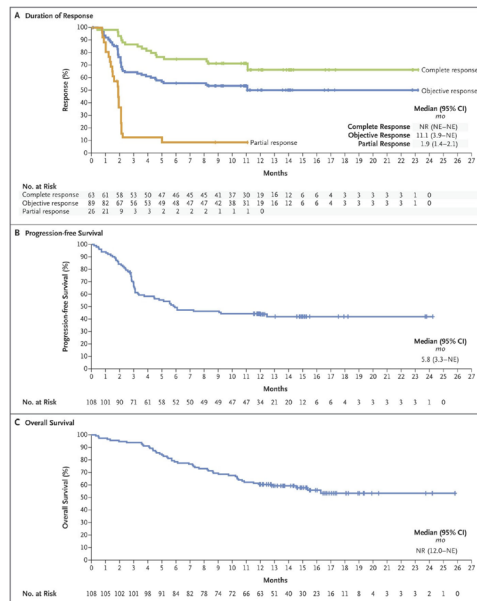
	Zuma-1 (Axicabtagene Ciloleucel)	Juliet (Tisagenlecleucel)	Transcend NHL 001 (Lisocabtagene Maraleucel)
Pts leukapheresed, n	111, 108 infused	141, 111 infused	102, 70 infused
Histologies	Cohort 1: DLBCL Cohort 2: PMBCL, tFL	DLBCL/tFL	DLBCL, PMBCL, tFL, FL3b (CORE) TMZL, MCL, Richter's
Efficacy in R/R DLBCL			
Best OOR	42%	52%	73%
Best CRR	40%	40%	53%
6 month CRR	40%	30%	33% R/R DLBCL DL1, 46% DL2
12-mo PFS		83% in CR/PR pts at 3mo	

1. Schuster SJ, et al. NEJM 2018; 2. Neelapu SS, et al. NEJM 2017; 3. Abramson JS, et al. ASCO 2019

Slide 39: CART 19 Therapy Outcomes in R/R LBCL

But, you can see that with each of them the outcomes are quite good. The overall response rate had varied from about 50 to 70% and complete response rates are also in the order of 40 to 50%. And, that is really beyond what was expected in patients who had progressed after 2 lines of therapy or including patients who had progressed after autologous stem cell transplant. So, even though the 40 to 50% does not really sound very good to the patient because we'd like that number to be 100%, and even though this data did not look as good as the data in B-cell ALL, it was still remarkable for this type of aggressive lymphoma.

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory LBCL



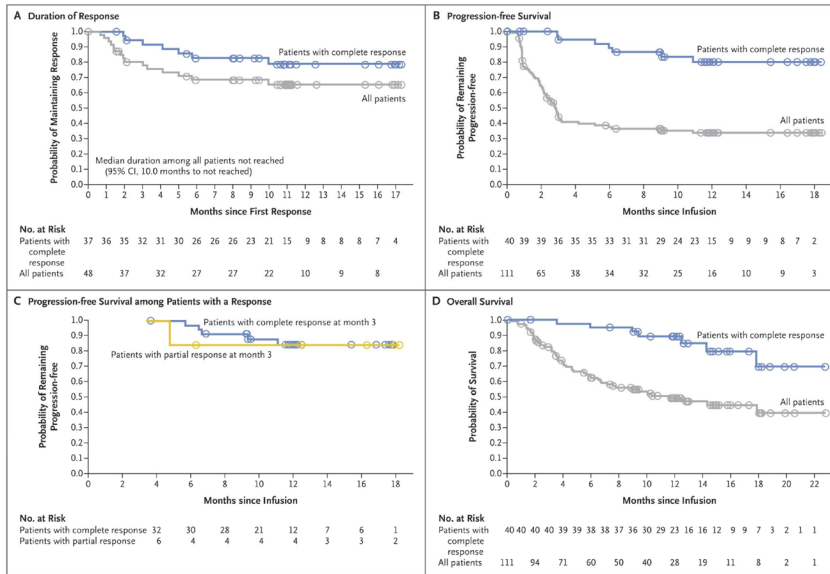
Kaplan-Meier Estimates of the Duration of Response, Progression-free Survival, and Overall Survival.

Neelapu SS et al. N Engl J Med ;377:2531-2544

Slide 40: Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory LBCL

And, what we can see for each of these studies, I show you here the survival curves, and the ability of patients to maintain remission based on the response they achieved to the therapy. You see here, the green line, is that patients who achieve complete response in the first 3 to 6 months after this type of therapy, actually were long-term responders and are likely cured.

Tisagenlecleucel in Adult Relapsed or Refractory DLBCL



Duration of Response, Progression-free Survival, and Overall Survival

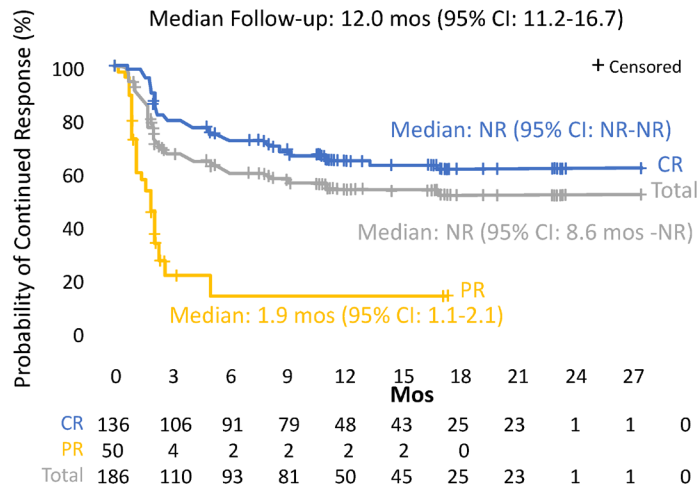
Schuster SJ et al. N Engl J Med 2019;380:45-56

Slide 41: Tisagenlecleucel in Adult Relapsed or Refractory DLBCL

And, this is also true for tisagenlecleucel, again, for patients in blue here who achieved complete response, they are long-term survivors, and these responses are very durable. They go beyond 2 years now. And we think that these patients are cured.

Lisocabtagene Maraleucel in Adult R/R LBCL

Efficacy-Evaluable Patients (N = 256)	
ORR (95% CI)	73 (67-78)
CR rate (95% CI)	53 (47-59)
Time to first CR or PR, median mos (range)	1.0 (0.7-8.9)
DoR at 6 mos, % (95% CI)	60.4 (52.6-67.3)
DoR at 12 mos, % (95% CI)	54.7 (46.7-62.0)



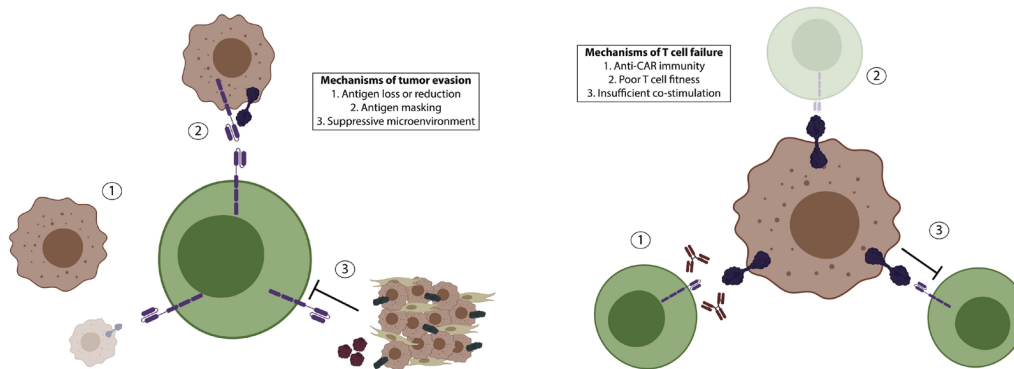
Abramson. ASH 2019. Abstr 241.

Slide 42: Lisocabtagene Maraleucel in Adult R/R LBCL

This is coming up, the third product, lisocabtagene, again the median duration of response was not reached. You can see here, compared to the patients who achieved partial response, you know that most of them progressed. The patients who achieved complete response are still in remission.

Why Doesn't CAR T-Cell Therapy Always Work?

- Leukemia relapse after CAR T-cells could be classified into 2 distinct types:
 - Loss of the CD19 target antigen on the surface of leukemia cells
 - Loss of CD19 CAR T-cells in blood (short persistence)



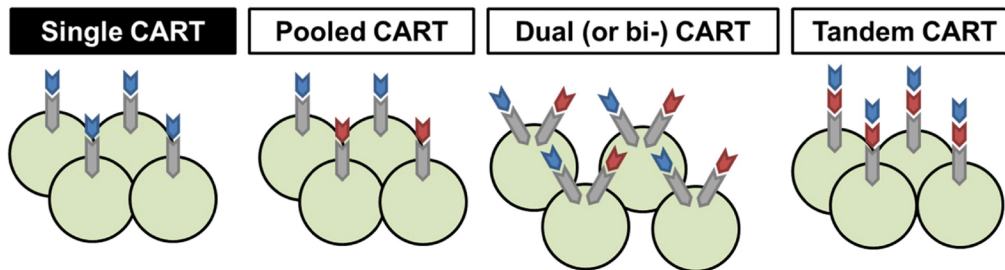
1. Grupp et al NEJM 2013; 2. Sotillo E, et al. *Cancer Discov.* 2015; 3. Jacoby E, et al. *Nat Commun.* 2016; 4. Turtle et al. *JCI* 2016
 5. Nathan Singh N et al. *Seminars in Cancer Biology*, Volume 65,2020, Pages 91-98

Slide 43: Why Doesn't CAR T-Cell Therapy Always Work?

So, why is there this group of patients who achieved only partial response after this type of therapy? Why are we not able to achieve complete response and cure everyone?

And, there are many reasons for that. After the first leukemia patients relapsed, it became clear that there are at least 2 mechanisms why CAR T-cell therapy sometimes fails. One is that the leukemia cells are smart and they lose this target protein, the CD19, they erase it from their surface. So, that's the first reason. And, the second reason is that the CAR T cells actually don't persist for a very long time in the blood.

Strategies to Avoid Antigen-Loss Relapses



Single CART – CAR T cells of same specificity (i.e. CD19)

Pooled CART – 1:1 mixture of single-specificity CART: each cell remains able to recognize only one target (i.e. one with specificity for CD19, and one with specificity for CD22)

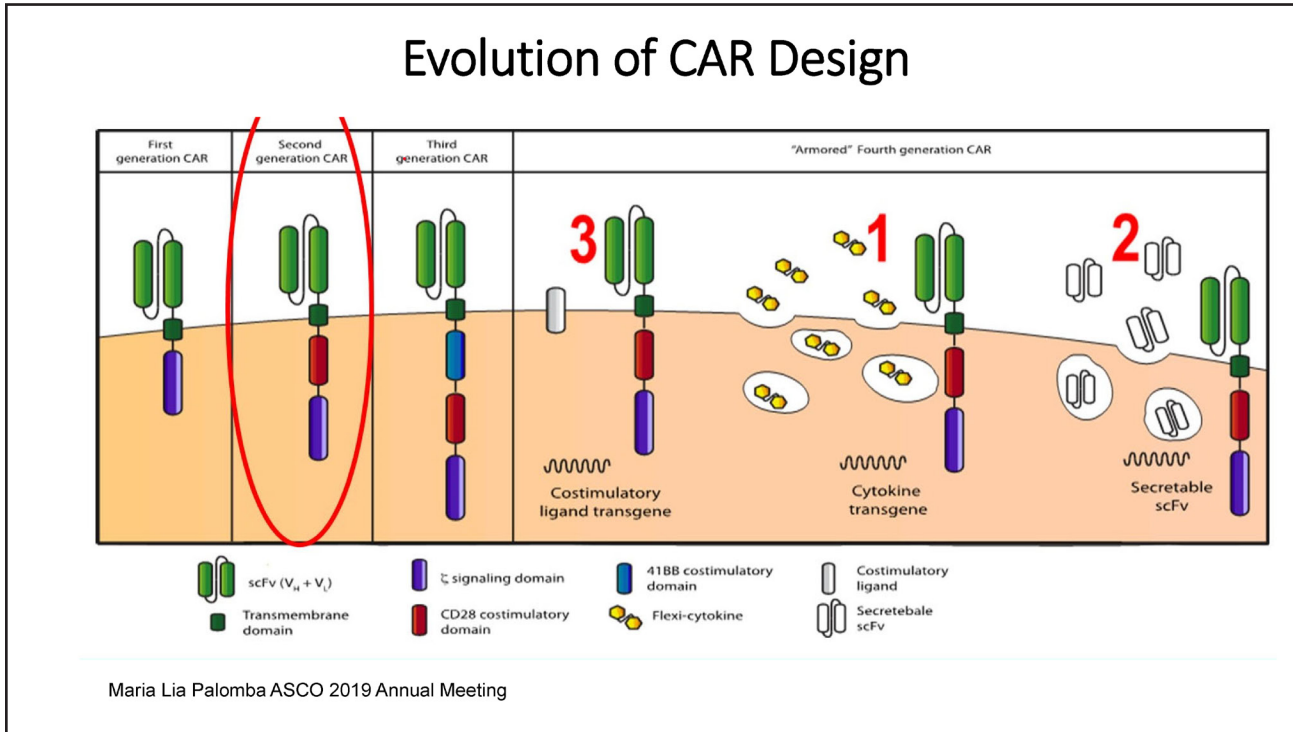
Dual (or bi-) CART – every T cell bears 2 distinct CAR structures able to recognize 2 different targets (i.e. one for CD19 and one for CD22)

Tandem CART – every T cell bears 1 CAR structure where 2 scFvs are built in series and are able to recognize 2 different targets

Marco Ruella, Marcela Maus. Computational and Structural Biotechnology Journal. 2016; (14):357-362

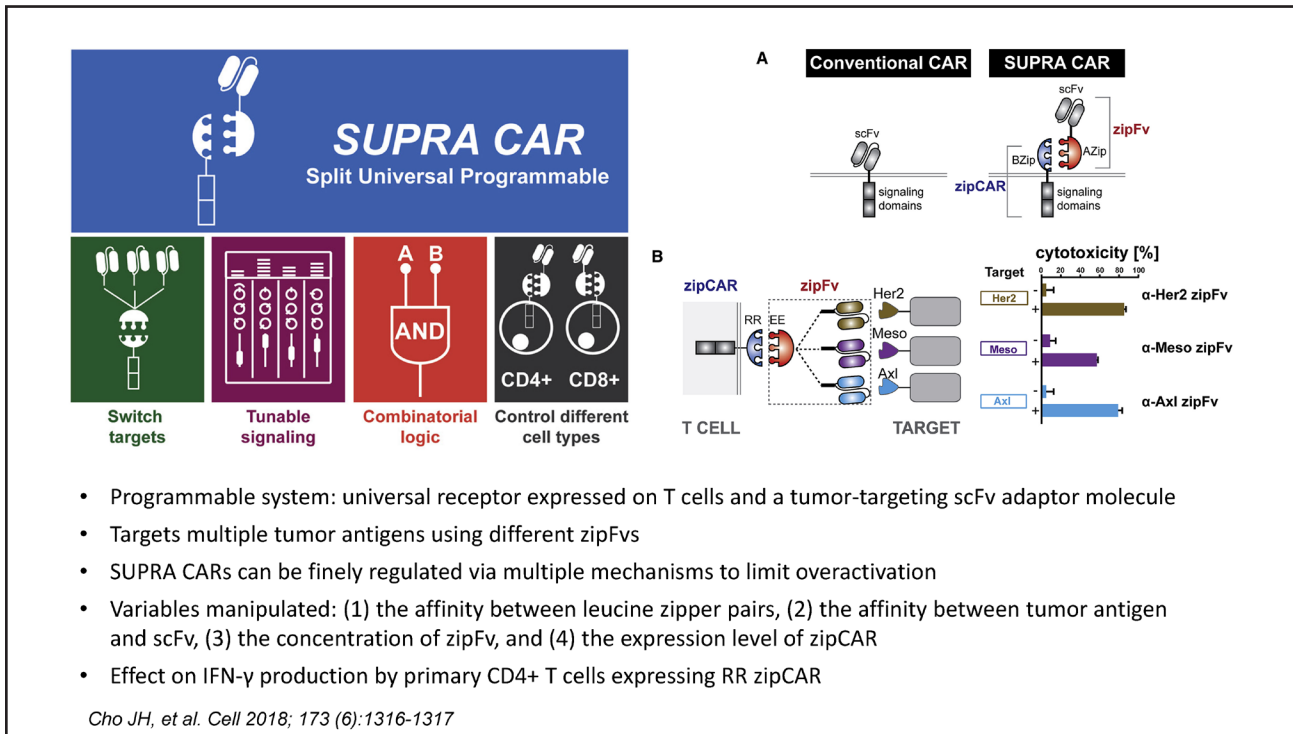
Slide 44: Strategies to Avoid Antigen-Loss Relapses

So, there are many strategies now to target the cell where we're not allowing them time to become resistant. So instead of targeting just CD19, for example, we have here these dual or bi-specific CARs that here in blue are recognizing CD19, but in red are also recognizing another antigen. So, it's called dual targeting. So, CD19 and CD20, CD19 and CD22.



Slide 45: Evolution of CAR Design

Other CAR T cells are also in development that are able to release these proteins that make them proliferate in a stronger way. And, that causes them to survive in the body for a longer period of time and not get killed.

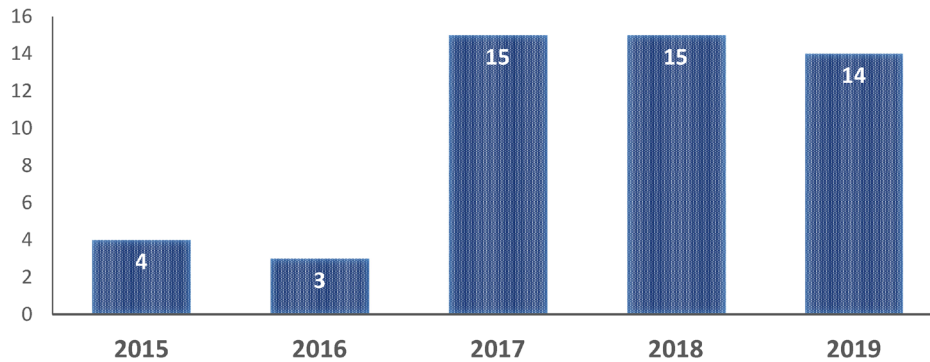


Slide 46: SUPRA CAR: Split Universal Programmable

There are also these SUPRA CARs that this technology is available, where they're called SUPRA CARs because you can program them, and they don't just recognize one antigen on the surface of the cancer cells, but they have the ability to recognize multiple antigens. And, they can also be turned on and off. We can limit the amount of activation or over-activation. We can manipulate them in many ways and really fine-tune their activity.

Why “humanize” CARs?

1. Immune rejection – loss of CAR cells (pedi- and adult B-ALL)
2. Superior efficacy? durability of response
3. Humanized CAR-T can rescue ~ 50% kids with B-ALL previously treated with murine CAR-T and relapsed (Shannon Maude, ASH 2017)



Number of trials utilizing humanized/fully human CAR constructs (binding domain/signaling domain. Data source: CellTrials.org)

Slide 47: Why “humanize” CARs?

And then, last but not least, we can humanize CARs. The CAR T cells that are available on the market now in the domain that recognizes the cancer cell, they are derived from mouse, from murine. And, we have the ability now to have these fully human CAR proteins, where the immune system of the patient does not recognize them as being foreign and it does not attack them, so they can persist in the circulation for a longer period of time.

Autologous CAR-T Cells vs Allogeneic CAR-T Cells

Patient Derived Limitations

- Cost
- Harvest and Manufacturing Failures
- Product Variability and Quality Control
- Disease Progression During Manufacture
- Contamination with Tumor cells
- Cancer Associated T-cell Dysfunction

Graham C, et al. *Cells* 2018, 7, 155

Donor derived

- Previous HSCT donor
- Virus-specific CAR-T cells
- Gene-edited healthy donor CAR-T cells

Donor Derived Advantages

- Easier and cost-effective manufacturing
- Reduced time to CAR-T infusion
- Potential to treat all eligible patients on demand within days, no need for bridging
- Increase probability of healthy CAR-T cell generation
- Convenience of repeat dosing

Donor Derived Barriers

- Graft Versus Host Disease (gene editing techniques do not reach 100% knockout)
- Rejection of CAR-T Cells (less persistence)
- Off Target Cleavage with Gene Editing

Slide 48: Autologous CAR-T Cells vs Allogeneic CAR-T Cells

There are limitations with these CAR T cells because they are derived from the patient and the patients have already received multiple lines of treatment, so the T-cells may be dysfunctional, we may not get a very good product. Or, we don't have oftentimes control on the variability. And it takes us 3 to 4 weeks to manufacture them.

There are now on the market, in clinical trials, but not yet on the market, allogeneic CAR T cells, where they're derived from donors, rather than patients themselves, that's why they're called allogeneic, and they can be produced in a number of days to a few weeks, only 1 or 2 weeks, they really reduce the time to the infusion, and you can treat multiple patients on demand at a time. They're typically healthier T cells than the T cells derived from the patient.

There are some barriers to delivering this type of therapy, patients can develop graft-versus-host disease (GVHD), which is one of the complications that we see after allogeneic transplants, where the donor's immune system recognizes the patient's immune system, and it tries to attack it. And, that is because these CAR T cells are derived from outside the body.

What's Else is Exciting in LBCL CAR-T?

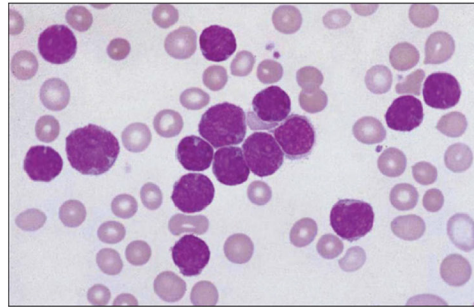
Trial	Phase	Treatment	Population
TRANSFORM (NCT03575351)	III	Lisocabtagene maraleucel vs SoC	Transplant-eligible R/R aggressive B-cell NHL
BELINDA (NCT03568461)	III	Tisagenlecleucel vs SoC	R/R aggressive B-cell NHL
ZUMA-12 (NCT03761056)	II	Axicabtagene ciloleucel	High-risk large B-cell lymphoma; no prior treatment (1 st line)
TRANSCEND-PILOT (NCT03483103)	II	Lisocabtagene maraleucel	R/R aggressive B-cell NHL after first-line immunochemotherapy, ineligible for ASCT
MB-CART2019.1 (NCT03870945)	I	Bispecific tandem CAR T construct against CD19 and CD20	R/R B-NHL without curative treatment option, or in 2 nd line, non-transplant eligible DLBCL patients
ALEXANDER (NCT03287817)	I	AUTO3, the first CD19/22 dual targeting with pembrolizumab	R/R DLBCL
ALPHA (NCT03939026)		ALLO-501 and ALLO-647 anti CD19	R/R large B-cell or follicular lymphoma

Slide 49: What Else is Exciting in LBCL CAR-T?

So, what else is exciting in large B-cell lymphoma? There are many trials now moving these CAR T-cell therapies into second line, comparing them to stem cell transplants, and even trying to move them to first-line therapy in patients that have high-risk disease.

CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- Diffuse Large B-Cell Lymphoma (DLBCL)
- **Mantle Cell Lymphoma (MCL)**
- Follicular Lymphoma
- Marginal Zone Lymphoma



Source: Estella Matutes, Barbara J Bain, Andrew Wotherspoon
Lymphoid Malignancies: An Atlas of Investigation and Diagnosis
Copyright © Evidence Based Networks Ltd.

1@MKC@kG=GU? ACH DI H <IO@ >@GTH KCJH <!
NCJRIB K@JH JMKCD >@GN

Slide 50: CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

So, what about mantle cell lymphoma?

Phase II ZUMA-2 Trial of KTE-X19 CAR T-Cell Therapy in Relapsed/Refractory Mantle Cell Lymphoma (MCL)

- Mantle cell lymphoma is an uncommon, aggressive B-cell NHL subtype with hallmark chromosomal translocation t(11;14)(q13;q32)
- KTE-X19: autologous CD19-targeted CAR T-cell therapy comprising a CD3 ζ T-cell activation domain and a costimulatory CD28 domain
- The phase II ZUMA-2 study sought to evaluate efficacy and safety of KTE-X19 in patients with relapsed/refractory MCL
- **First CAR T-cell therapy, brexucabtagene autoleucel, FDA approved in 2020 for treatment of adults with R/R MCL**

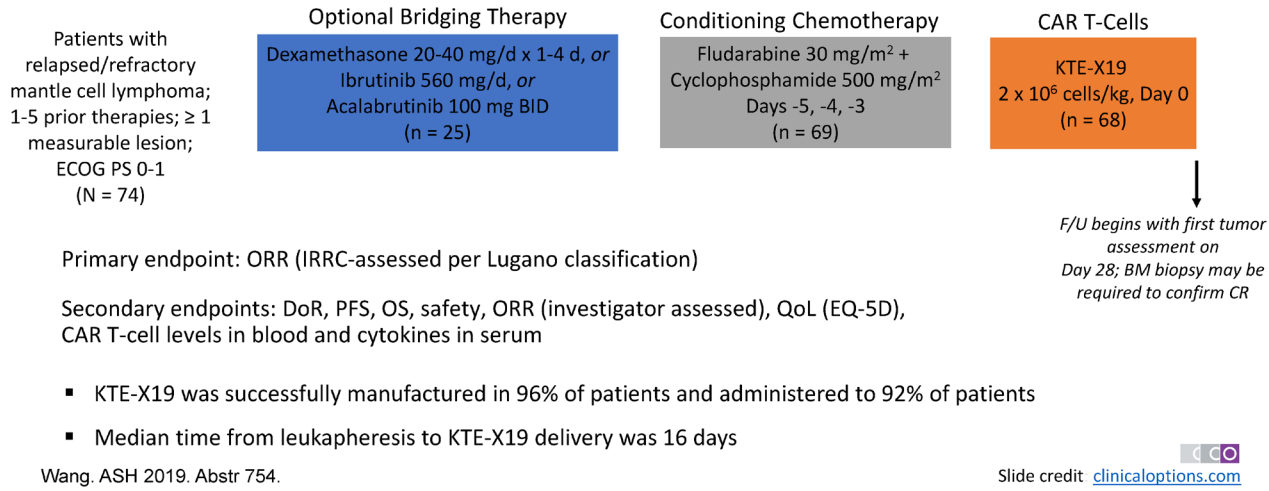
1. Martin. Blood. 2016;127:1559. 2. Jain. Br J Haematol. 2018;183:578. 3. Epperla. Hematol Oncol. 2017;35:528. 4. Sabatino. Blood. 2016;128:1227. 5. Wang. ASH 2019. Abstr 754.

Slide 51: Phase II ZUMA-2 Trial of KTE-X19 CAR T-Cell Therapy in Relapsed/Refractory Mantle Cell Lymphoma (MCL)

There was also this large study called ZUMA-2 that took place in patients that have mantle cell lymphoma, which is another aggressive B-cell lymphoma, that is less common. And, this type of CAR T cell also targeted CD19. And, it was the first type of CAR T-cell therapy that became, just this year, approved for treatment of adults with relapsed/refractory mantle cell lymphoma.

ZUMA-2: Study Design

- Multicenter, global phase II trial



Slide 52: ZUMA-2: Study Design

This is how the study was done. Patients had had several lines of prior therapies. They had the T cells collected, we gave them conditioning chemotherapy, and then once the T cells returned we infused the patients and monitored them for side effects and also for efficacy.

ZUMA-2: Baseline Characteristics

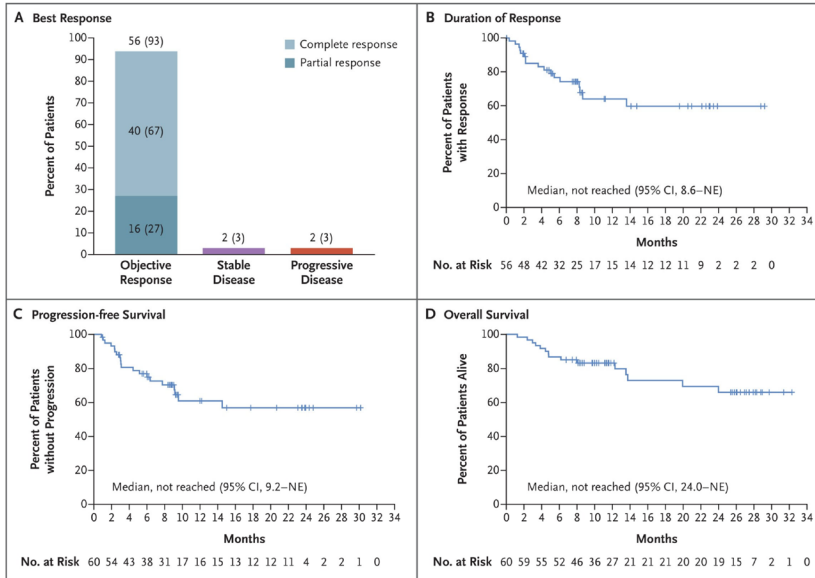
Characteristic	N = 68
Median age, yrs (range)	65 (38-79)
▪ ≥ 65 yrs, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV, n (%)	58 (85)
ECOG PS 0-1, n (%)	68 (100)
Int/high-risk MIPI, n (%)	38 (56)
Ki-67 index ≥ 50%, n/N (%)	34/49 (69)
TP53 mutation, n/N (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)	38 (56)
MCL morphology, n (%)	
▪ Classical	40 (59)
▪ Pleomorphic	4 (6)
▪ Blastoid	17 (25)

Wang. ASH 2019. Abstr 754.

Slide 53: ZUMA-2: Baseline Characteristics

Patients had very advanced disease, and some of them had very high-risk disease. They had certain mutations like TP53 or certain types of mantle cell lymphoma like blastoid or pleomorphic variant, which are more aggressive.

ZUMA-2: Objective Response, Duration of Response, Progression-free Survival, and Overall Survival



Wang M et al. N Engl J Med 2020;382:1331-1342

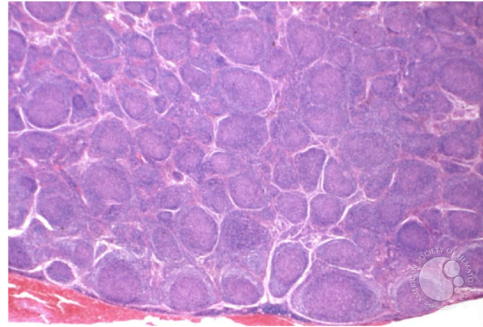
- **ORR of 93% (CR: 67%)**
- Median DoR: not reached (95% CI: 8.6-NE)
 - 57% of all responders and 78% of those with a CR remained in remission
- Median f/u for initial 28 patients treated: 27 mos (range: 25.3-32.3)
 - 43% remained in remission without additional treatment
- ORR consistent across subgroups

Slide 54: ZUMA-2: Objective Response, Duration of Response, Progression-free Survival, and Overall Survival

And, the responses were actually remarkable. So, 93% of patients achieved some response, with 67% of patients achieving a complete response. And, the median duration of response in the study has not yet been reached. And, if we follow these patients long-term, so beyond 2 years, 43% of them have remained in remission without requiring additional therapy. Whereas we know that with most available targeted therapies that we have, duration of remission is typically less than 2 years.

CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- Diffuse Large B-Cell Lymphoma (DLBCL)
- Mantle Cell Lymphoma (MCL)
- **Follicular Lymphoma**
- **Marginal Zone Lymphoma**



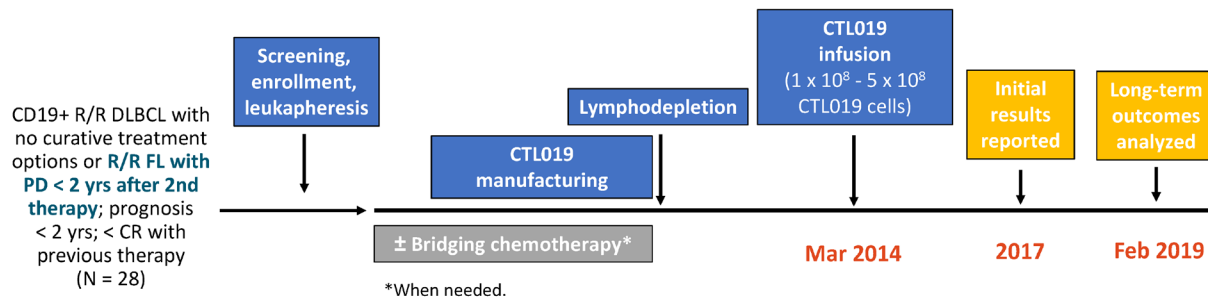
ASH Image Bank – American Society of Hematology

Slide 55: CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

What about follicular lymphoma and marginal zone?

UPenn CAR-T-cells (CTL019) in R/R CD19+ B-Cell NHLs

- Single-center trial at University of Pennsylvania; CTL019 construct: α -CD19-4-1BB-CD3 ζ



- Primary endpoint: ORR at 3 mos
- Secondary endpoints: PFS, RD, OS

Schuster. NEJM. 2017;377:2545. NCT02030834

Slide credit: clinicaloptions.com

Slide 56: UPenn CAR-T-cells (CTL019) in R/R CD19+ B-Cell NHLs

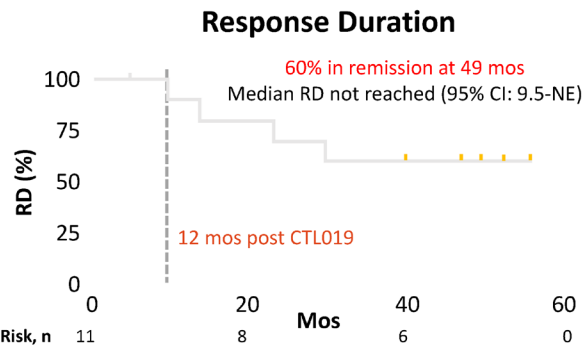
We have several trials in this area as well, and I will not mention them all, but I will go back to the University of Pennsylvania CAR T-cell study targeting CD19 in B-cell non-Hodgkin lymphomas that included patients with follicular lymphoma, because this is the study that has the longest follow-up.

Patients had high-risk follicular lymphoma, typically had had several lines of therapy, and many of them had progressed within 2 years of their initial treatment, which usually is associated with a worse outcome in follicular lymphoma.

UPenn CTL019 in Follicular Lymphoma: 4-Yr Follow-up

Characteristic	FL
Enrolled, N	16
Infused, n	14
Median age, yrs (range)	59 (43-72)
Female, n (%)	9 (64)
Prior Rx, median n (range)	5 (2-10)
Advanced stage, n (%)	14 (88)
ECOG PS, median (range)	0 (0-1)
Prior HCT, n (%)	4 (25)
Bridging therapy, n (%)	10 (71)

Best ORR: 78%; CR, 71% (10/14); PR, 7% (1/14)
Median PFS: 32 mos (95% CI: 3.5-NE);
 60% progression free at 49 mos
OS: 64% alive at 49 mos



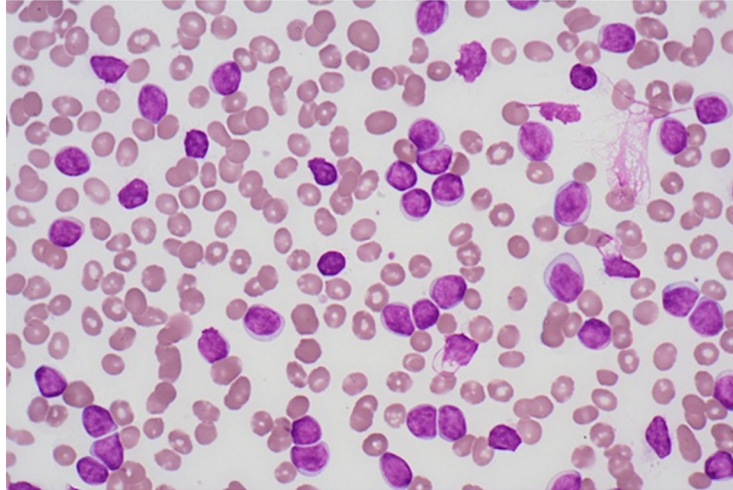
Chong. ICML 2019. Abstr 090.

Slide credit: clinicaloptions.com

Slide 57: UPenn CTL019 in Follicular Lymphoma: 4-Yr Follow-up

You can see here that the median number of prior therapies the patients had were 5 and they vary from 2 to 10. Best overall response rate was 78%, with complete response rate of 71%. And, with several year follow-up, with 49 months now, 60% of those patients still remain in remission, so really remarkable.

CAR T-Cell Therapy in Chronic Lymphocytic Leukemia (CLL)

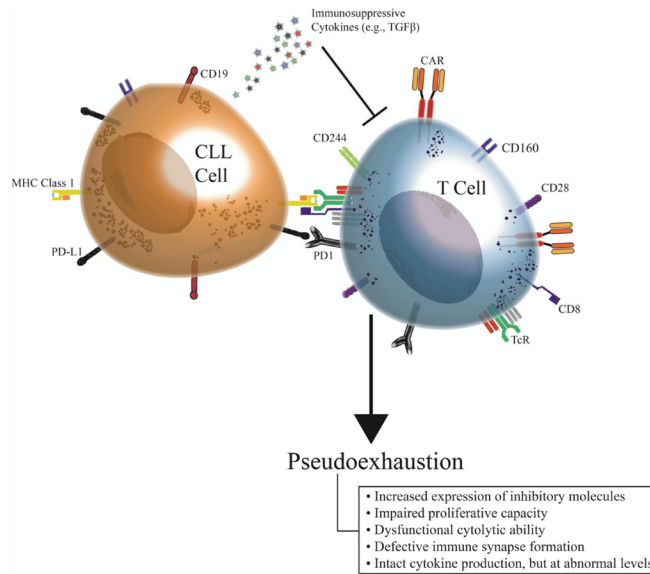


Increased numbers of mature lymphocytes
in peripheral blood

Slide 58: CAR T-Cell Therapy in Chronic Lymphocytic Leukemia (CLL)

I am moving from one disease to the next because I still have quite a bit to cover, so I will move to chronic lymphocytic leukemia now.

Improving CLL Therapy with CAR T-cells



Fraietta JA, Schwab RD, Maus MV. Semin Oncol. 2016 Apr;43(2):291-9.

Slide 59: Improving CLL Therapy with CAR T-cells

And, as you know, this is the most common type of leukemia that we see. And, the clinical course in patients with CLL is very variable. Some patients don't require treatment at all and others have a more rapidly progressive disease course.

Feasibility and efficacy of JCAR014 CD19-targeted CAR T cells with concurrent ibrutinib* for CLL after ibrutinib failure

Patient Characteristics (n=36)	Ibr Cohort (n=17)	No-Ibr Cohort (n=19)	P value
Number of prior therapies	5 (4,7)	5 (4,6)	0.55
Prior progression on Ibrutinib	16 (94%)	18 (95%)	1.00
CRS			
None	4 (24%)	2 (11%)	0.39
Any grade	13 (76%)	17 (89%)	0.39
CRS grade 0-2	17 (100%)	14 (74%)	0.05
CRS grade 3-5	0 (0%)	5 (26%)	0.05
Neurotoxicity			
None	12 (71%)	11 (58%)	0.50
Any Grade	5 (29%)	8 (42%)	0.50
OR at 4 wks 2008 iwCLL	14 (88%)	10 (56%)	0.06
Nodal response at 4 wks CR/PR	10 (83%)	10 (59%)	0.23

* Ibrutinib was scheduled to begin ≥2 weeks before leukapheresis and continue for ≥3 months after CAR T-cell infusion.

Gauthier et al., Blood, 2018

Slide 60: Feasibility and efficacy of JCAR014 CD19-targeted CAR T cells with concurrent ibrutinib* for CLL after ibrutinib failure

Typically, we reserve treatment for patients who are symptomatic and disease progresses very rapidly. And, we do have many targeted therapies now like BTK inhibitors, like ibrutinib, acalabrutinib, or BCL2 inhibitors like venetoclax, but this disease still remains incurable, with the exception of allogeneic stem cell transplant, that for many patients is not an option because of age and other comorbid illnesses.

So, you know, what can we do to improve on the response of the Bruton tyrosine kinase and BCL2 inhibitors in CLL? Several CAR T-cell studies were done in this area as well and were reported by multiple different cancer centers, including the National Cancer Institute, Sloan-Kettering Cancer Center, Baylor, University of Pennsylvania. And, what became evident is that the overall response rates in CLL and the complete response rates were much lower than patients with ALL or with diffuse large B-cell lymphoma.

CAR-T and Ibrutinib in CLL: Sequential or simultaneous?

- CD19 CAR T-cell therapy with concurrent ibrutinib is well tolerated.
- The 4-week ORR using 2018 International Workshop on CLL (iwCLL) criteria is higher with Ibrutinib combination, and more patients achieve a minimal residual disease (MRD)-negative marrow response by *IGH* sequencing.
- The 1-year overall survival and progression-free survival (PFS) probabilities are higher higher with Ibrutinib combination.
- Compared with CLL patients treated with CAR T cells without ibrutinib, CAR T cells with concurrent ibrutinib were associated with lower CRS severity and lower serum concentrations of CRS-associated cytokines, despite equivalent in vivo CAR T-cell expansion.

Slide 61: CAR-T and Ibrutinib in CLL: Sequential or Simultaneous?

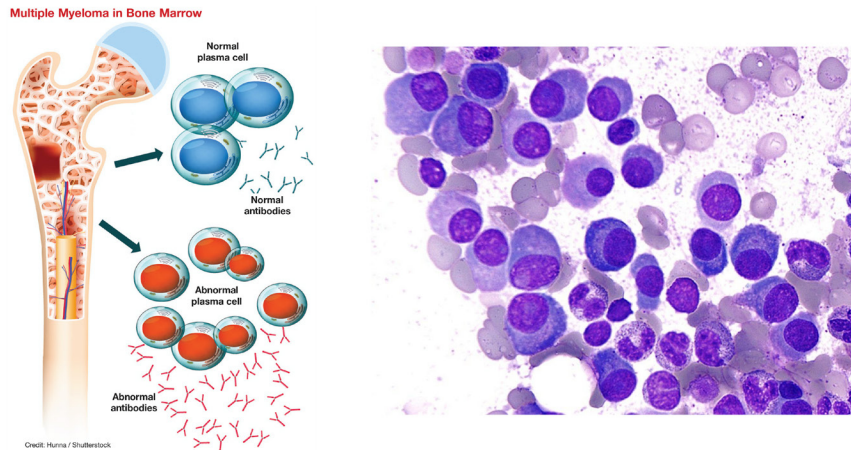
So why is that? Why are the responses with CAR T-cell therapy lower in CLL?

Data from CLL studies has shown that the T lymphocytes are not able to mount as strong immune response against the CLL cells. And, it has to do with the environment within which the leukemia B cells reside, which is an environment that really promotes their survival. And, it is key to the abilities of the T cells to provide immune surveillance.

The T cells that have been isolated from CLL patients have markers of what we call exhaustion. So, they're really tired T cells. And they also, the CLL cells, also release certain factors that suppress the T cells, the CAR T cells from working. So, the environment within which the CLL cells reside is very different from the environment in diffuse large B-cell lymphoma, for example, and it's very different from ALL, where most of the disease is not in lymph nodes but it's actually circulating in the bloodstream, which makes it easier for the CAR T cells to target.

One of the remarkable studies actually looked at combining CAR T-cell therapy with ibrutinib in patients whose disease had progressed on prior treatment with ibrutinib. And, this was based on some preclinical data, so data before studied in humans that showed that it could really improve on the efficacy of the CAR T cells and also reduce cytokine release syndrome. And, that is indeed what they saw, is that when they combined the T cells, the CAR T cells with ibrutinib in CLL, you can see that Grade 3 and 5, which are the most advanced grades of cytokine release syndrome, were not seen. So, zero. And, while some patients developed cytokine release syndrome, it was very manageable because it was early grade. And, you can see that at 4 weeks the overall response rate was 88% and that 83% of patients had either a complete remission or a partial remission of their lymph nodes. So, this was really remarkable. The combination was very efficacious and also caused less toxicity. This therapy was well tolerated. The progression-free survival was higher with this combination, compared to CAR T-cell therapy alone. And, it was associated with lower toxicity.

CAR T- Cell Therapy in Multiple Myeloma (MM)



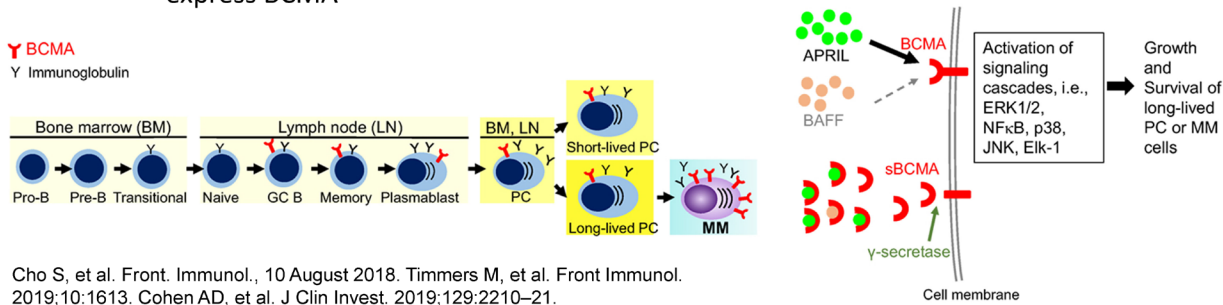
Clinician Reviews. 2018 January;28(1):16-18,20-21

Slide 62: CAR T- Cell Therapy in Multiple Myeloma (MM)

I will now change gears to multiple myeloma. And as you know, that is a cancer of these very mature B cells in the body, called plasma cells.

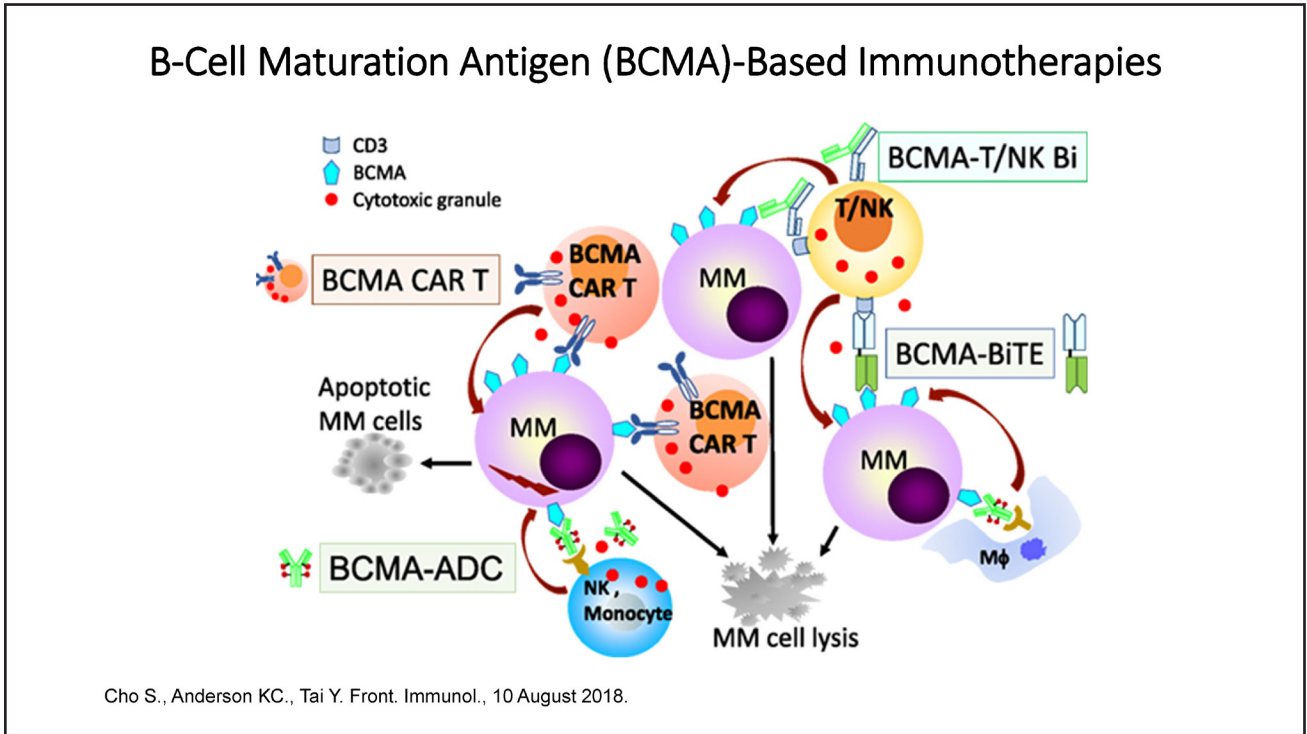
B-cell Maturation Antigen (BCMA)

- Functions to maintain long-lived plasma cell homeostasis
 - Essential in regulating B-cell maturation and differentiation
- Highly expressed on malignant plasma cells in MM
 - Increased expression associated with progression of disease
- BCMA shed from the surface of plasma cells leads to soluble BCMA (sBCMA) detectable in circulation
- Higher concentrations of sBCMA associated with poorer outcomes
 - Low level expression on healthy differentiated B-cells; no other normal cells/tissues express BCMA



Slide 63: B-cell Maturation Antigen (BCMA)

While there are some studies that have looked at CD19 as a target in multiple myeloma, the majority of the studies have focused on this protein called B-cell maturation antigen or BCMA, on the surface of the plasma cells. This protein is very important to maintain the homeostasis or the survival of the plasma cells. It regulates maturation and differentiation under normal circumstances, but it's also expressed very highly on the surface of the malignant plasma cells. And, high expression of this protein on the surface is associated with progression of the disease.



Slide 64: B-Cell Maturation Antigen (BCMA)-Based Immunotherapies

There are many types of therapies targeting BCMA and the field is very rapidly evolving, and really impressive responses have been seen. The treatment modalities include antibody drug conjugates, they include these BiTEs, so bi-specific T-cell engagers target BCMA and engage the T cells, and then importantly there are BCMA targeting CAR T cells, which don't rely just on the patient's own T cells to target BCMA but bring in these genetically modified CAR T cells that are able to proliferate in high numbers and live long in the body.

Phase I NCI BCMA CAR

- Single-center, open-label phase I trial in patients with R/R MM, **N=16**
- CD28 costimulatory domain, gamma-retroviral vector, dose levels: 0.3, 1, 3, and 9 ×10⁶ CAR T-cells/kg
- Lymphodepletion: Flu 30 mg/m² and Cy 300 mg/m² daily on days -5 to -3

Baseline Characteristics		Results		Adverse Events and Management	
Median lines of prior therapy	9.5	PR or better	13 (81%)	Grade 3-4 CRS	6 (37.5%)
High risk cytogenetics	40%	Median EFS	31 weeks	Tocilizumab	5 (31%)
Del(17p)	33%	DoR >1 year	5 (31%)	Tocilizumab + steroids	4 (25%)
Refractory to last treatment	63%	DoR > 6 months	9 (56%)		

Brudno JN, et al. J Clin Oncol. 2018;36:2267–80.

Slide 65: Phase I NCI BCMA CAR

So, this is an early study, a Phase I study done by the NCI (National Cancer Institute) targeting BCMA. And, what they saw is that in patients who had had multiple lines of prior therapies, so about 9; 81% of them achieved at least a partial remission, and that there were some of the toxicities that we expected with CAR T, such as cytokine release syndrome and neurotoxicity.

Phase I Data: BCMA-Directed CAR T Cells in Multiple Myeloma

	BB2121 (BLUEBIRD) Idecabtagene vicleucef	LCAR-B38M (LEGEND)	JCARH125 (JUNO)
Population	33	57	44
# Prior Tx	7	3	7
CART Dose	50-800 x 10 ⁶	0.07-2.1 x 10 ⁶ /kg	50-450 x 10 ⁶
ORR	85%	88%	82%
CR	45%	74%	27%
CRS All Grades (Grade 3/4)	76% (6%)	89% (7%)	80% (9%)
Med Onset of CRS	2d	9d	3d
Neurotox All Grades (Grade 3/4)	42% (3%)	2% (0%)	25% (7%)
Med PFS	11.8 months	15 months	-

Raje et al, NEJM 2019; Zhao et al, ASH 2018, Mailankody et al, ASH 2018.

Slide 66: Phase I Data: BCMA-Directed CAR T Cells in Multiple Myeloma

So, based on that early phase data, there are now several studies that have been ongoing looking at BCMA in Phase II and in Phase III, where large numbers of patients are included in the trials, and they're looking not just at safety but also efficacy. And you can see that the response rates are remarkable. Overall response rates in the order of 80 to 88%. And then, even complete response rate in the order of 50 to 75%. So really remarkable in patients who had had multiple lines of therapy.

Future Directions of Most Advanced CAR T Products in Multiple Myeloma

- Race to FDA Approval in the USA
 - Global Pivotal Trial (KarMMa) of Idecabtagene vicleucel just completed enrollment
 - Legend/Janssen enrolling on pivotal trial of LCAR-B38M or JNJ-68284528
- Use Beyond the Refractory Setting
 - Trials in earlier phase of disease
 - KarMMa 3 – randomized Phase 3 of bb2121 vs SOC in pts with 2-4 priors
 - KarMMa 2 – cohort of pts with early relapse 9 (with or without ASCT), bb2121 as 2nd line
 - Trials in conjunction with ASCT/Consolidation in MRD
 - KarMMa2 – Cohort 2C upfront in pts with inadequate response to ASCT
- Dual antigen targeting to mitigate Ag escape
 - UPenn/Novartis (BCMA CART with or without CART19) [NCT03549442] – in pts responding to 1st or 2nd line therapy for high-risk MM

Slide 67: Future Directions of Most Advanced CAR T Products in Multiple Myeloma

So, what does the future bring for multiple myeloma? It's actually a race right now to get FDA approval. So, idecabtagene vicleucel is probably the one that's closest to approval, based on data from the KarMMa study. And then, another product that has very favorable data and very high complete remission rates is pivotal trial of LCAR-B38M by J&J.

There are trials that are ongoing using these cells beyond the refractory setting, so moving them into earlier phases of disease, combining them with transplant or used as a consolidation after transplant, and also dual antigen targeting CAR T cells, that I mentioned earlier, so that we can avoid relapse. For example, CAR T cells that are targeting BCMA and CD19 at the same time.

So, it's a very exciting field and I think in the near future we are going to see more and more investigational allogeneics, so off-the-shelf CAR T cells that are derived from donors are healthier, and have a very short manufacturing time, or they're really off-the-shelf and available when you need them.

Investigational Allogeneic CAR T-cells in Hematologic Malignancies

Trial	Phase	Planned N	Primary Endpoints	Treatment
NCT02746952 (CALM)	I	30	DLT, Safety	UCART19, anti-CD19 allogeneic CAR T-cell in adult R/R ALL
NCT02808442 (PALL)	I	18	Safety	UCART19, anti-CD19 allogeneic CAR T-cell in pediatric R/R ALL
NCT03939026 (ALPHA)	I/II	24	DLT, ORR	ALLO-501, anti-CD19 allogeneic CAR T-cell in R/R LBCL or FL
NCT03190278 (AMELI-01)	I	59	DLT, Safety	UCART123, anti-CD123 allogeneic CAR T-cell in R/R AML
NCT04093596 (UNIVERSAL)	I	90	DLT	ALLO-715, anti-BCMA allogeneic CAR T-cell in R/R MM
NCT04142619 (MELANI-01)	I	18	Safety	UCARTCS1A, anti-CS1 allogeneic CAR T-cell in R/R MM
NCT03971799	I/II	34	DLT, ORR	CD33CART, anti-CD33 allogeneic CAR T-cell in R/R AML

www.clinicaltrials.gov. Accessed December 12, 2020

DLT: Dose limiting toxicity

Slide 68: Investigational Allogeneic CAR T-cells in Hematologic Malignancies

As I showed you here, they are targeting CD19, they're targeting BCMA, and other proteins like CS1 in multiple myeloma, they're targeting AML, for example, and so I think all of this is what we're going to be looking forward to in the near future.

Conclusions

- CD19 CAR T-cells are the most successful and best known CAR therapy providing durable responses in pediatric/young adult B-cell ALL, adult LBCL and MCL
- Unique toxicities of CRS and neurotoxicity may occur
 - Strategies for uniform grading to be used across clinical trials and the post-approval clinical setting recently published
- Clinical trials evaluating the use of CAR T-cells alone or in combination with other agents, in other malignancies, and versus standard of care therapies are ongoing
- Allogeneic CAR T-cell therapy may overcome barriers to current FDA approved products

Slide 69: Conclusions

So, in summary, even though these CAR T cells were approved as a target for CD19 in ALL and lymphoma, I think that the data is very exciting in other diseases as well, and soon we will have approvals in other disease settings, either alone or in combination with other agents. And, that these off-the-shelf ones will really overcome some of the barriers that we've encountered with the current FDA approved products.

And, this concludes my presentation and I'm really happy to take questions.

Q&A SESSION

Advances in CAR T-cell Therapy

- **Ask a question by phone:**
 - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
 - Click “Ask a question”
 - Type your question
 - Click “Submit”

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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Slide 70: Q&A Session

Ms. Figueroa-Rivera:

Thank you so much, Dr. Isufi, for volunteering your time and expertise with us today, especially during these busy times.

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

And Doctor, our first question from the web. Julia asks, can I, or should I ask for a double dose of CAR T be manufactured in case a second infusion is required? And, she does go on to say that she is 71 years old and a lot of folks are asking, if there is an age limit for CAR T-cell therapy?

Dr. Iris Isufi:

Yes. So, that's an excellent question, Julia. There is currently no age limit for CAR T-cell therapy, although it is important to note that there were very few patients in their 80s in the trials and no patients in their 90s. But, there were certainly patients in their late 70s in the trials. And, it is a therapy that is better tolerated than high-dose chemotherapy and autologous stem cell transplant. So, we are able to take patients into CAR T that don't necessarily meet the criteria for autologous stem cell transplant. The patients can have less lung reserve, they can have less cardiac reserve or heart function, and they're still able to tolerate CAR T cells.

And, it's also important to note that the products are different from each other. Some of them have been associated with, for example, less neurologic toxicity, others with less cytokine release syndrome, so that we are able to tailor the CAR T-cell therapy to the patient's age and comorbidities. So, you know, that's regarding the age.

Now, regarding the other question of storing T cells, that's also an excellent question, but as I mentioned, T cells from patients who have had multiple lines of therapy are not always healthy. And sometimes, there're just enough for us to generate what we need.

In the event that more cells than expected are collected and produced, the company or the treatment center is able to freeze those cells and keep them for future use. However, in patients who, whose disease comes back after CAR

T-cell therapy, it is also a discussion with your physician whether the same CAR T cells could be used based on the response that you had to the first CAR T therapy, or whether a different CAR T type of therapy can be used.

I would say that if the remission lasts beyond 3 months after the first CAR T, it's certainly reasonable to use CAR T again if it has been stored or to get a different CAR T cell product.

Ms. Figueroa-Rivera:

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

Operator:

Certainly. Thank you, Lizette. We'll hear from Greg in Illinois. Please go ahead, your line is open.

Greg:

Yeah, kind of in line with what you discussed about healthy T cells being used in CAR T, is there any consideration in any of the research or trials that you've heard of, the use of donor cells from 100% HLA matched donors to be used for engineering CAR T cells?

Dr. Iris Isufi:

Yes. So, in patients who have already had an allogeneic transplant where a donor is available, that has been looked at in ALL, for example, where those healthy cells have been obtained from the donor. But, it is very difficult to, and very time-consuming, to actually match the patient's HLA to a donor. For example, for allogeneic stem cell transplant, that can take 2 months. And, as you know, 2 months is a very long time when patients have a diagnosis of leukemia and lymphoma. That's why the efforts are really to use non-HLA matched allogeneic CAR T cells, but to devise ways where the patient's immune system does not recognize them as being foreign. So, there are genetic manipulations that we can do, where the body's not recognizing them foreign, and we don't really have to fully HLA match them. But, that's an excellent question.

Ms. Figueroa-Rivera:

Thank you. And, Doctor, the next question comes from Judith. She's asking if the COVID vaccine is recommended for CAR T cell patients?

Dr. Iris Isufi:

That's also another excellent question and I can tell you that my e-mail and phone line have been very busy trying to answer this question. And unfortunately, we do not have data about cancer patients in general, transplant patients, or CAR T cell patients, because the studies really enrolled healthy patients, and we really need large numbers of cancer patients to generate that kind of data. So, until that becomes available, I think that it will be on a case-by-case basis and it will depend on how far out you are from CAR T-cell therapy, and how well your immune system is doing. And, we can certainly check the B cells and the T cell subsets in the blood to see if the body's immune system has recovered after CAR T and try to use that as a guidance.

I don't necessarily, and again this is my personal opinion, there is no data, I don't necessarily think it's going to be harmful. But, the question is, is it going to work, is it going to provide protection, because you need a functioning immune system for these vaccines to work.

Ms. Figueroa-Rivera:

Thank you. And, our last question today is from Mary Jo. Mary Jo's asking about the cost and whether it is typically covered by Medicare or other insurances.

Dr. Iris Isufi:

The first products that were approved varied in cost, anywhere from \$375,000 to \$475,000, and that is just the cost of the product itself. The reimbursement from insurance companies, including Medicare is low, and it does not cover the entire cost of the products. That being said, the major academic medical centers that are offering this type of therapy are sort of eating up the rest of the costs from what is not being reimbursed and they're always in negotiations with insurance companies to cover as much as possible, because hospitalization and, and in terms of care unit stay, can be quite costly. But, this is not something that the patients are necessarily stuck with a bill. But, for the time being, if there are clinical trials available and patients are having difficulty with insurance coverage, we do tend to offer a clinical trial, so that as many patients as possible can get this type of therapy.

But yes, I've treated many Medicare and Medicaid patients in my clinic with CAR T-cell therapy and they have not been asked to pay.

Ms. Figueroa-Rivera:

Thank you so much for your question, Mary Jo, which was our final question today. And, thank you so much, Dr. Isufi, for your continued dedication to patients.

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Slide 71: LLS EDUCATION & SUPPORT RESOURCES

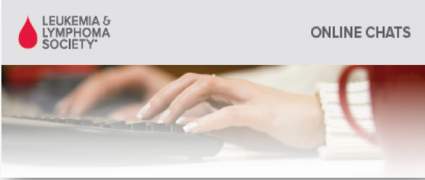
Ms. Figueroa-Rivera:

And, for those of you who participated in today’s program, we hope the information presented today will assist you and your families in your next steps.


If we weren’t able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us at infocenter@LLS.org.




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Patient Podcast
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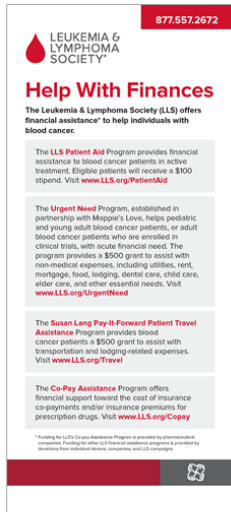
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Slide 72: LLS EDUCATION & SUPPORT RESOURCES

We also have a Clinical Trials Support Center (CTSC), where Clinical Trial Nurse Navigators, who are registered nurses with expertise in blood cancers, can assist you in finding out if a CAR T-cell clinical trial is right for you. And, you can find them at www.LLS.org/Navigation.

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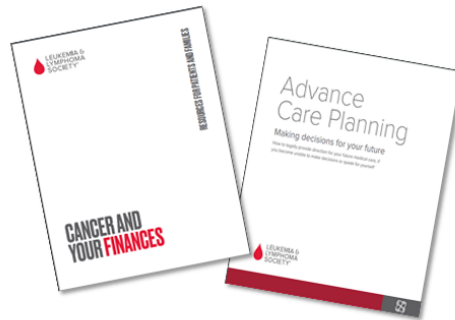
The **Susan Lang Pay-It-Forward Patient Travel Assistance** Program provides blood cancer patients a \$500 grant to assist with transportation and lodging-related expenses. Visit www.LLS.org/Travel

The **Co-Pay Assistance** Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit www.LLS.org/CoPay

*Funding for LLS Co-pay Assistance Program is provided by pharmaceutical companies. Funding for other LLS financial assistance programs is provided by individuals who have voluntarily donated to the program. Amount of grant may vary.

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer:

www.LLS.org/Finances



To order free materials: www.LLS.org/Booklets

BEATING CANCER IS IN OUR BLOOD.



Slide 73: LLS EDUCATION & SUPPORT RESOURCES

Again, we would like to acknowledge and thank Bristol Myers Squibb, CRISPR Therapeutics, Kite, a Gilead Company, and Novartis for support of this program.



Slide 74: THANK YOU

Dr. Isufi, thank you again for volunteering your time with us today.

And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

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