Slide 1: WHAT IS NEW IN CAR T-CELL THERAPY?

Slide 2: WELCOMING REMARKS

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

Welcome to all of you. And thank you all for joining us today to discuss CAR-T cell therapy as a potential treatment option for you or your loved one, as well as how CAR-T cell therapy has benefitted many patients and continues to bring hope to our blood cancer patients.

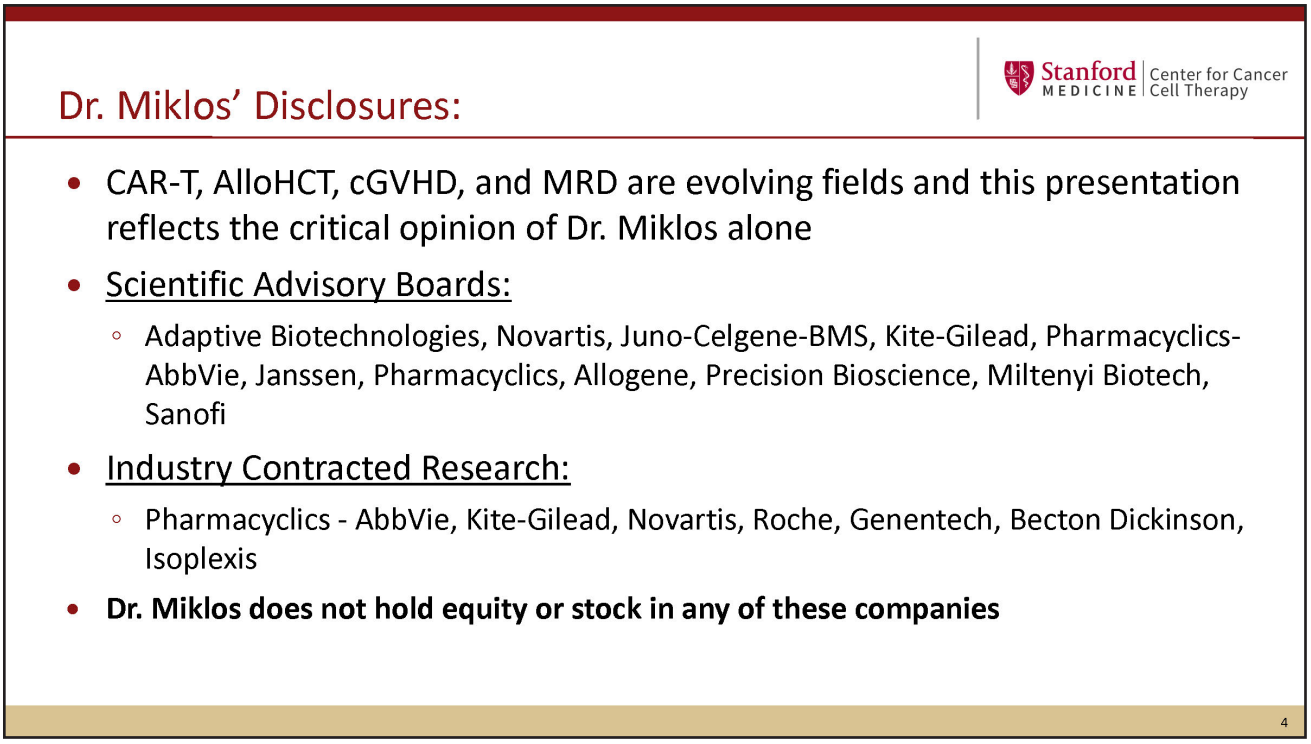
For this program we would like to acknowledge and thank Bristol Myers Squibb, CRISPR Therapeutics, Kite, a Gilead Company, and Novartis Oncology for their support of this program.

I am now pleased to introduce Drs. David Miklos and Surbhi Sidana from the BMT and Cell Therapy Division at Stanford University in Stanford, CA. Dr. Miklos, I'm privileged to turn the program over to you.

Slide 3: Advances in Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma

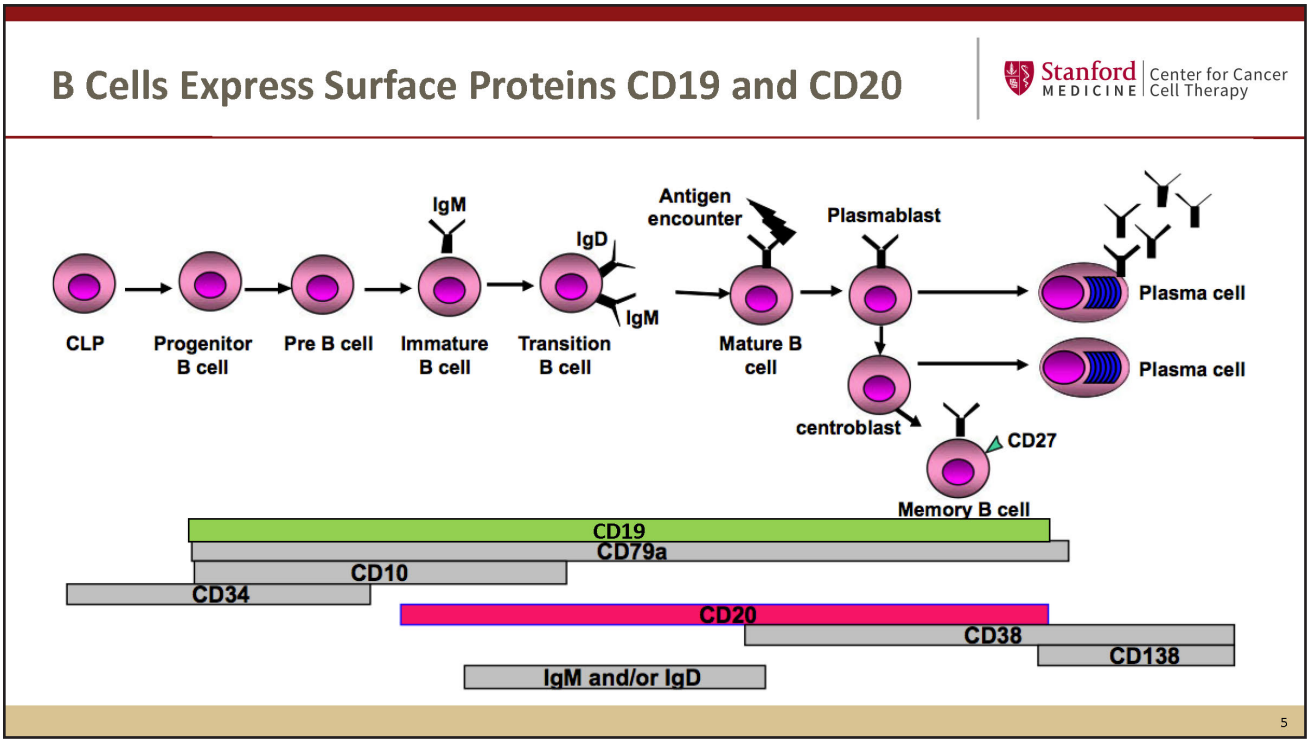
Dr. David Miklos:

Thank you, Lizette and thank you to The Leukemia & Lymphoma Society. They've supported research, they've helped all of our patients. It's a really wonderful organization. I welcome over 5000 guests to this telecast and Dr. Sidana and I are here in California. Sounds like you're around the world. I'm going to get right to it.



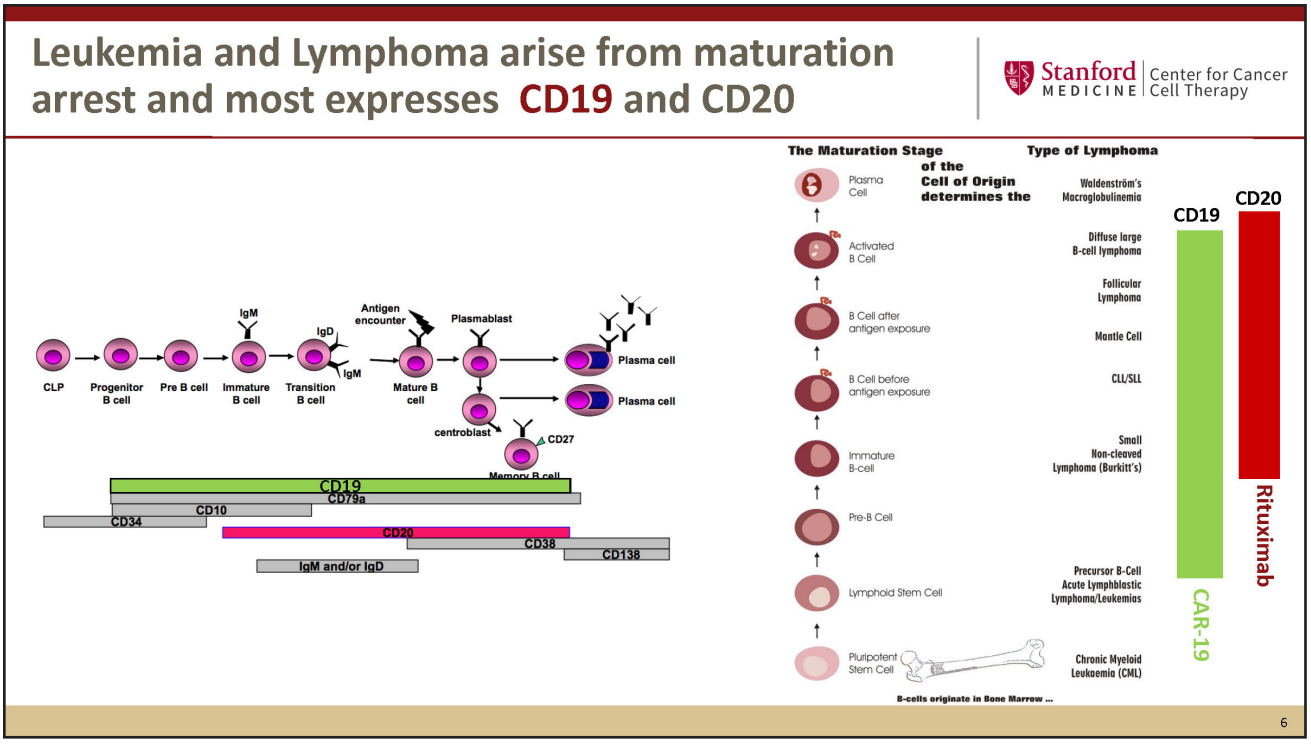
Slide 4: Dr. Miklos' Disclosures

Disclosures are available if you need to see them.



Slide 5: B Cells Express Surface Proteins CD19 and CD20

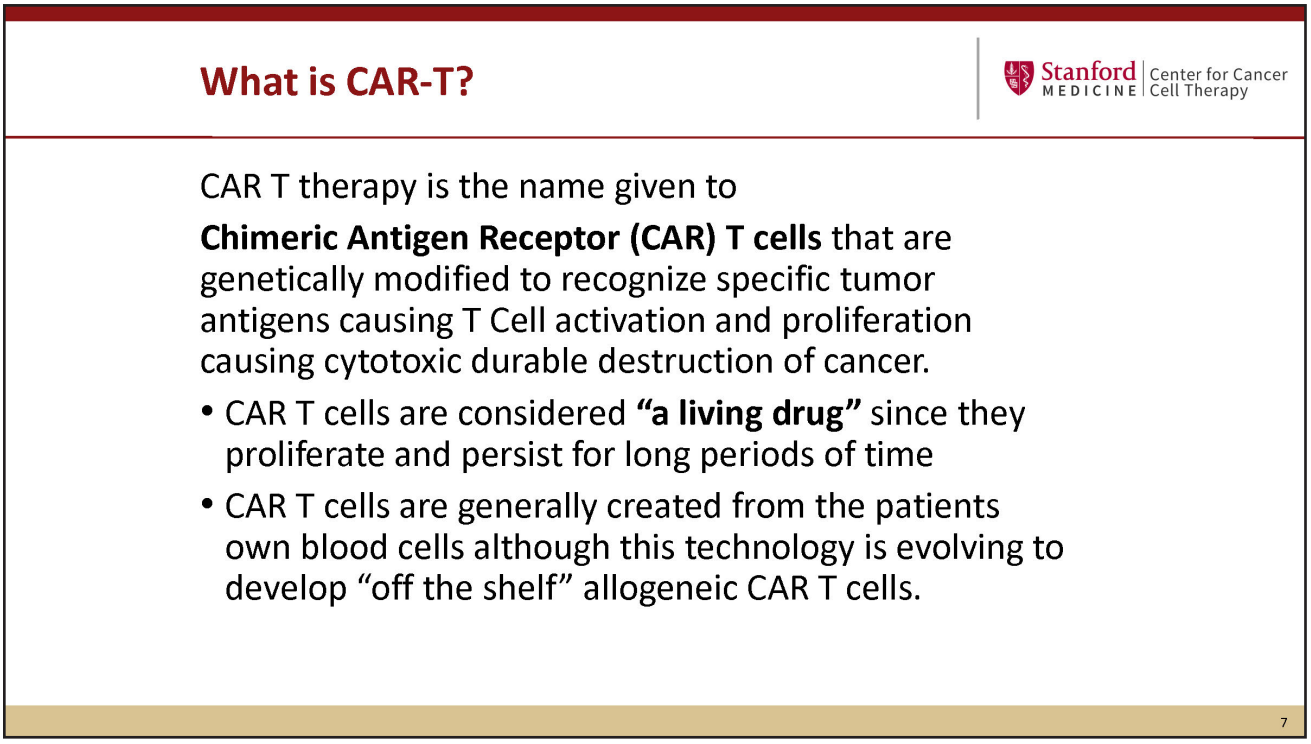
I think it's important that we remind all of us at The Leukemia & Lymphoma Society that the B cell cancers are a common problem for all people. The attention given to large cancers like lung cancer and prostate and breast cancer are important. Had we named all of the cancers, the Hodgkin's disease, the lymphoma, the CLL, as a B cell cancer, there'd be 150,000 newly diagnosed patients every year needing our care. And, this slide makes that point, that as we look at the developing B lymphocyte from early stem cell, common lymphoid progenitor on the left, to a mature plasma cell secreting antibodies, and now in the pandemic of COVID, we all know what antibody production is about, we understand that the maturation is associated with the expression of proteins on the surface of the B cells. Two proteins particularly I want to draw your attention to: CD19 and CD20. They are only expressed on B cells and they come on their early development of the B cell, they persist, but they're not there on the plasma cell at the end of B cell development.



Slide 6: Leukemia and Lymphoma arise from maturation arrest and most expresses CD19 and CD20

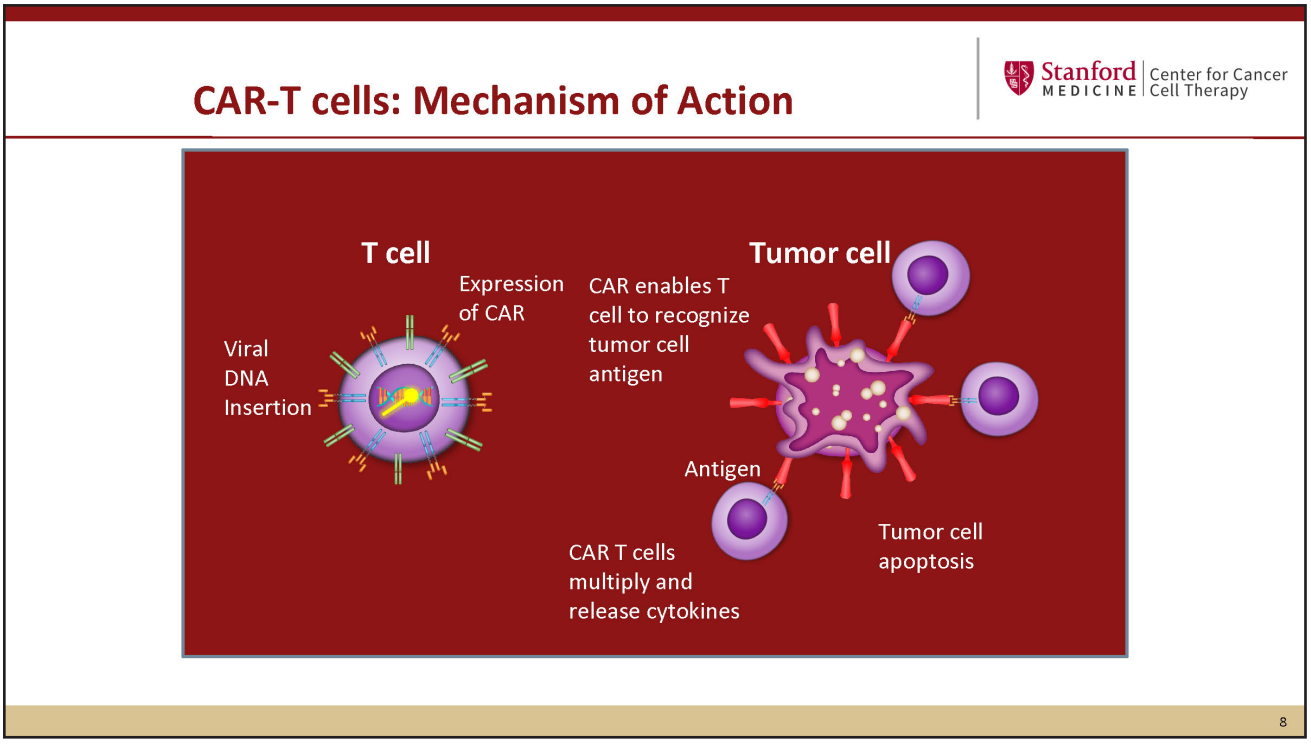
Now, I'm going to step further into this comparison of expression of proteins by showing on the right that the maturation arrest occurring at different stages of B cell development are associated with the types of cancers that are listed in the right-hand column. And early progenitor cells form acute lymphoblastic leukemia, late B cells form the basis of plasma cells. You may find variety of cancers, maybe some of you unfortunately are experiencing these cancers yourself, like follicular lymphoma, chronic lymphocytic leukemia, and mantle cell or large cell lymphoma.

What you see on the far right with that stripe of green and red is the expression of these 2 proteins, CD19 and CD20. Now, all of you are aficionados and understand that rituximab (Rituxan®), obinutuzumab (Gazyva®), ofatumumab (Arzerra®), these are monoclonal antibodies targeting CD20 that have been part of our armamentarium for 25 years. But for the last 5 years we've developed CAR-T cells against CD19. And this green stripe makes it evident to you that patients who have acute lymphoblastic leukemia, all the way through the late diffuse large B cell, could benefit from CAR-T cell therapy. That's the point of this slide.



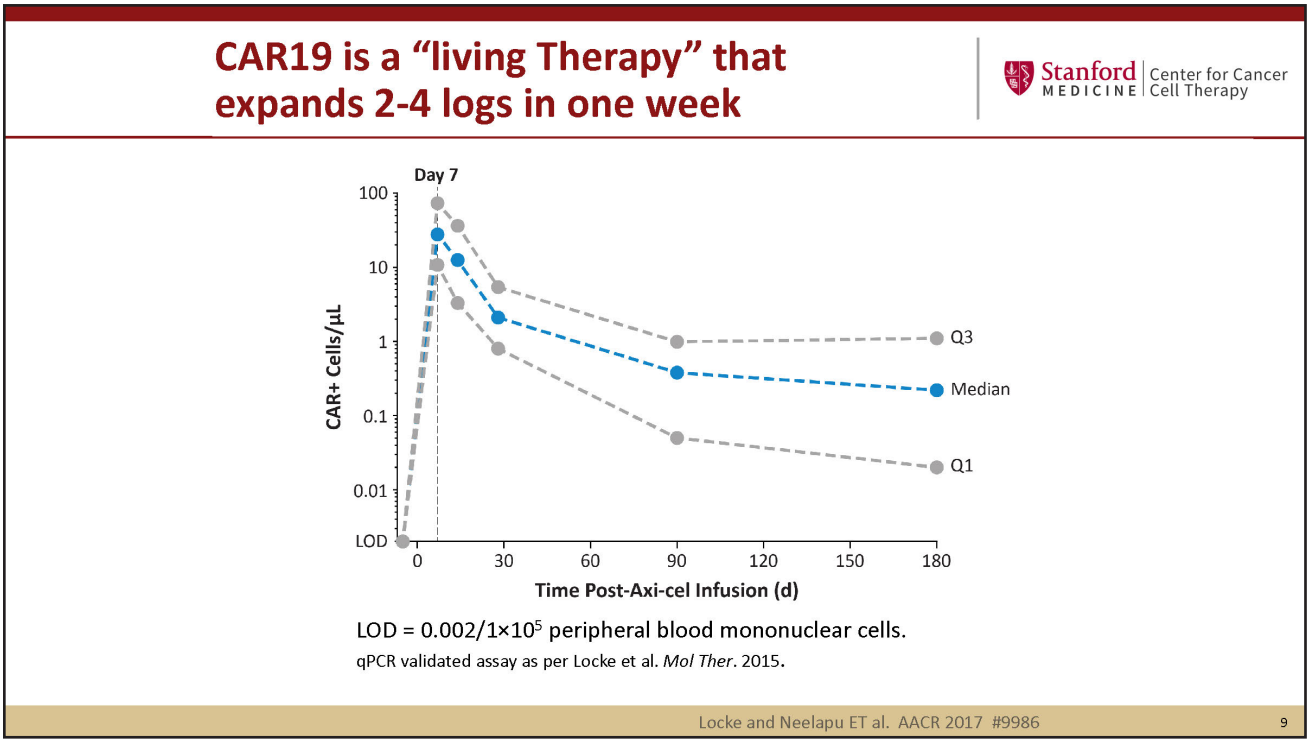
Slide 7: What is CAR-T?

What is CAR-T? CAR-T is the name given to chimeric antigen receptor T cells that are genetically modified to recognize these specific tumor antigens causing T cell activation and proliferation. They cause cytotoxic durable destruction of the cancer. We are hijacking the immune system and we are eradicating cancer with immunology. CAR-T cells are considered a living drug since they proliferate and they persist for long periods of time, and CAR-T cells are generally created from the patient's own blood cells. This is personalized therapy, although technology is being advanced to do off-the-shelf allogeneic CAR-T cells as well.



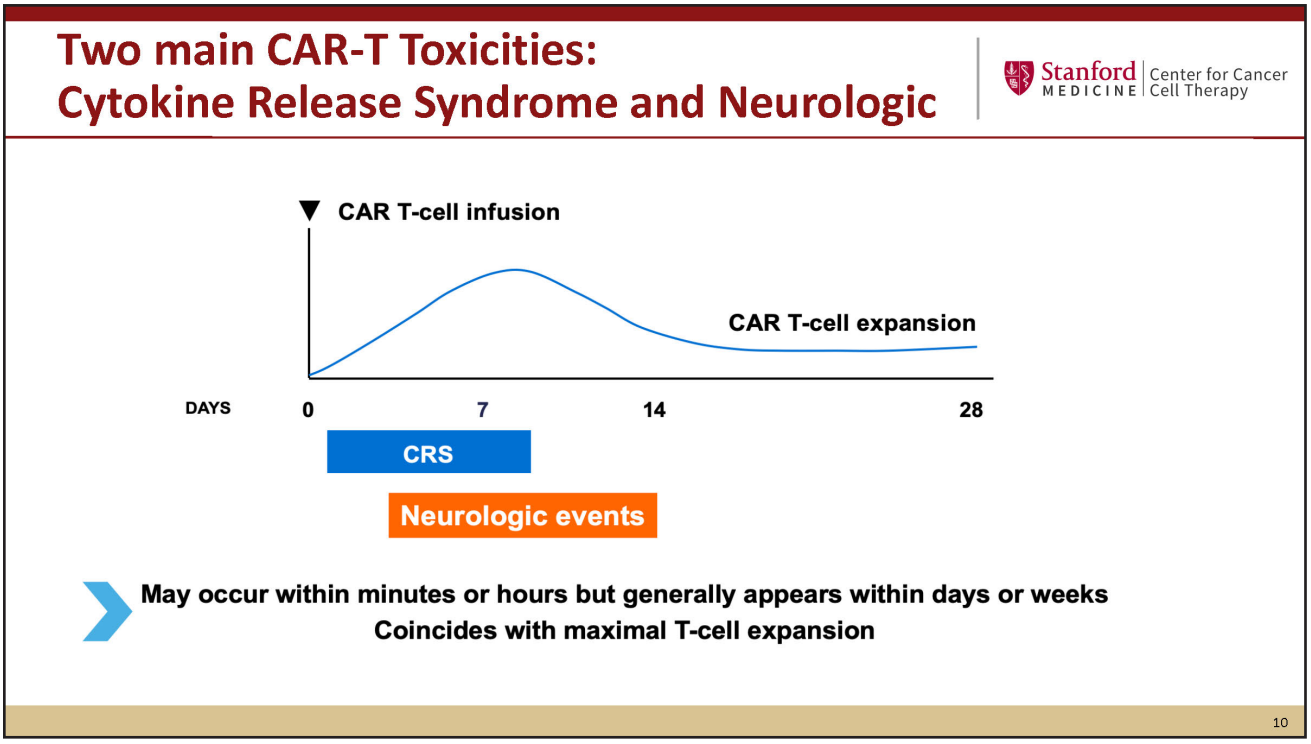
Slide 8: CAR-T cells: Mechanism of Action

This is an animated image and I'll try to walk us through some animation. Here on the left we see a patient's T cell and you can see that the DNA content in the center, that it's going to be genetically modified to express a new protein called the CAR, it's chimeric antigen of 3 things together. With this new protein targeting the lymphocytes, it moves into the tumor space, and it starts to attack by binding to the antigens on the tumor itself. So, here we have the cell moving into the tumor, kissing that antigen, and now releasing cytokines, killing molecules, and watch this tumor just eradicate through apoptosis.



Slide 9: CAR19 is a "living Therapy" that expands 2-4 logs in one week

Okay, that is dramatic. In scientific terms, a living therapy is one that we introduce into the body, and it expands exponentially, dividing every 7 hours, 2, 4, 8, 16, it's like the RAM in your computer, and after 7 to 14 days, these CAR-T cells have expanded 2 to 4 logarithms. That means, if we've entered 2 million cells, there's 2 billion cells 7 days later, frequently they represent 50% of the lymphocytes in a patient's blood system at the peak CAR expression. And, you can see on that curve that it also persists.

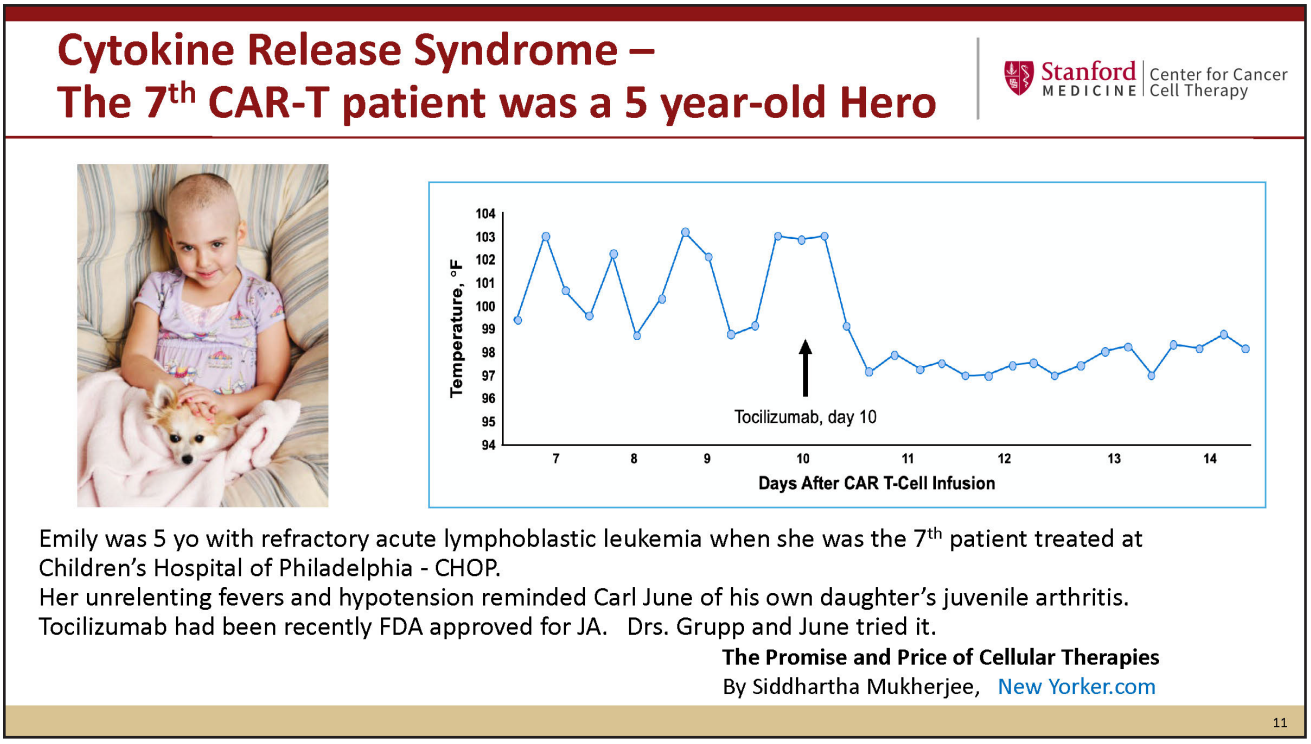


Slide 10: Two main CAR-T Toxicities: Cytokine Release Syndrome and Neurologic

Now in a more generalized form, this expansion of the CAR-T also correlates with 2 toxicities that we're all familiar with now: cytokine release syndrome or what I call the flu syndrome; and the neurological confusion or lack of attention that can follow the expansion of the CAR-T cell. So, in this schema of the blue increasing CAR-T, we see the block of cytokine release syndrome developing frequently 2 to 4 days after the cell infusion. This is the immune response of the T cell. Similar to the last time you had influenza or another gastroenteritis, achy, tired, fatigue, lack of appetite, bright lights bothered you, and you had a high fever, you may have felt lightheaded because of low blood pressure, that's cytokine release syndrome.

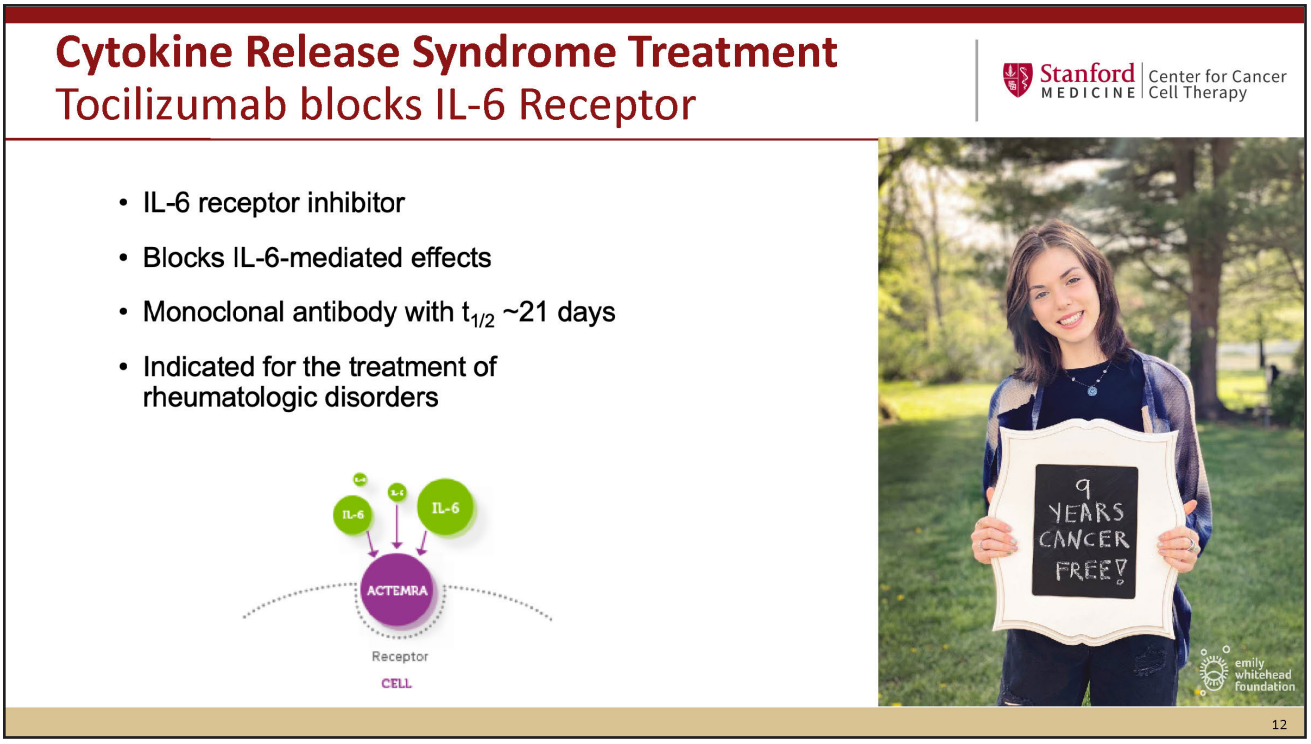
The confusion, lack of attention, sometimes even seizures that follow this are due to the cytokine inflammation, especially in the brain space.

Now, as we've gained experience with CAR-T cells we've been able to better manage these therapies. And, it's important to remind the audience that the non-relapse mortality of CAR-T therapy remains less than 2% through the 6-month treatment period.



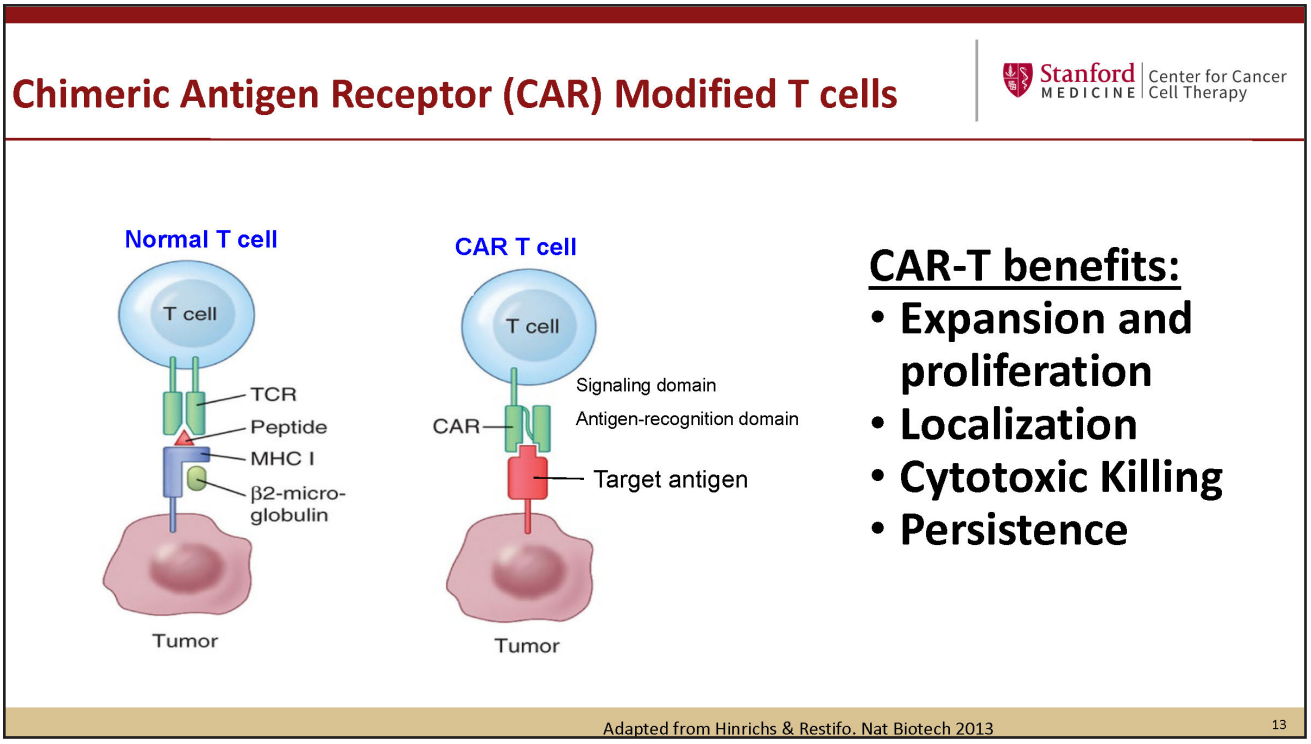
Slide 11: Cytokine Release Syndrome – The 7th CAR-T patient was a 5 year-old Hero

In addition, we've been gaining from heroes of CAR-T therapy, and here I show Emily Whitehead, a well-known popular advocate of CAR-T from the Children's Hospital of Philadelphia. Emily was 5, one of the first patients treated with acute lymphoblastic leukemia by Carl June and Steve Grupp, and her unrelenting fevers reminded Carl of his own daughter's juvenile arthritis, where those patients frequently receive tocilizumab (Actemra®), a monoclonal antibody that binds to the receptor of IL-6, and with that idea, that insight, Dr. June tried toci and it's become now one of our therapies for the prevention of cytokine release syndrome or the management.



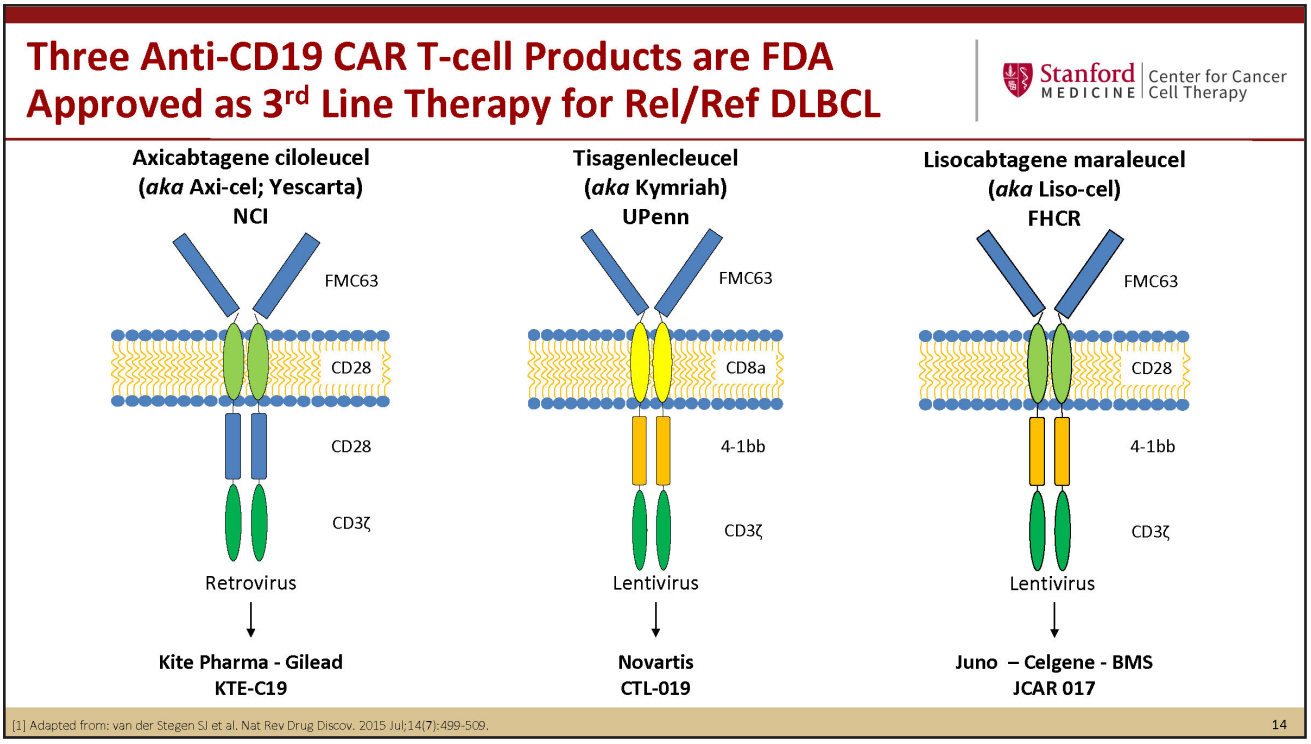
Slide 12: Cytokine Release Syndrome Treatment – Tocilizumab blocks IL-6 Receptor

And here is Emily nine years later, having never received another therapy, cancer-free and one of our greatest advocates for the advances of CAR-T cell therapy. Sidd Mukherjee's article that I cited there is a wonderful read in The New Yorker and I highly recommend you look that up for another insight into the advances of cell therapy.



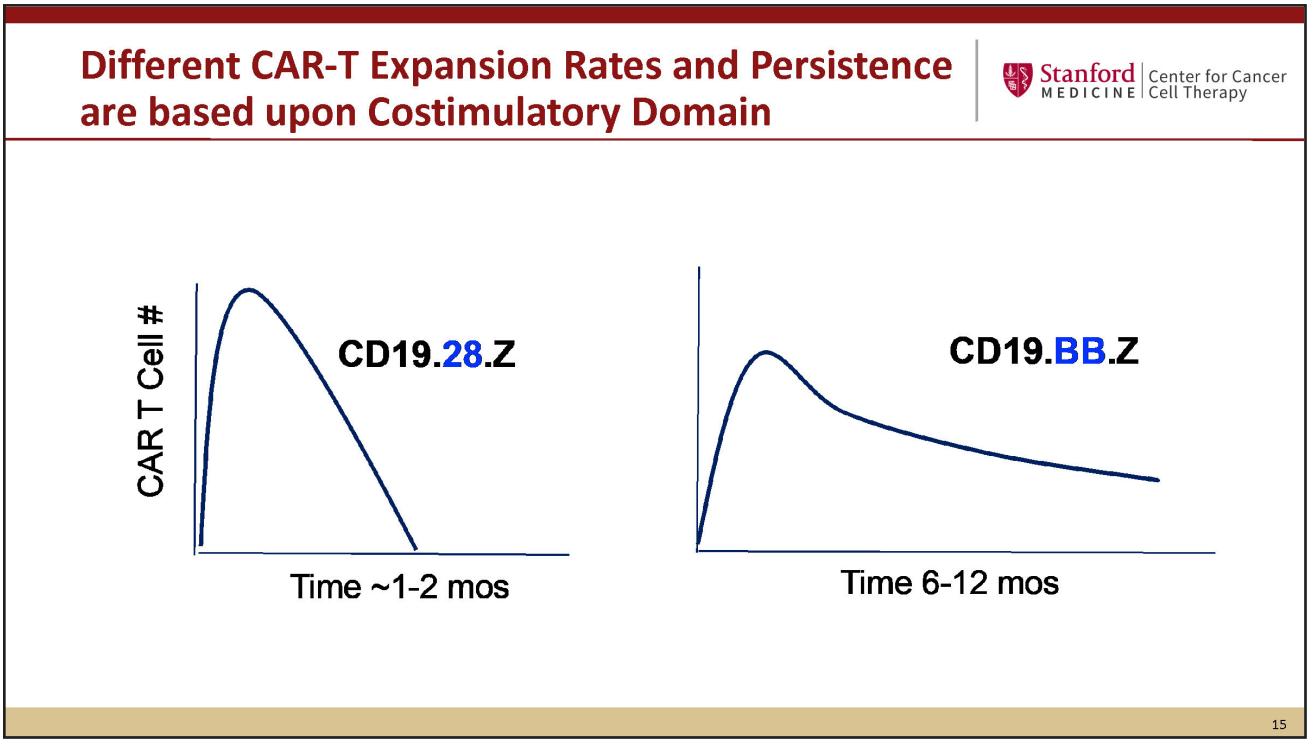
Slide 13: Chimeric Antigen Receptor (CAR) Modified T cells

So, now that we're all immunologists in this pandemic that we suffered through together, we understand that there are ways to elicit the immune system through vaccination, that the tumor could also put proteins on its surface that might be unique, eliciting immune responses from the patient's own immune system, and many of us have probably benefited from this surveillance of cancer without ever knowing that we even had an abnormality. But we've never been able to truly vaccinate against cancer or take advantage of the immune system until now. With CAR-T cells we are, again, hijacking the patient's own T cells in order to force them, enslave them, to making an antigen that is able to express the chimeric antigen receptor that uniquely binds to the tumor antigen and contains all aspects to activate that T cell and cause proliferation. And together this creates 4 benefits that have never been available before CAR-T in the patients receiving even monoclonal antibodies. That is, this therapy, again, is living, expands, proliferates. It localizes to the tumor, so that it avoids off-site toxicity. It kills through cytotoxic killing, which has been, again, optimized through 10,000 generations of evolution. And it persists, providing surveillance against the cancer as needed for each individual patient.



Slide 14: Three Anti-CD19 CAR T-cell Products are FDA Approved as 3rd Line Therapy for Rel/Ref DLBCL

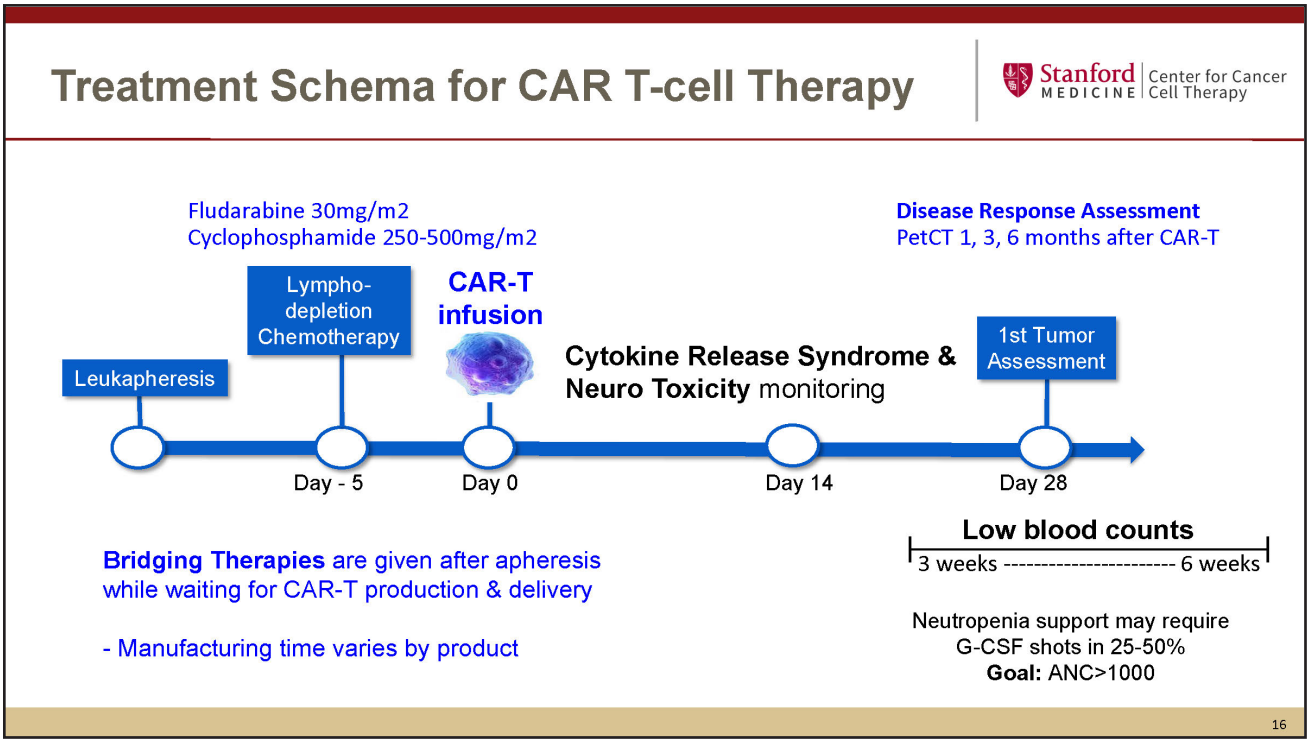
The commercial products in large cell lymphoma are well known to this audience. There's axi-cel (Yescarta®), tisa-cel (Kymriah®), and liso-cel (Breyanzi®), from the companies of Kite, Novartis, and Bristol Myers Squibb. They're very similar molecules. You see in this schematic that the binding domains on the top are all identical. They're called FMC63, they bind CD19. They are also activating, used in the T cell zeta, but they have different costimulatory domains, CD28 versus 4-1bb. I call that the motor of the CAR and results in the proliferation and the persistence of this CAR.



Slide 15: Different CAR-T Expansion Rates and Persistence are based upon Costimulatory Domain

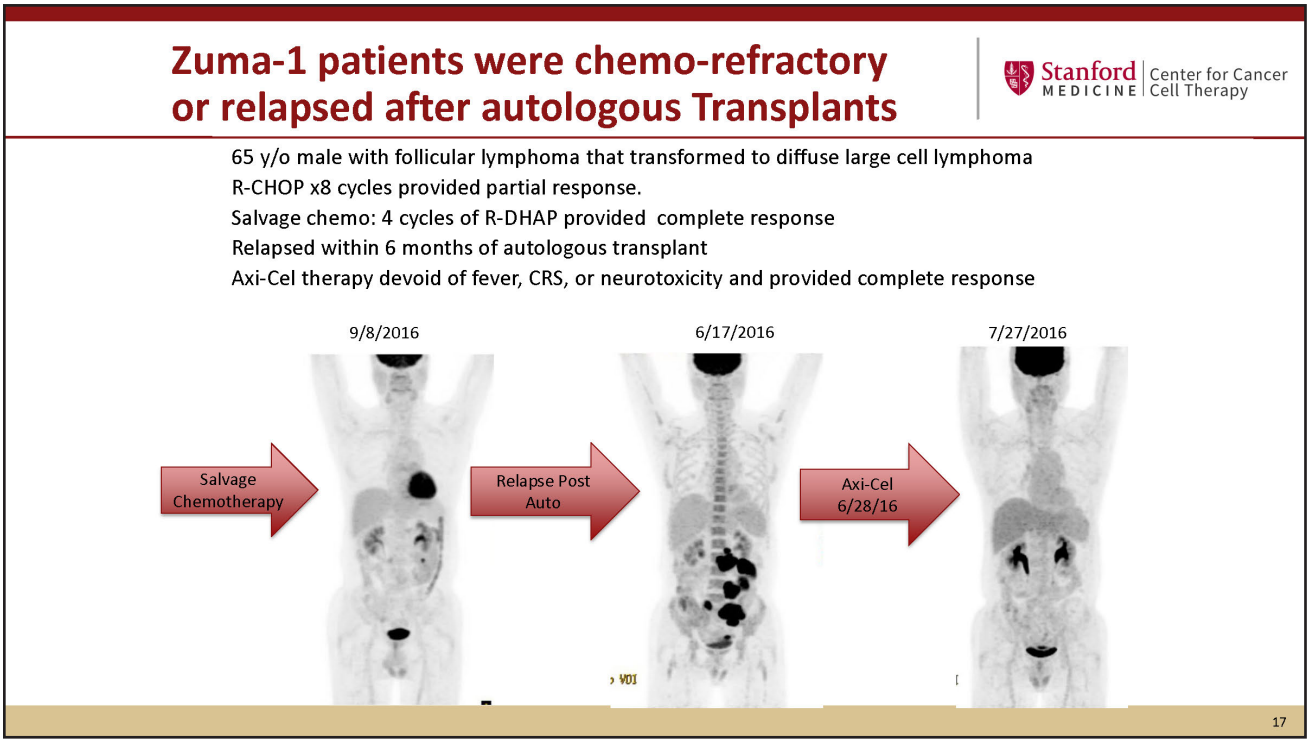
Schematically, you can imagine that the CD28 has a faster trajectory, maybe zero to 60 in 3 seconds, and an earlier off, and goes down towards lower levels more quickly than the 4-1bb. But, in truth the experience of individual patients is widely heterogenous, and everybody experiences both proliferation and persistence, it's a relative comparison. A lot of questions about that 4-1bb, CD28.

And remember this is a personalized therapy, so we have to manufacture each therapy for the individual patient.



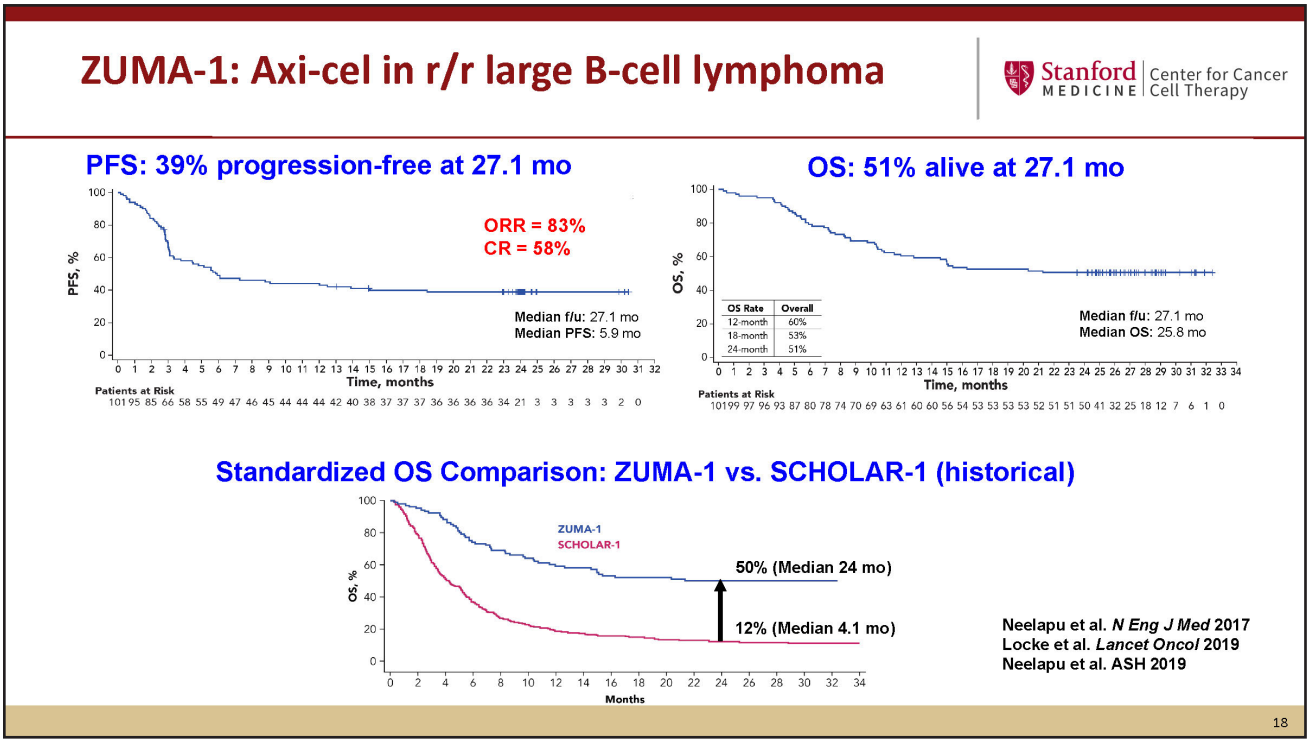
Slide 16: Treatment Schema for CAR T-cell Therapy

Here, I'm showing this schematically. Cells are collected from the patient's blood system using leukapheresis, the same type of collection that platelet donors are providing at the Red Cross every day safely. The cells go off to a Good Manufacturing Practice (GMP) laboratory and they're manufactured. That time for manufacturing varies by product but can be as short as 17 to sometimes a month for production. While this is going on, some patients are receiving bridging therapies. Others are able to wait and then when the cells are available undergo lympho-depletion, using 2 common drugs, fludarabine, cyclophosphamide. The goal is to decrease your own T cells, so your body starts to make all the signals to expand and grow T cells. Then, when we put the super-charged CAR-T cell into the blood system on day 0 on the patients, then have the cytokines and they're ready to grow, because those cells are going to expand 4-logs over the next 7 to 14 days. And, in that period of time they may experience cytokine release syndrome, neurological toxicity, and having this therapy at experienced cell therapy centers is important. The patients are discharged from the hospital. Some patients are even receiving this therapy outpatient, never having even cytokine release syndrome developing. They're followed in the local area and really at this point it's very important that patients stay in the same area as their treating physician for the first 28 days in order to look at the problems of cytokine release syndrome, neurological toxicity, and sometimes low blood counts occurring from 3 to 6 weeks afterwards. Some patients require filgrastim (Neupogen®) or granulocyte colony-stimulating factor (G-CSF) or filgrastim-sndz (Zarxio®) shots. Patients receive PET/CT scans at 1, 3, and 6 months to assess how the response was. And we expect this.



Slide 17: Zuma-1 patients were chemo-refractory or relapsed after autologous Transplants

This is an example. One of the first patients I treated on the ZUMA-1 study, 65-year-old, had large cell lymphoma, had received CHOP chemotherapy, had relapsed, got an auto (autologous) transplant, but then after auto relapsed. And here these black spots are indicative of the patient's lymphoma in the abdomen. With axi-cel back in 2016 and you can see a clear PET scan, only those kidneys, that's normal and this patient remains disease-free for the following 4 years. One of my good friends. And, what I hope all of you in the audience will experience using CAR-T therapy.



Slide 18: ZUMA-1: Axi-cel in r/r large B-cell lymphoma

We have studied thousands of patients. This is the first of the indication studies, ZUMA-1, 100 patients with large cell lymphoma, and we now know that at 5 years, 40% of these patients are alive and doing well. And you can see that the patients benefit and the progression-free survival, that is that they're not developing a new problem, with this plateau from 6 months on out. And this really leads us to the observation and really a lot of confidence, that the patients are really being cured and that this therapy is allowing them to live disease-free for long periods of time.

In comparison to the therapies that were available before 2016, shown on this lower line, I think it's obvious that the CAR-T cells are providing new hope and benefits to all patients.

Rel/Ref DLBCL Multicenter Trials in NHL

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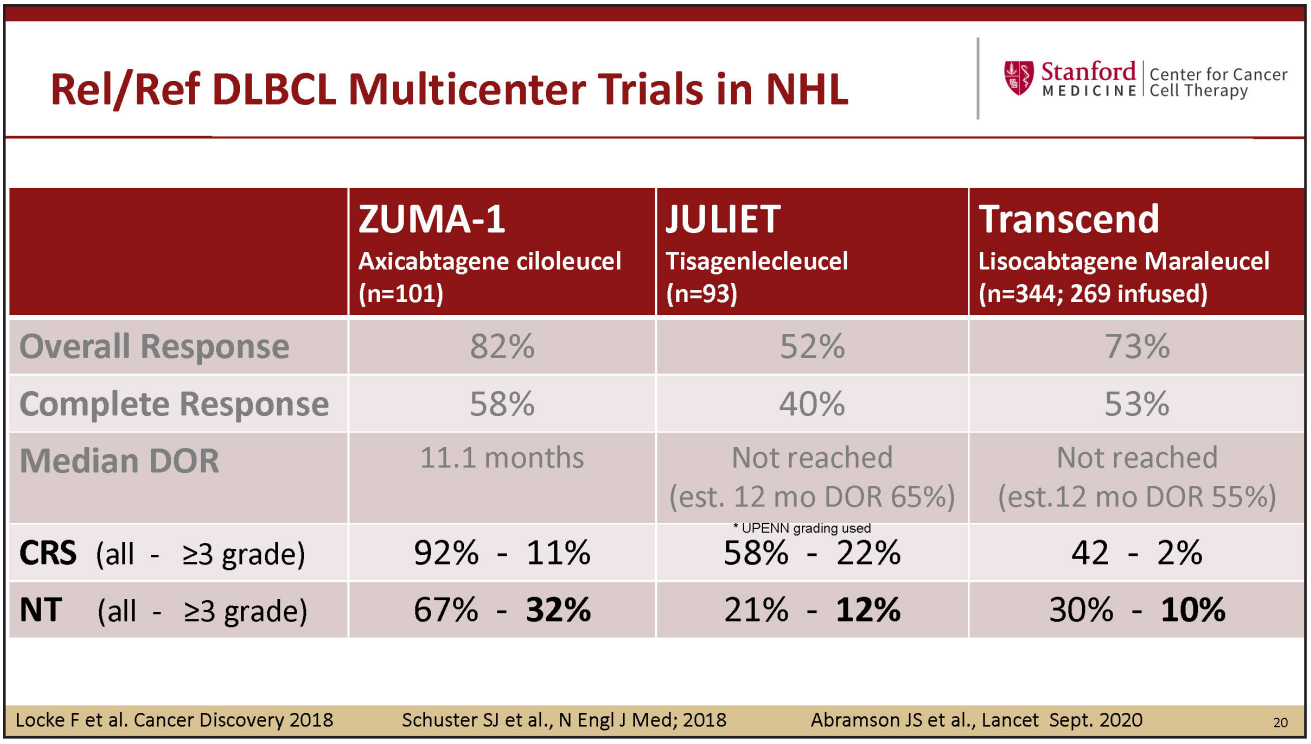
	ZUMA-1 Axicabtagene ciloleucel (n=101)	JULIET Tisagenlecleucel (n=93)	Transcend Lisocabtagene Maraleucel (n=344; 269 infused)
Overall Response	82%	52%	73%
Complete Response	58%	40%	53%
Median DOR	11.1 months	Not reached (est. 12 mo DOR 65%)	Not reached (est.12 mo DOR 55%)

Locke F et al. Cancer Discovery 2018 Schuster SJ et al., N Engl J Med; 2018 Abramson JS et al., Lancet Sept. 2020 19

Slide 19: Rel/Ref DLBCL Multicenter Trials in NHL

There are 3 commercial products, I only showed you slides from the axi-cel, but the other 2 products are equally effective in benefiting patients. Here, I'm showing a comparison of the published complete response and durable response rates. The point of this slide is not to compare head-to-head, but to state that all 3 of these are providing lifesaving benefits to the patients in the community, and that the choice of which product is a discussion between you and your doctor.



Rel/Ref DLBCL Multicenter Trials in NHL

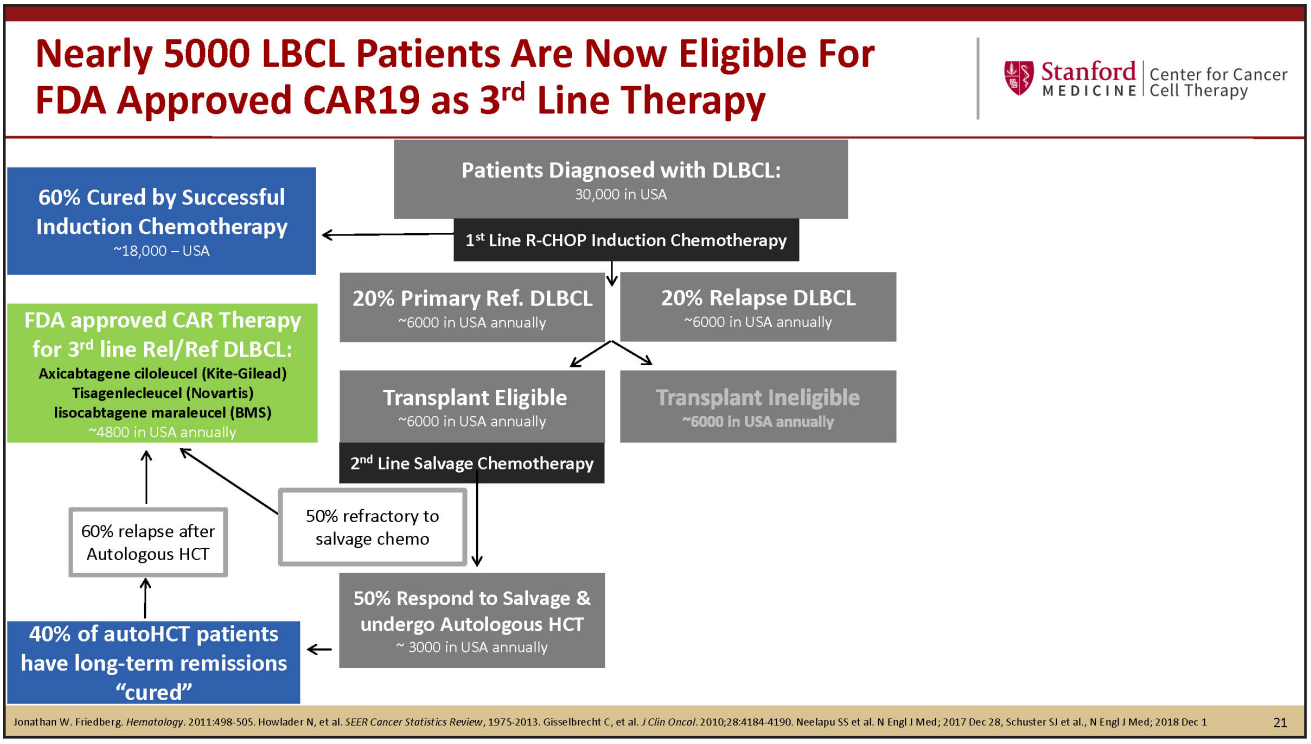
Stanford MEDICINE | Center for Cancer Cell Therapy

	ZUMA-1 Axicabtagene ciloleucel (n=101)	JULIET Tisagenlecleucel (n=93)	Transcend Lisocabtagene Maraleucel (n=344; 269 infused)
Overall Response	82%	52%	73%
Complete Response	58%	40%	53%
Median DOR	11.1 months	Not reached (est. 12 mo DOR 65%)	Not reached (est.12 mo DOR 55%)
CRS (all - ≥3 grade)	92% - 11%	58% - 22% * UPENN grading used	42 - 2%
NT (all - ≥3 grade)	67% - **32%**	21% - **12%**	30% - **10%**

Locke F et al. Cancer Discovery 2018 Schuster SJ et al., N Engl J Med; 2018 Abramson JS et al., Lancet Sept. 2020 20

Slide 20: Rel/Ref DLBCL Multicenter Trials in NHL

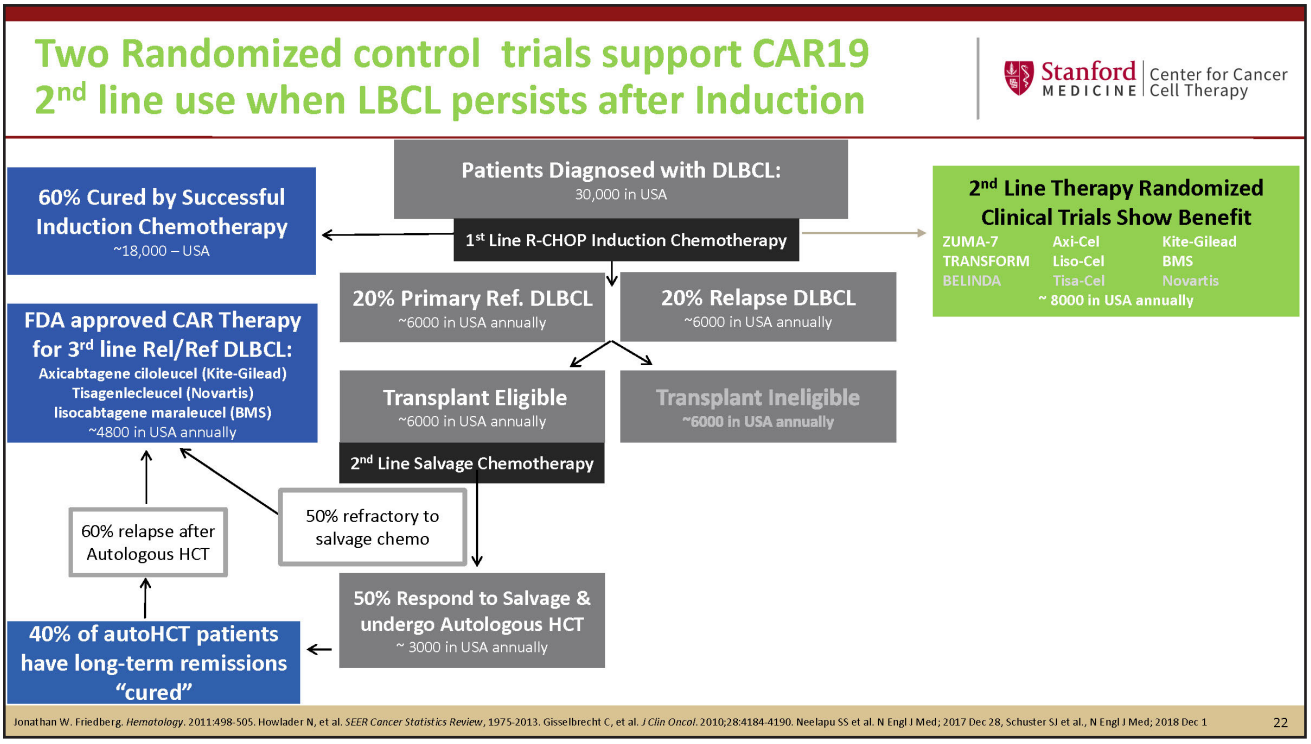
The toxicities of these vary as you might imagine, and some of the concerns for, the more rapid uptake of the CAR-T cell expansion, especially with axi-cel, leads to a higher concern for these toxicity managements that are effectively managed in centers that use these therapies all the time. But you'll hear much discussion about benefit, efficacy, and toxicity comparisons. It's my conclusion that all 3 of these therapies are very effective and they're providing cure, hope, and benefit to patients across the globe, as you're learning.



Slide 21: Nearly 5000 LBCL Patients Are Now Eligible For FDA Approved CAR19 as 3rd Line Therapy

So what have we done to the patients' treatment plan for large cell lymphoma? Here in the United States, there's 30,000 patients diagnosed with large cell lymphoma as I show in the center of this slide. Most patients receive CHOP chemotherapy and 60% are cured. I don't think that CAR-T cell will replace first-line therapy when you're curing 60% with the standard treatment that's been going on for 30 years. When patients have either not responded to the CHOP or are relapsing after CHOP, then historically they've received a second line of chemotherapy with an intent to show chemo benefit, and if they do, they receive high-dose chemotherapy or an auto transplant, and I move patients down into that lower box. You can see moving from 30,000 to the 3,000 patients being cured with auto that that's only 10% of the patients and that, again, 60% are going to have progression even after auto. And it's these patients who didn't respond to the second-line salvage chemotherapy, or who relapsed after these therapies or after auto transplant that the initial commercial approval for CAR-T was identified with axi-cel, tisa-cel, and liso-cel.

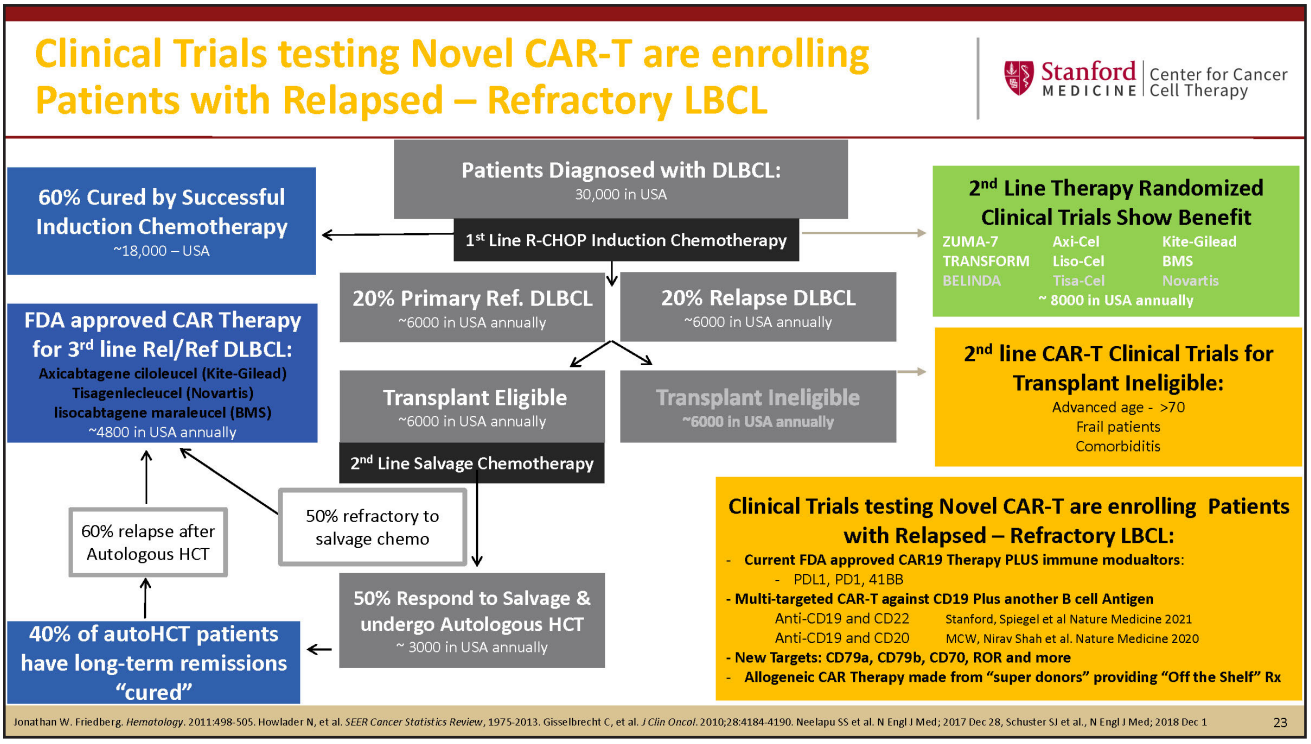
Now there's 5,000 patients a year that are really capable of getting this therapy and sadly only 20% of those patients are finding their way to CAR-T treatment so far.



Slide 22: Two Randomized control trials support CAR19 2nd line use when LBCL persists after Induction

Now, what is also exciting is that there's been 3 randomized control trials showing benefit in 2 of these trials, clear benefit, such that patients who have either not responded to the CHOP chemotherapy or relapsing early after CHOP therapy will now be able to receive CAR-T cell therapy. I said will now, I think that's a projection of what's going to happen over the next 2 months with an anticipated Food and Drug Administration (FDA) approval.

Another observation is that patients who are considered transplant ineligible, too old, too frail, are shown to benefit from CAR-T therapy as well, and maybe one of those lower toxicity therapy CAR-Ts may be just right for that patient population who's age over 70, frail, or has comorbidities.



Slide 23: Clinical Trials testing Novel CAR-T are enrolling Patients with Relapsed – Refractory LBCL

And finally, there's thousands of important clinical trials that are going to be available to patients who have failed other treatments at this point, and these trials are looking at combinations of CAR-T with immune modulators or multi-targeted CARs or new targets for the CAR therapies or even off-the-shelf CARs. These slides are available, I realize this is a complex slide, but I think it's important to help you with your understanding of your treatment progression through your disease management.

Zuma-7 (axi-cel) and Transform (liso-cel) RCT for DLBCL Patients with Induction Failure or Relapse within 1 year

Stanford MEDICINE | Center for Cancer Cell Therapy

- First-Line Therapy Chemotherapy-Resistant DLBCL and relapsed DLBCL within one year have poor Prognosis

2nd line RCT Eligibility

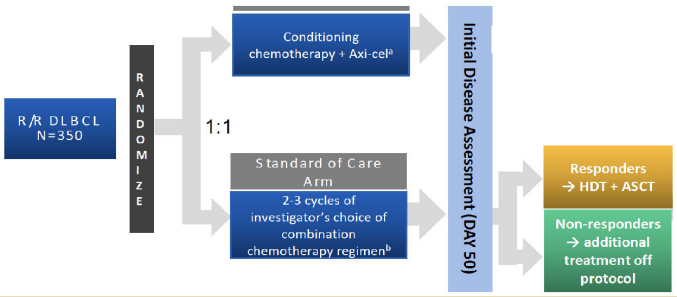
DLBCL or TFL with:

- Stable disease after 4 cycles of R-CHOP
- Progressive disease after 6 cycles of R-CHOP
- Relapse within 1 year of induction

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR			3-Year Event-Free Survival		3-Year Overall Survival	
		No. of Patients	%	P	%	P	%	P
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saaIPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; saaIPI, secondary age-adjusted International Prognostic Index.



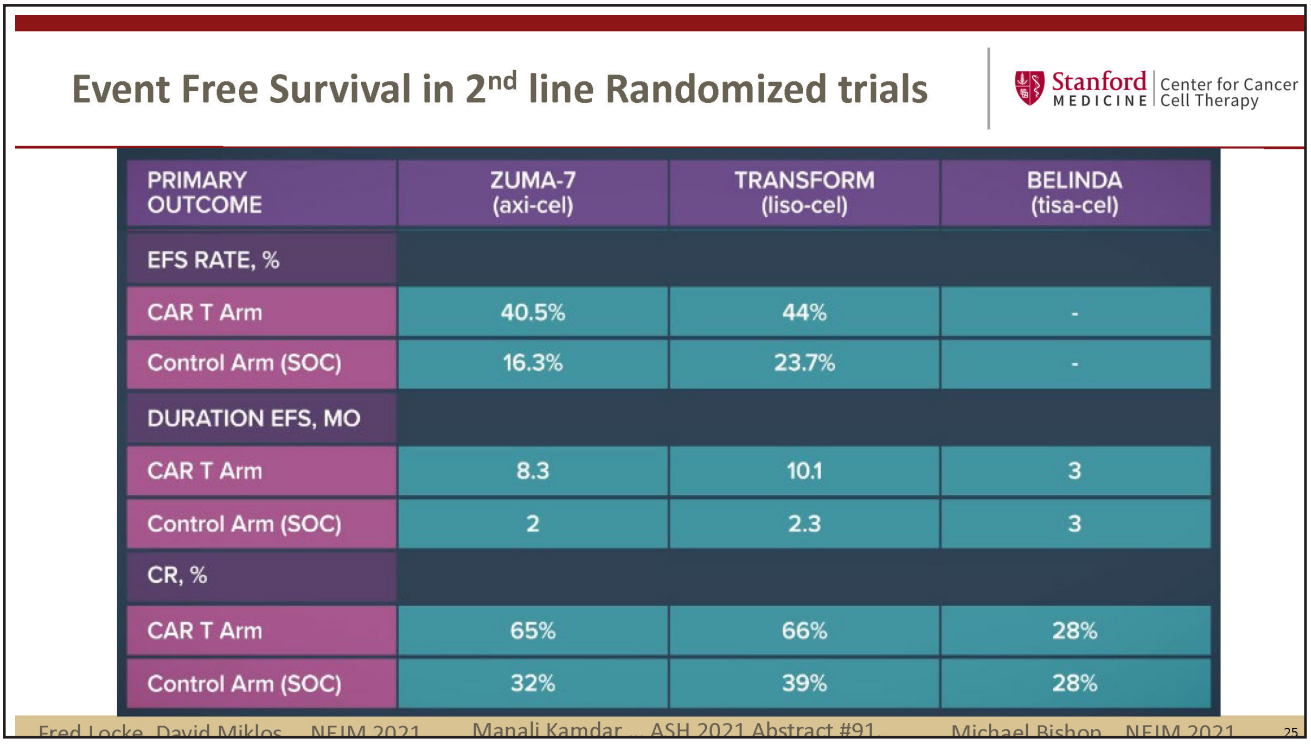
Gisselbrecht et. al, JCO 2010 2010 Sep 20;28(27):4184-90

24

Slide 24: Zuma-7 (axi-cel) and Transform (liso-cel) RCT for DLBCL Patients with Induction Failure or Relapse within 1 year

I want to talk about those randomized trials I showed you on the top right of the last slide.

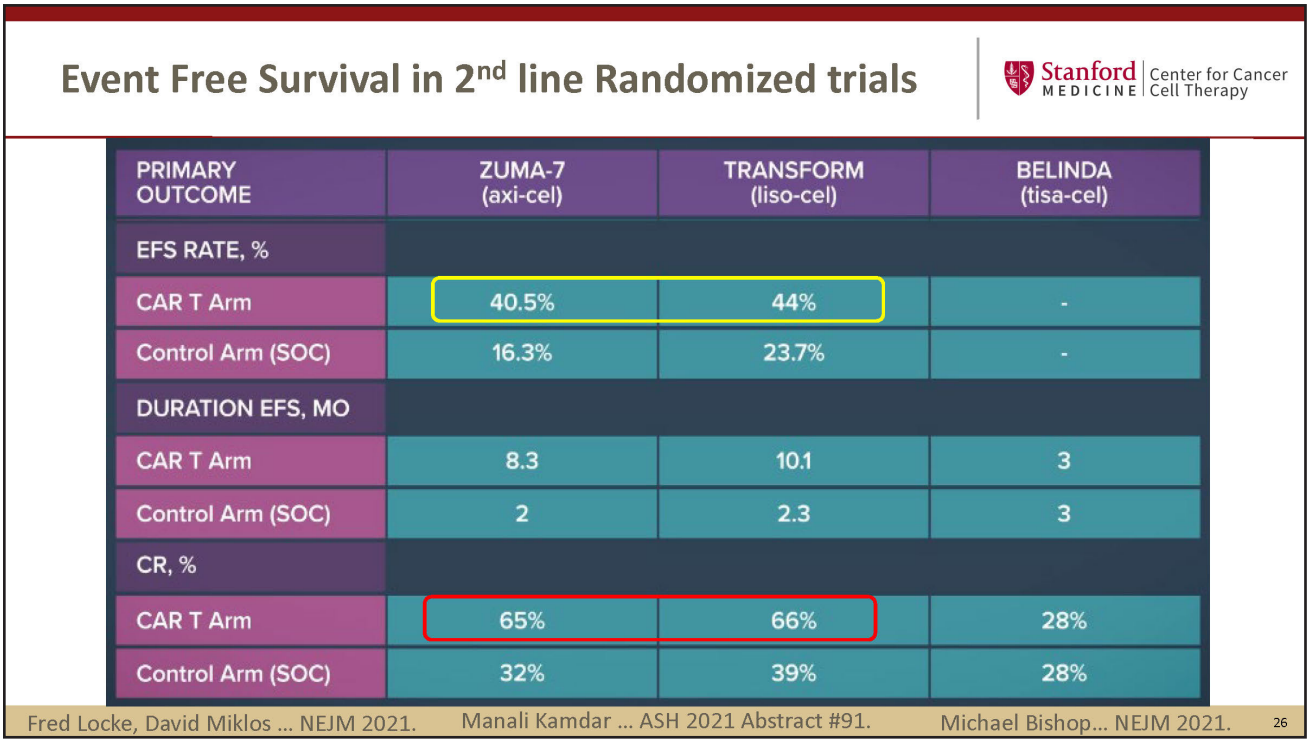
There were 3 studies being done and 2 of these studies, ZUMA-7, which tested axi-cel, and TRANSFORM, testing liso-cel, have been discussed and presented at the Blood meeting called American Society of Hematology (ASH) in December of this year, and many of you've seen these on the internet because they were very positive, showing benefit after progression in front-line therapy, so that the second-line treatment is likely to be switching to CAR-T cells. In these studies patients who had had either progression with CHOP or early relapse were randomized to receive conditioning chemotherapy and a CAR-T cell, or opportunities to receive salvage chemotherapy, RICE, ICE, DHAP, with an intent to go to an auto transplant.



PRIMARY OUTCOME	ZUMA-7 (axi-cel)	TRANSFORM (liso-cel)	BELINDA (tisa-cel)
EFS RATE, %			
CAR T Arm	40.5%	44%	-
Control Arm (SOC)	16.3%	23.7%	-
DURATION EFS, MO			
CAR T Arm	8.3	10.1	3
Control Arm (SOC)	2	2.3	3
CR, %			
CAR T Arm	65%	66%	28%
Control Arm (SOC)	32%	39%	28%

Slide 25: Event Free Survival in 2nd line Randomized trials

The randomization was 50/50 and patients would stay on that treatment assignment until they failed to benefit, and it's that event-free survival that was being compared.



Event Free Survival in 2nd line Randomized trials

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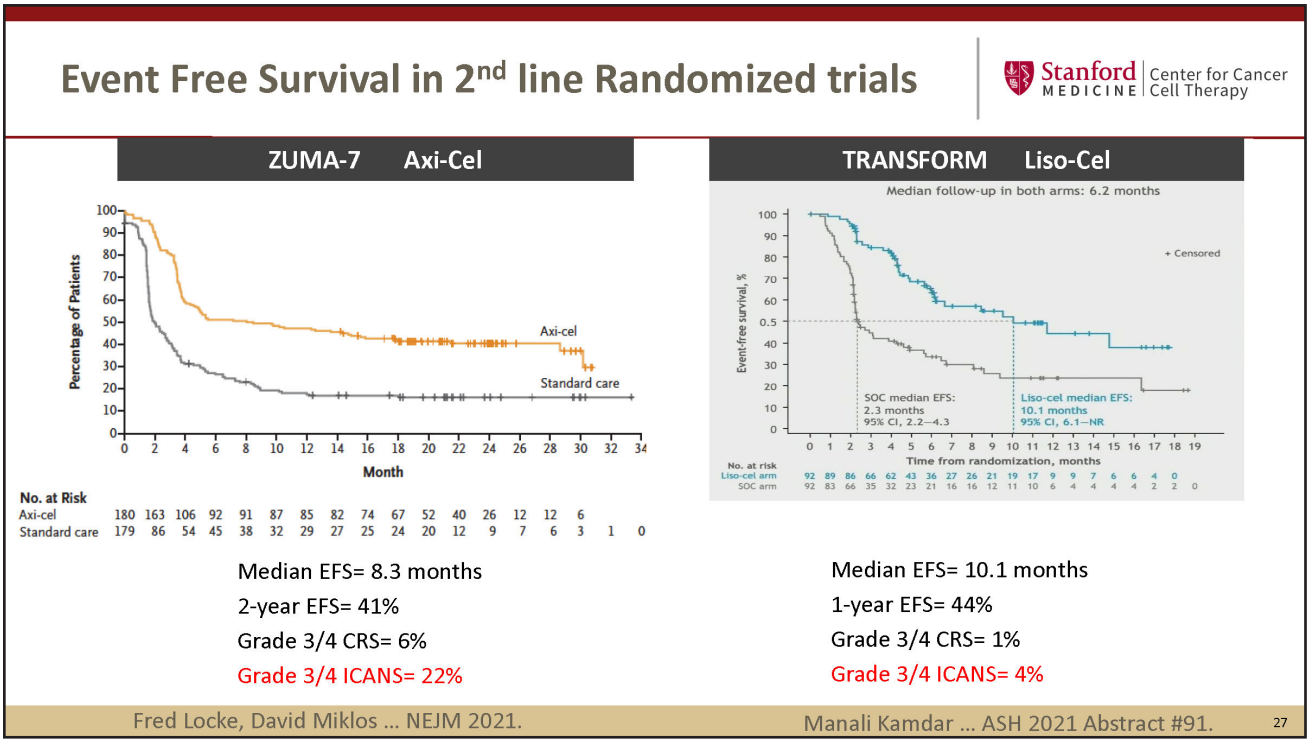
PRIMARY OUTCOME	ZUMA-7 (axi-cel)	TRANSFORM (liso-cel)	BELINDA (tisa-cel)
EFS RATE, %			
CAR T Arm	40.5%	44%	-
Control Arm (SOC)	16.3%	23.7%	-
DURATION EFS, MO			
CAR T Arm	8.3	10.1	3
Control Arm (SOC)	2	2.3	3
CR, %			
CAR T Arm	65%	66%	28%
Control Arm (SOC)	32%	39%	28%

Fred Locke, David Miklos ... NEJM 2021. Manali Kamdar ... ASH 2021 Abstract #91. Michael Bishop... NEJM 2021. 26

Slide 26: Event Free Survival in 2nd line Randomized trials

The dramatic differences are here, shown in a table, and I'm going to just draw attention, using a box where in the yellow we're showing that both ZUMA-7 and TRANSFORM CAR-T cell therapies had a 40-44% event-free survival plateau and that in comparison to the salvage chemo or auto transplant, 16 to 23%. There were 3-fold greater event-free survival. The overall complete response rate of the 2 therapies were almost identical at 65 and 66%, as was anticipated.

The BELINDA study, it's beyond what I can discuss today, but it was complicated by some of the design features of the study. It did not show a positive benefit

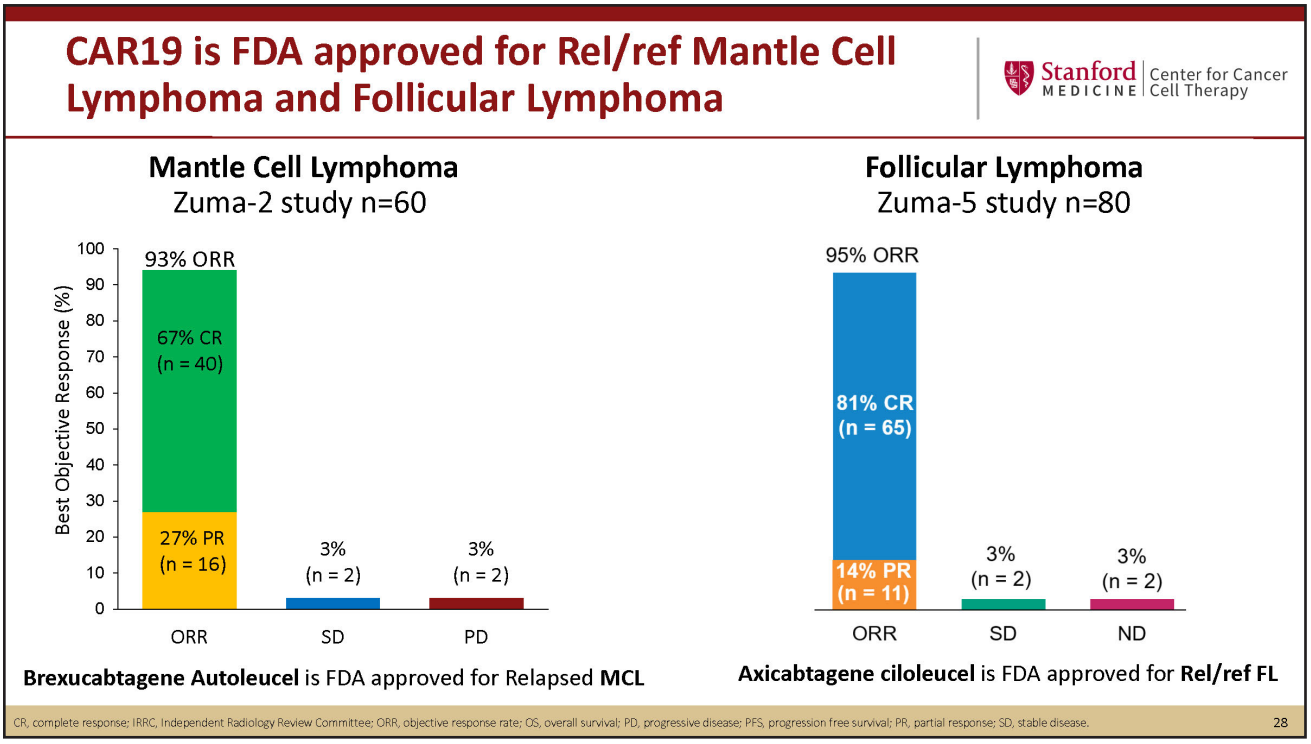


Slide 27: Event Free Survival in 2nd line Randomized trials

The benefit of CAR-T on the upper curves of the slide shown here on the left, axi-cel, on the right, liso-cel, is evident, and this is also evident that patients who got to an auto transplant have a plateau and did benefit, but those were only about 20% or 30% of the patients in the 2 populations, versus 40% of the patients.

So, event-free survival remains 40% and the clear benefit to the patients with long-term disease-free survivals are being collected.

The results of this study are anticipated to change treatment from third-line CAR-T to second-line CAR-T in the next couple of months. And I applaud the investigators who conducted these complicated randomized control trials that will change practice.



Slide 28: CAR19 is FDA approved for Rel/ref Mantle Cell Lymphoma and Follicular Lymphoma

The other advance in CAR-T is by moving the therapy into some of those other B cell malignancies. Here I'm showing results of the ZUMA-2 for patients with mantle cell lymphoma, where there was 93% overall response rate with 67% complete response rates. And on the right, the ZUMA-5 where follicular lymphoma patients had an 81% complete response rate. And both of these studies have supported FDA indications that are already available so that the treatment is now indicated for patients in relapsed/refractory mantle cell and follicular lymphoma.

CAR-T Cell Therapy in Adult B cell Acute Lymphoblastic Leukemia: What's New?

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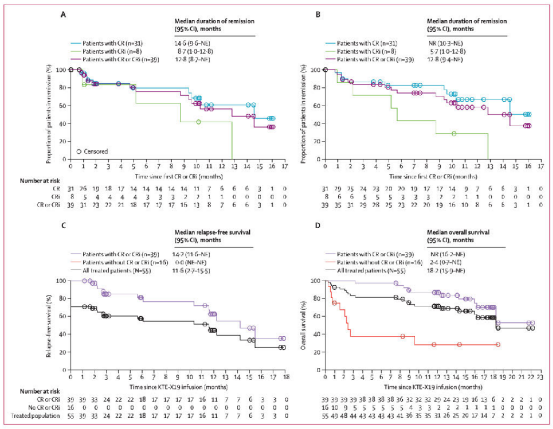
- **Brexucabtagene Autoleucel (Tecartus) is first FDA approved CAR-T for adults with r/r B-ALL**
- **Phase II Zuma 3 (N=55):**
  - 71% CR/Cri; 97% of whom were MRD-neg
  - Median DOR: 12.8 months
  - Median LFS: 11.6 months
  - 13% Grade 3-4 CRS
  - 25% Grade 3-4 ICANs

KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study



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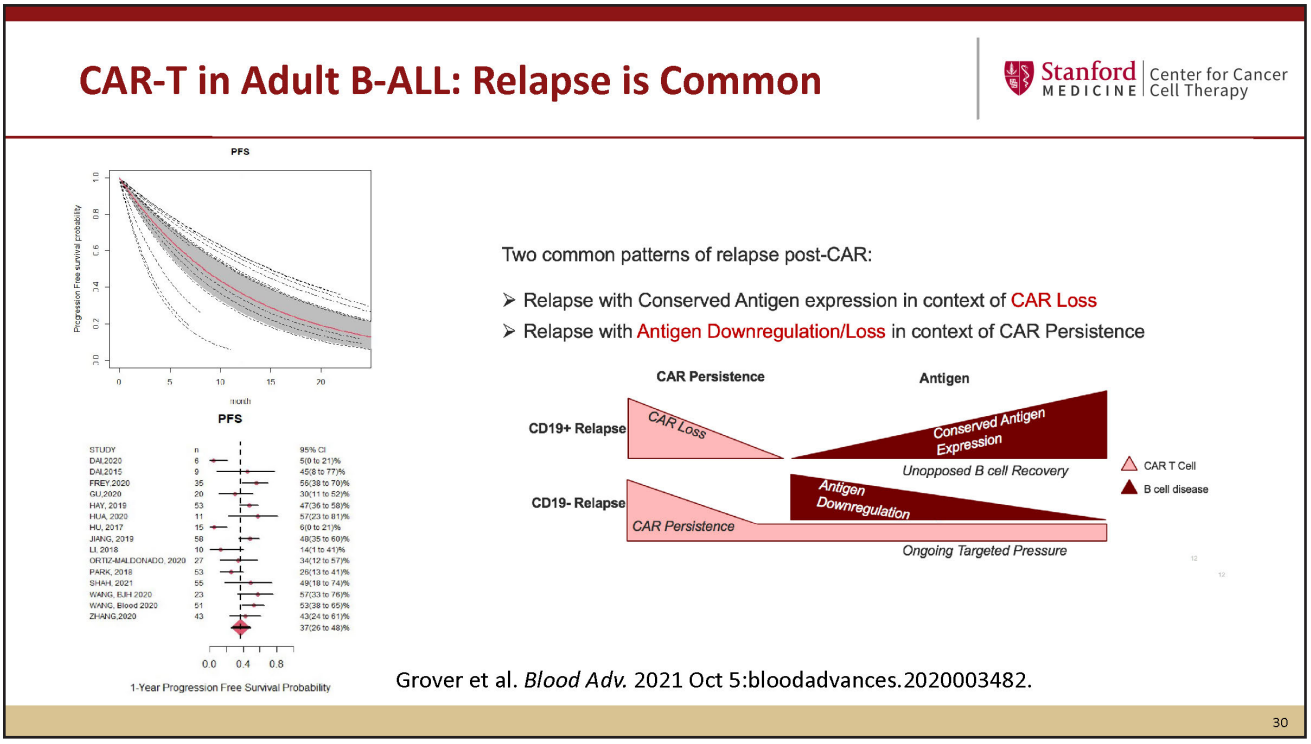
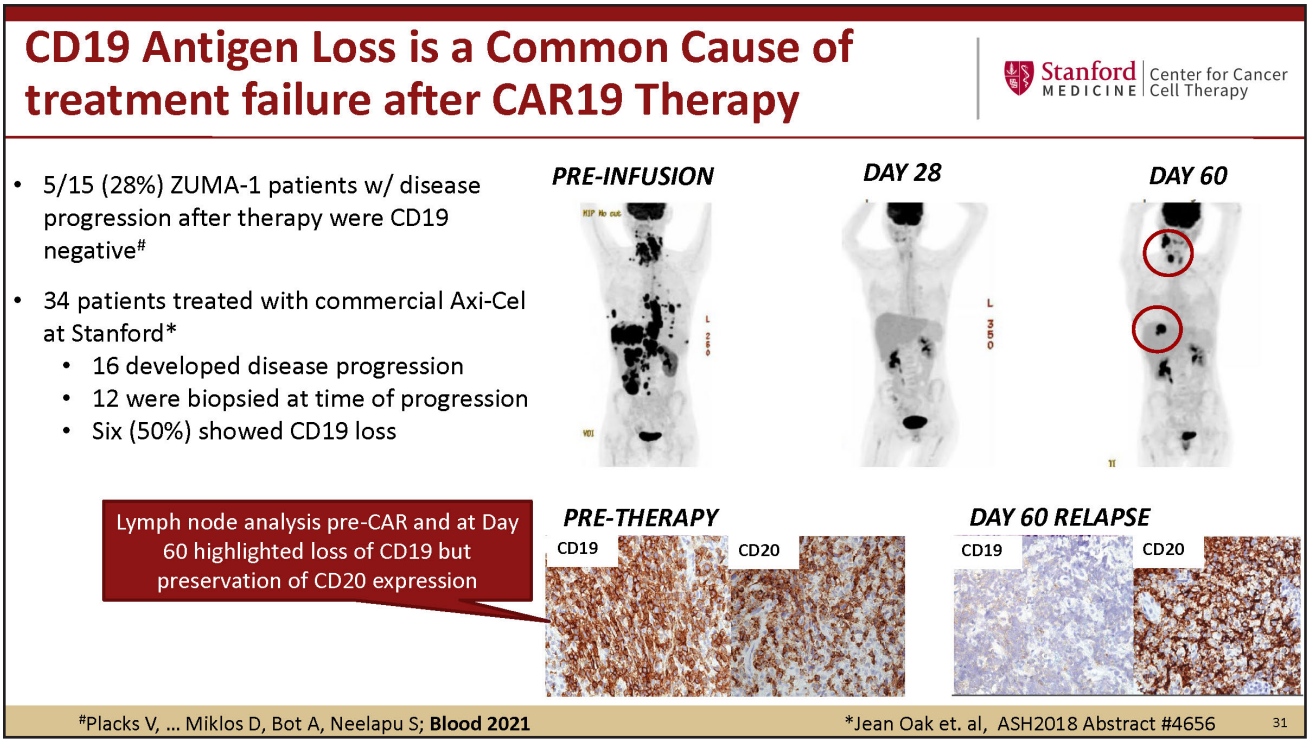
Slide 29: CAR-T Cell Therapy in Adult B cell Acute Lymphoblastic Leukemia: What's New?

What about acute lymphoblastic leukemia? So, what about leukemia? We've heard much about the children with leukemia, but the early indication for tisa-cel was limited to patients under the age of 28. Now this year, brexucabtagene or Tecartus® has been FDA approved in adults for relapsed/refractory B cell lymphoblastic leukemia. And, this was the ZUMA-3 study, showing a 71% complete response rate and some toxicities with Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANs), and I realize the curves on the right are awfully small.



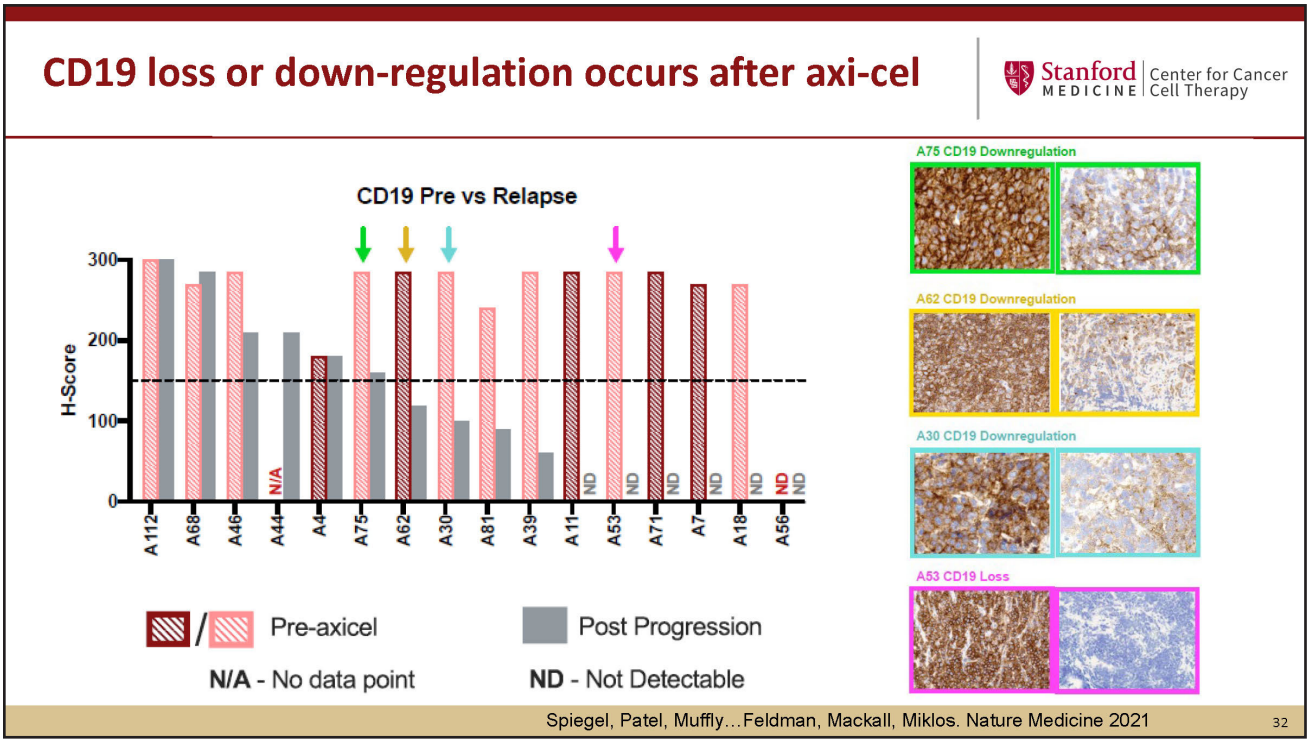
Slide 30: CAR-T in Adult B-ALL: Relapse is Common

Let me move to a slide provided by my colleague Dr. Lori Muffly which really makes this clear. She and Dr. Punita Grover have created a nice meta-analysis of the adult lymphoblastic leukemia study shown on the left. The observation is that the progression-free survival doesn't plateau the way we see with the lymphoma large cell patients, and that this continuing movement towards the relapsing of the patients is evident across all of these studies shown below. And really, we believe there's 2 common patterns to relapse in the CAR-T patients. One would be that patients are just simply losing their CARs. The CARs are not persisting or they're exhausting or they're not remaining functional. And the second is that the target for the CAR, CD19 molecule, which is not essential for the survival of the B cell, is being lost through genetic mutation and those cells are selectively growing out. So, those are the 2 problems that we work on as we think about advancing the benefits of CAR-T.



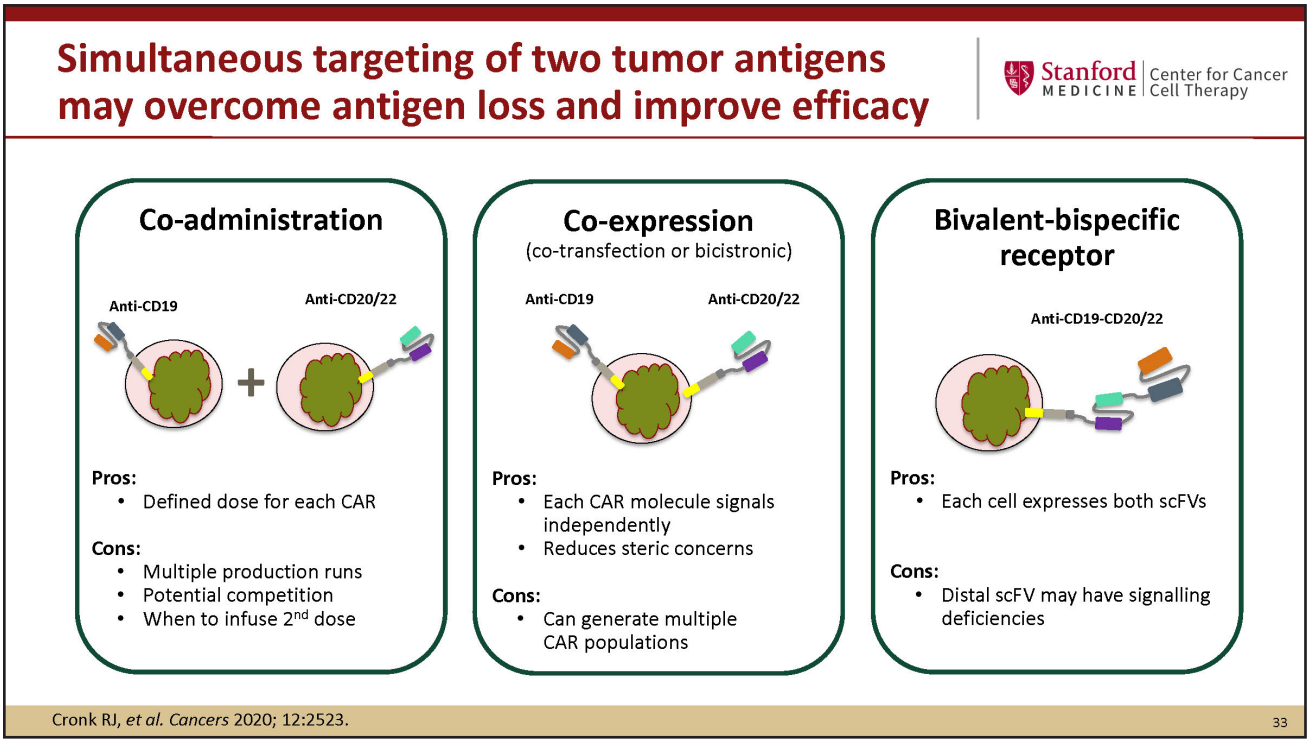
Slide 31: CD19 Antigen Loss is a Common Cause of treatment failure after CAR19 Therapy

Let me move to a slide provided by my colleague Dr. Lori Muffly which really makes this clear. She and Dr. Punita Grover have created a nice meta-analysis of the adult lymphoblastic leukemia study shown on the left. The observation is that the progression-free survival doesn't plateau the way we see with the lymphoma large cell patients, and that this continuing movement towards the relapsing of the patients is evident across all of these studies shown below. And really, we believe there's 2 common patterns to relapse in the CAR-T patients. One would be that patients are just simply losing their CARs. The CARs are not persisting or they're exhausting or they're not remaining functional. And the second is that the target for the CAR, CD19 molecule, which is not essential for the survival of the B cell, is being lost through genetic mutation and those cells are selectively growing out. So, those are the 2 problems that we work on as we think about advancing the benefits of CAR-T.



Slide 32: CD19 loss or down-regulation occurs after axi-cel

And this is the best example I can give you. We showed back in 2017, this was happening in about 50% of the patients. Recently we published an extension of this work showing 47 patients treated with axi-cel, who when they progressed in 17 patients, were biopsied and here I'm comparing the before and after expression of CD19 on the right-hand side and you can see the loss of that brown signal, meaning that these patients below the hashmark are losing expression of CD19. Antigen loss is the most common problem for loss of CAR-T benefit. And so, overcoming this is really going to be requiring multi-targeted CAR-T cells.

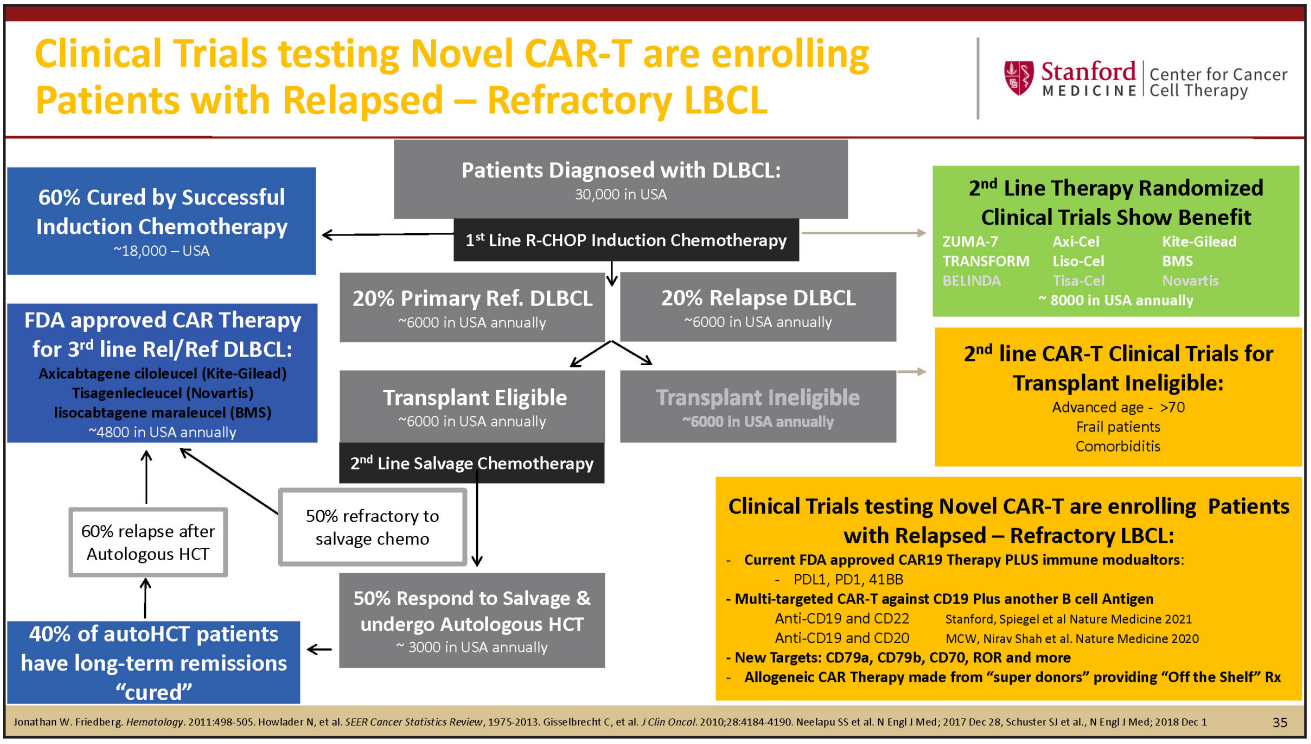


Slide 33: Simultaneous targeting of two tumor antigens may overcome antigen loss and improve efficacy

Now here's a simple example. We could put a CAR that's manufactured 2 different ways, one targeting CD19, the other one's targeting CD20 or CD22. Infuse them the same time or sequentially. Of course, we could also put those 2 constructs into the same viral insertion and have them in the same one cell, one T cell, during manufacturing. And finally, we could make a polypeptide that has unique binding domains for CD19 and CD22.

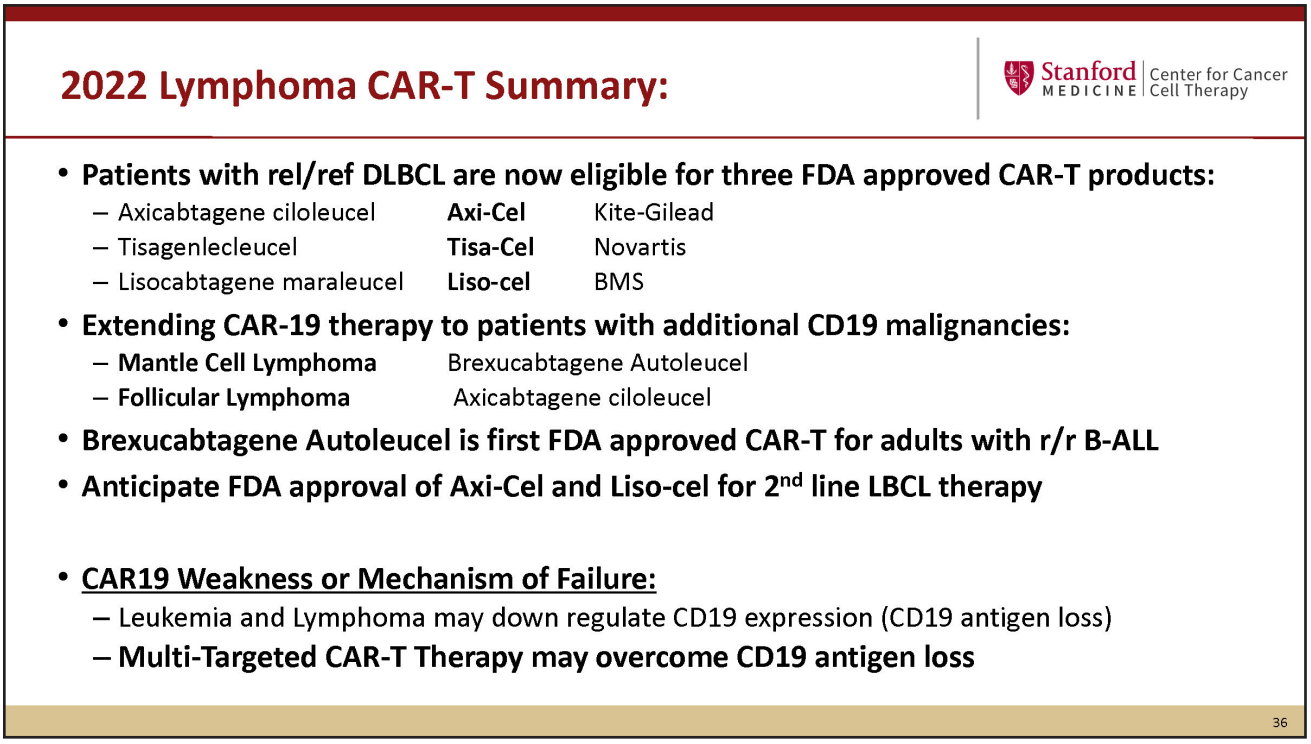
Slide 34: CAR-T Targeting both CD19 and CD20 Simultaneously

And I assure you, all of these different clinical trials are ongoing at this time. We are at Stanford, for example, currently testing 2 clinical trials, one with the polypeptide strategy sponsored by Miltenyi, binding CD19 in green, CD20 in the blue on the right, through a tethered CAR and at the same time opening this new bi-cistronic, and you can see there's a gene insertion that makes CD19 on the left and CD20 on the right, so each of the cells has both molecules and able to bind CD19 alone, as shown on the left panel, 20, or both. And this type of clinical trial work is absolutely necessary and the next step for advancing the benefits of CAR-T. And I predict we'll be able to gain another 15 to 20% benefit for patients if we can avoid antigen loss in leukemia and lymphoma.



Slide 35: Clinical Trials testing Novel CAR-T are enrolling Patients with Relapsed – Refractory LBCL

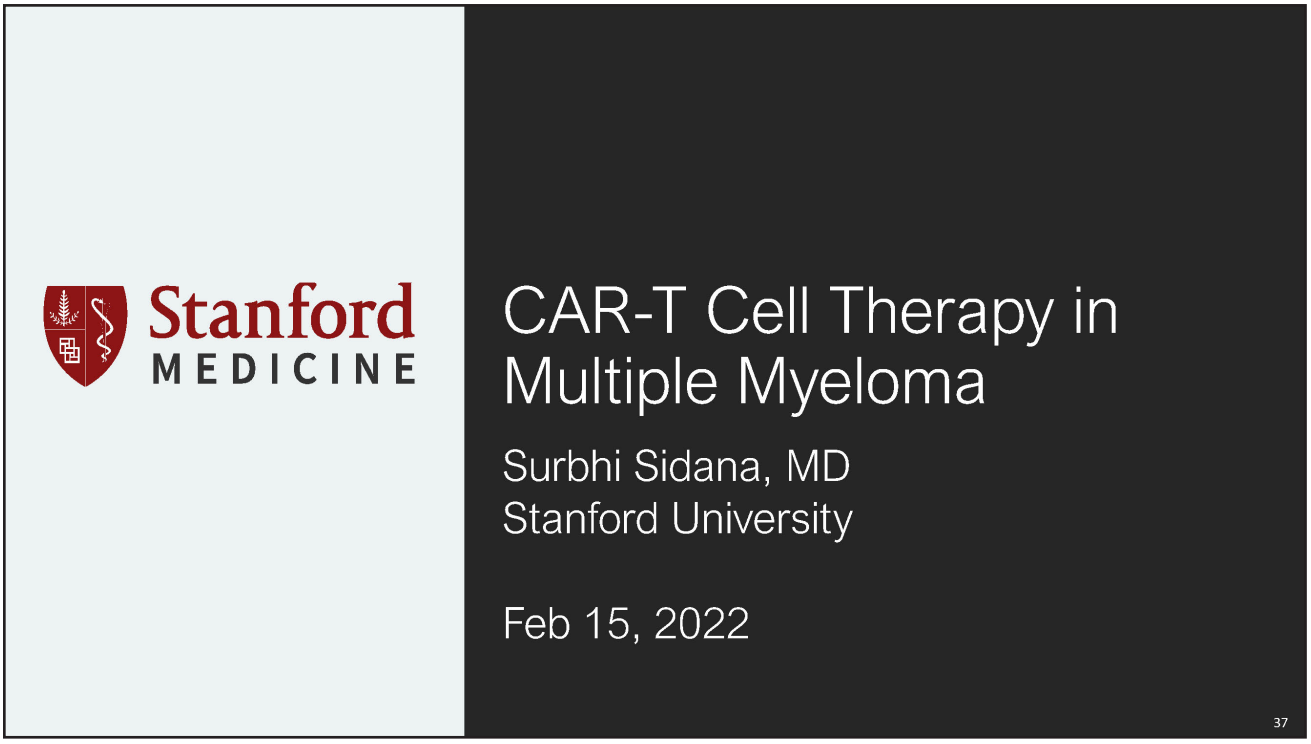
So I remind you again, the advances of your treatment are dependent on where your treatment is in the progression of front-line, second-line, or third-line therapy. That there are new FDA approvals for large cell, mantle cell, and follicular lymphoma. And that we have clinical trials that your doctors will be offering to you. And I highly encourage you to participate, especially if the commercially approved products have not benefited you, it's time to move on to the next generation of CAR-T cells.



Slide 36: 2022 Lymphoma CAR-T Summary

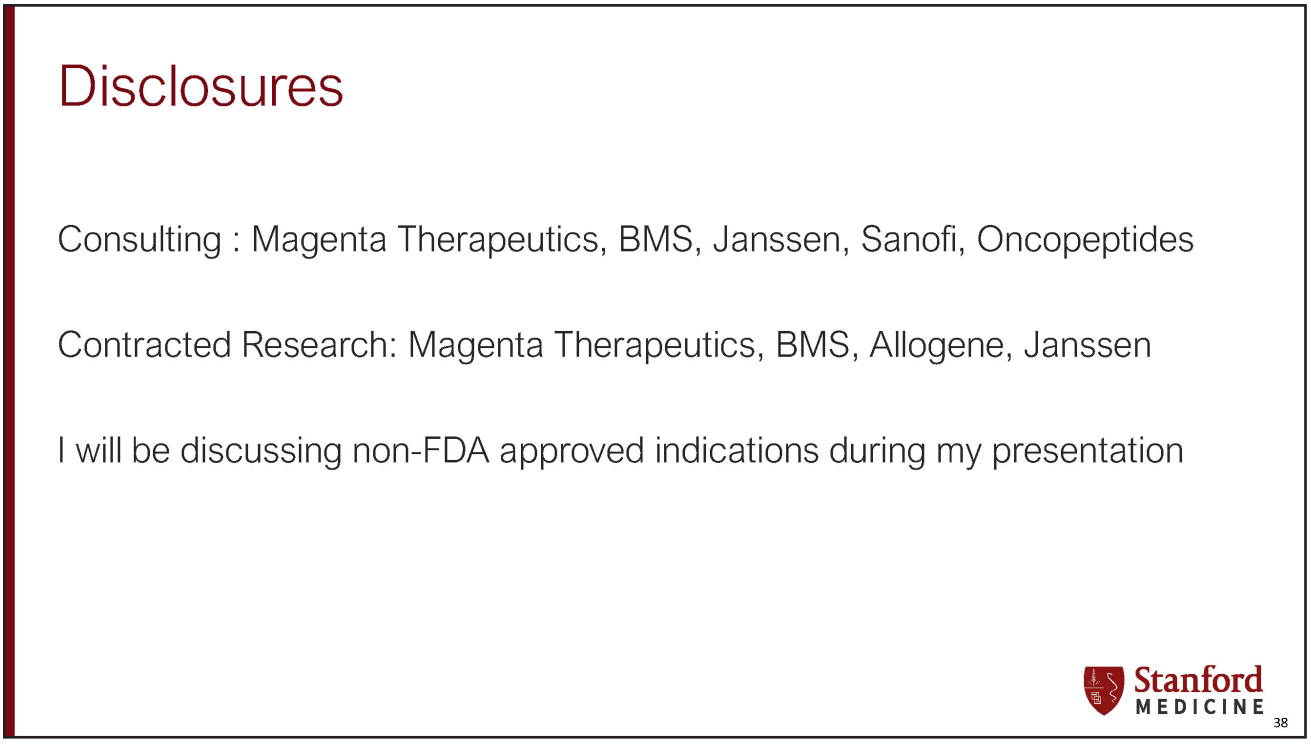
So in summary, today I told you that patients with relapsed/refractory have 3 FDA approved products, axi-cel, tisa-cel, liso-cel. That extending CAR-T therapy to additional malignancies is happening and FDA approvals are now available for mantle cell, follicular lymphoma. That brexucabtagene is now the first FDA approved therapy for adults with B cell relapsed acute lymphoblastic leukemia. And that we anticipate FDA approval of second-line CAR-T therapy for large cell lymphoma patients. And I hope I emphasized the importance of 2 is better than 1, and that targeting more than 1 target at a time is the next important advancement in CAR-T therapy.

So with that I'm going to stop my discussion and I'm going to advance the discussion to my colleague at Stanford and my friend and really wise multiple myeloma physician, Dr. Surbhi Sidana. She's going to present on multiple myeloma. Welcome, Surbhi.



Slide 37: CAR-T Cell Therapy in Multiple Myeloma

Thank you, Dr. Miklos, that was a great discussion about B cell malignancy. And, thanks to The Leukemia & Lymphoma Society for this opportunity to speak with all of you today.



Slide 38: Disclosures

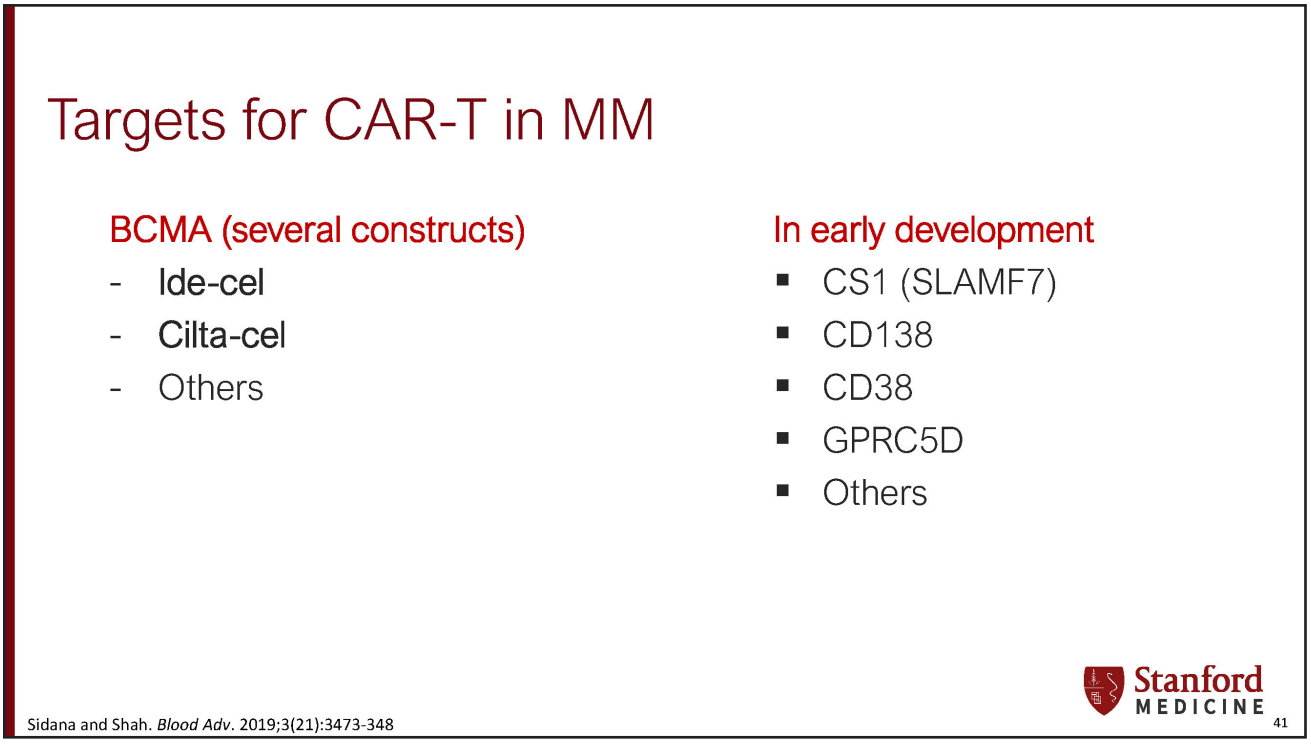
These are my disclosures.

Slide 39: Objectives

So today I want to focus on multiple myeloma and review the FDA approved CAR-T cell therapy, as well as CAR-T cell therapies under investigation in multiple myeloma.

Slide 40: CAR-T Therapy in MM

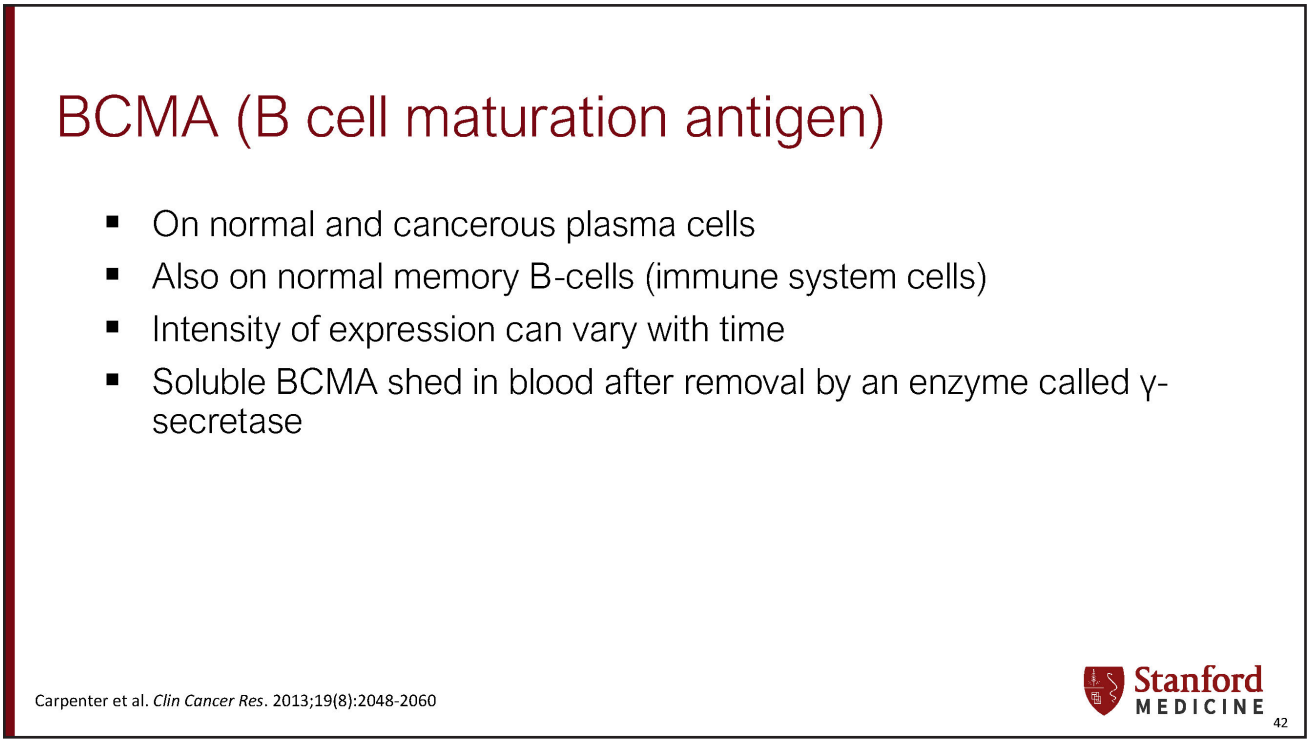
So there's only one FDA approved CAR-T cell therapy in multiple myeloma at present. It's called idecabtagene vicleucel, ide-cel, or the commercial brand name Abecma®. But there are several other commercially CAR-T cell therapies that are currently under investigation or under FDA review.



Slide 41: Targets for CAR-T in MM

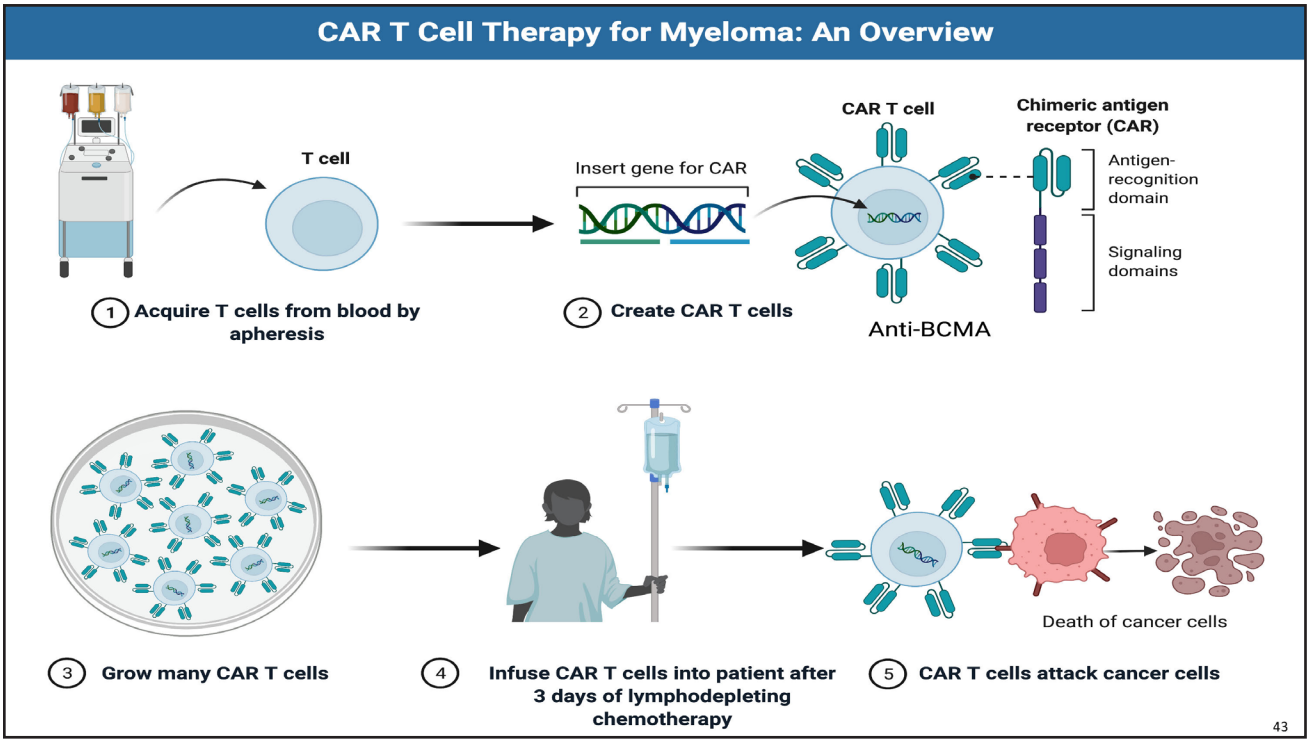
So, Dr. Miklos showed you that CD19 and CD22 are targets in B cell malignancies. The targets in multiple myeloma are slightly different because the myeloma cells express different proteins than the leukemia or lymphoma cells. The most commonly used target is B cell maturation antigen or BCMA, and ide-cel, cilta-cel (ciltacabtagene autoleucel or Carvykti™), several other CAR-T cell therapies target BCMA.

There's also other targets in early clinical development, as shown on the slide. SLAMF7, CD138, CD38, GPRC5D, and several others.



Slide 42: BCMA (B cell maturation antigen)

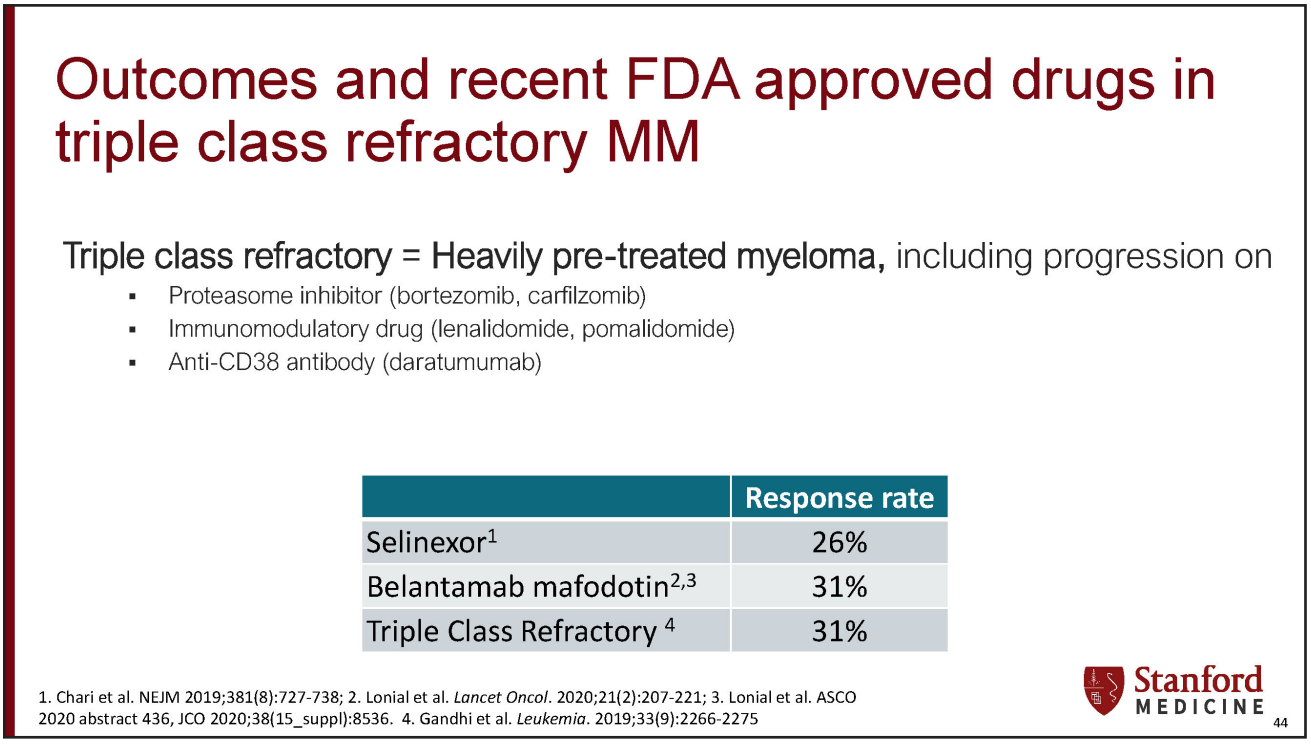
So B cell maturation antigen is present on normal plasma cells, which make antibodies, and also cancerous plasma cells that are responsible for multiple myeloma. It's also present in a subset of other immune cells in our body. And while it's present in B cell, the intensity of expression can vary over time. And what happens is, sometimes there's an enzyme in our body that actually takes them off the surface of these plasma cells and this can come in handy when we try more innovative strategies against multiple myeloma and CAR-T cell therapy.



Slide 43: CAR T Cell Therapy for Myeloma: An Overview

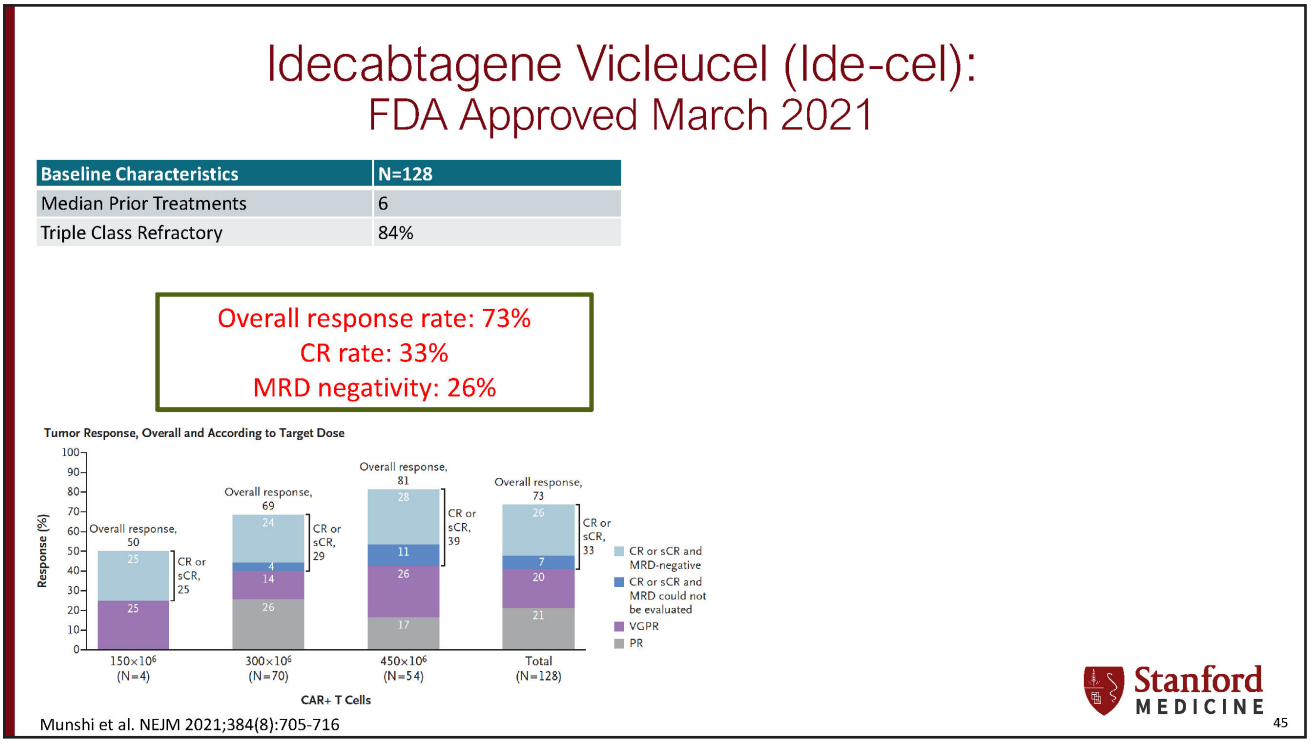
So the process of CAR-T cell therapy in multiple myeloma is very similar to what Dr. Miklos described for leukemia and lymphoma. The first step, as shown on this slide, is to get a patient's B cells through a process called apheresis, which involves a few hours of sitting on a machine while the machine processes blood. And then those cells are sent to a lab, which usually typically through a virus, we insert the genetic code for the CAR-T cell in your own cells. Once this genetic code is inserted, your own cells start expressing this protein called the chimeric antigen receptor. And these cells then are grown in the lab for several days to make millions of these cells, a living army, that is then given back to patients after giving them a 2 or 3 day course of chemotherapy. And, once these cells go in, they expand, and they grow, and they go into the cancer cells that they're targeted towards.

So before I go into what are the response rates with CAR-T cell therapy myeloma, I just want to give you a context of what happens in patients who don't get CAR-T cell therapies but get all of the other new advanced therapies we have.



Slide 44: Outcomes and recent FDA approved drugs in triple class refractory MM

So in patients with heavily treated myeloma, what we call triple-class refractory disease, that has seen a proteasome inhibitor like bortezomib (Velcade®) or carfilzomib (Kyprolis®), has seen an immunomodulatory drug like lenalidomide (Revlimid®) or pomalidomide (Pomalidomide®), as well as an anti-CD38 antibody called daratumumab (Darzalex®), and these are the most powerful drugs we have, if someone's progressed through all of this, typically we see that with the newer drugs we have or whatever we use, the response rates are about 30%, so that's the benchmark we are comparing these CAR-T therapies to, a 30% response rate



Slide 45: Idecabtagene Vicleucel (Ide-cel): FDA Approved March 2021

So this is data for idecabtagene vicleucel, ide-cel or Abecma®, which was FDA approved in March 2021, so less than a year ago, based on the results of the KarMMa clinical trial. 128 patients received the therapy on the clinical trial and 80% of them had received all of the drugs we talked about. And the response rate in this population was 73%. And as I just showed you, it's double than what we've historically seen. This got us all very excited about CAR-T cell therapy and multiple myeloma.

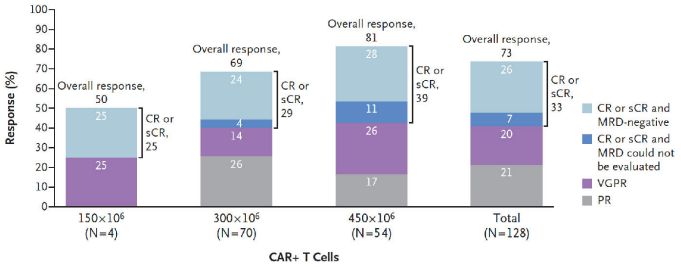
The complete response rate was 33% and this is very impressive, and this led to the FDA approval of this therapy in myeloma.

Idecabtagene Vicleucel (Ide-cel): FDA Approved March 2021

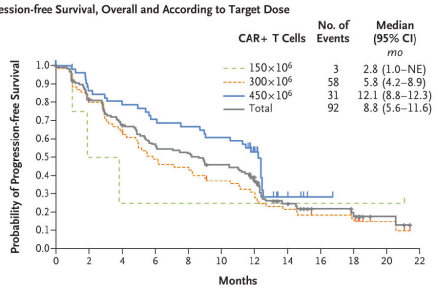
Baseline Characteristics	N=128
Median Prior Treatments	6
Triple Class Refractory	84%

Overall response rate: 73%
CR rate: 33%
MRD negativity: 26%

Tumor Response, Overall and According to Target Dose



Progression-free Survival, Overall and According to Target Dose



No. at Risk

150×10⁶	4	2	1	1	1	1	1	1	1	1	1	0
300×10⁶	70	56	42	33	29	24	17	14	11	7	3	0
450×10⁶	54	44	40	36	34	31	17	4	1	0	0	
Total	128	102	83	70	64	56	35	19	13	8	4	0

Survival Outcomes	
Median progression free survival	8.8 months
Median PFS in CR	20.2 months
Median OS	19.4 months

Munshi et al. NEJM 2021;384(8):705-716

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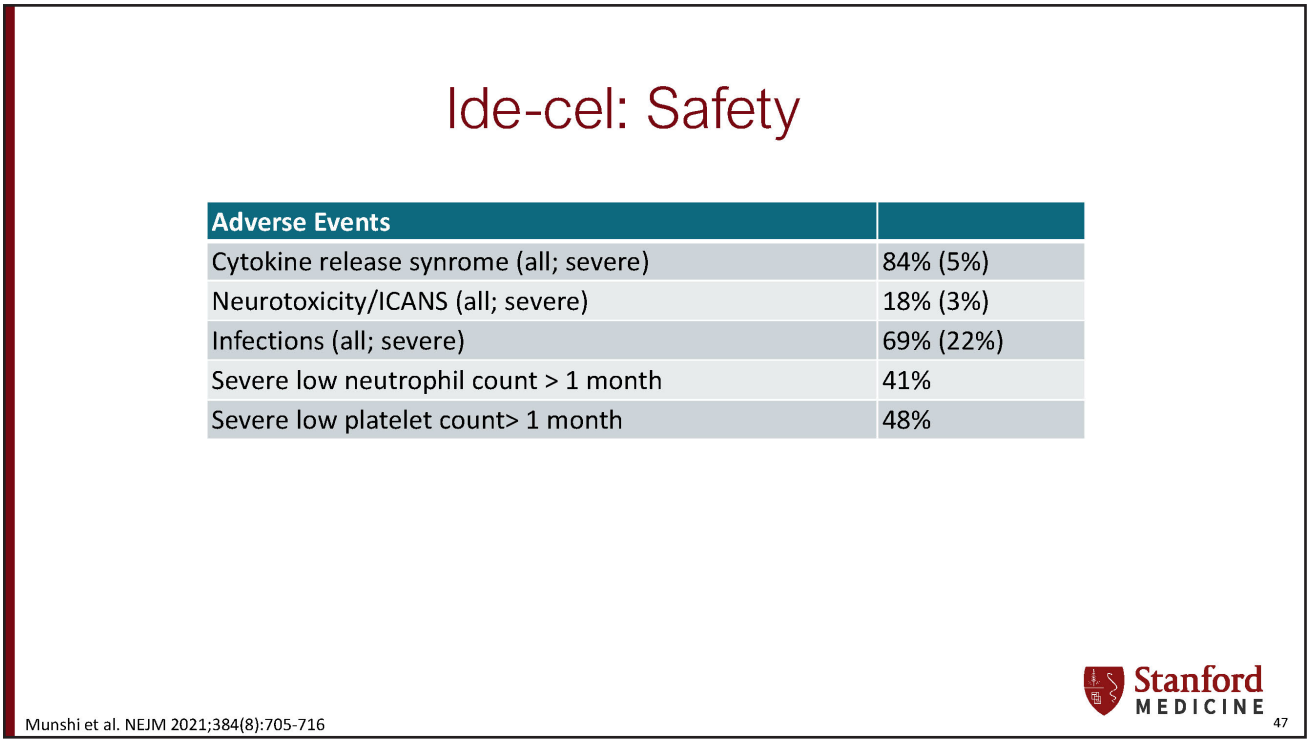
46

Slide 46: Idecabtagene Vicleucel (Ide-cel): FDA Approved March 2021

When we look at how long this response lasts, unlike lymphoma, we're not seeing a plateau in the response, meaning patients continue to progress. The average time the response lasts is about 9 months and if patients get a very deep response, like complete response, the response lasts about 20 months.



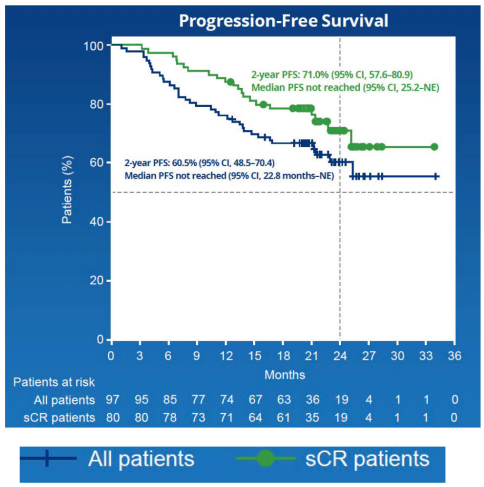
Slide 47: Ide-cel: Safety

What about side effects? Dr. Miklos described side effects like cytokine release syndrome and neurotoxicity. These happen, these happen early, but mostly are mild. Severe side effects happen less than 5% of the time for these 2 side effects. The other things that happen are infections, which can be severe in about 20% of patients, and low blood counts, which can continue beyond a month. So that's something that your doctor needs to follow up on after your CAR-T cell therapy is done.

Ciltacabtagene Autoleucel (Cilta-cel)

Baseline Features	
Patients	97
Median prior treatments	6
Triple Class Refractory	88%

Efficacy	
Overall response rate	**98%**
sCR rate	83%
MRD negative rate (10^{-5})	58%[2]
PFS	2 year: 61%, median NR
OS	2 year: 74%, median NR



1. Martin et al. ASH 2021 *Blood* (2021) 138 (Supplement 1): 549.
2. Usmani et al ASCO 2021. JCO 2021;39(15_suppl):8005.

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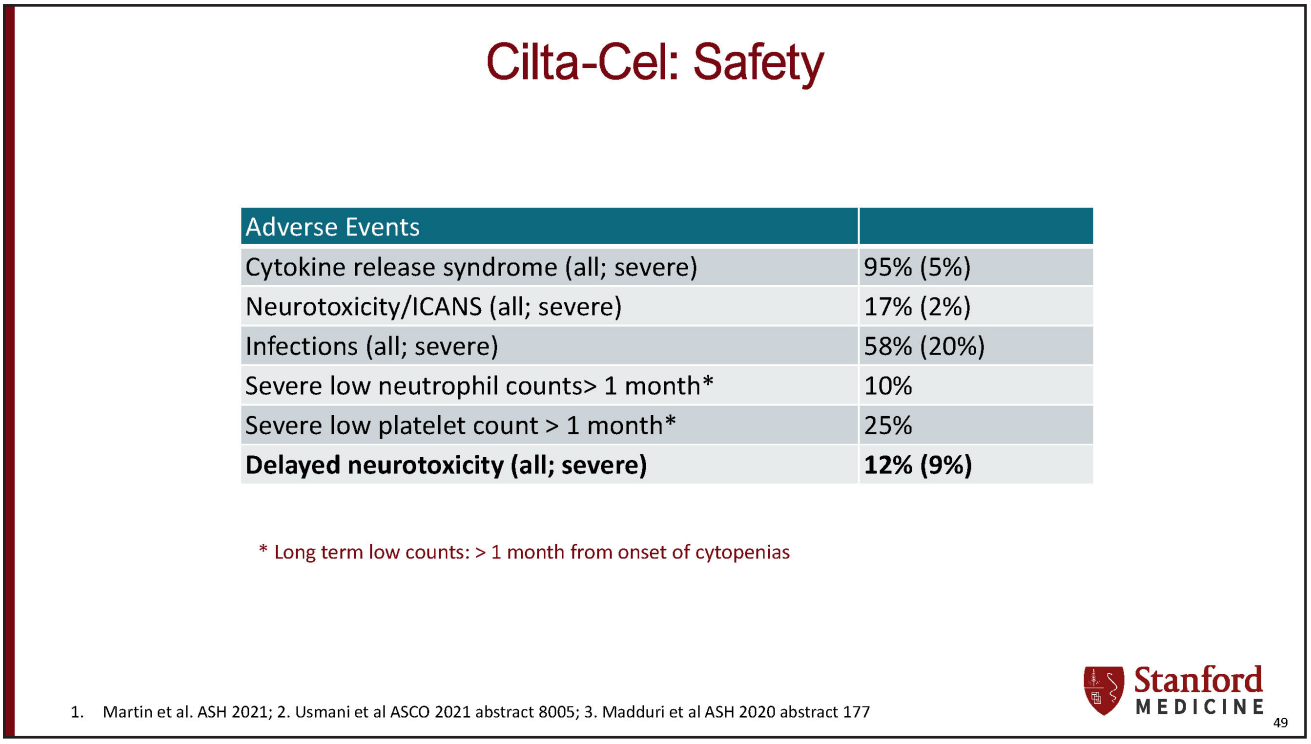
48

Slide 48: Ciltacabtagene Autoleucel (Cilta-cel)

Then let's talk about the other BCMA targeted CAR-T cell therapy, ciltacabtagene autoleucel or cilta-cel. This is a product manufactured by Janssen. It's currently under FDA review for approval and we expect to hear a decision by the 28th of February of this year. Again, the patient population on this clinical trial was very similar to the other trial, very heavily pretreated patients, and we saw response in 98% of patients. To me, this is unprecedented, never seen before in such a heavily pretreated population.

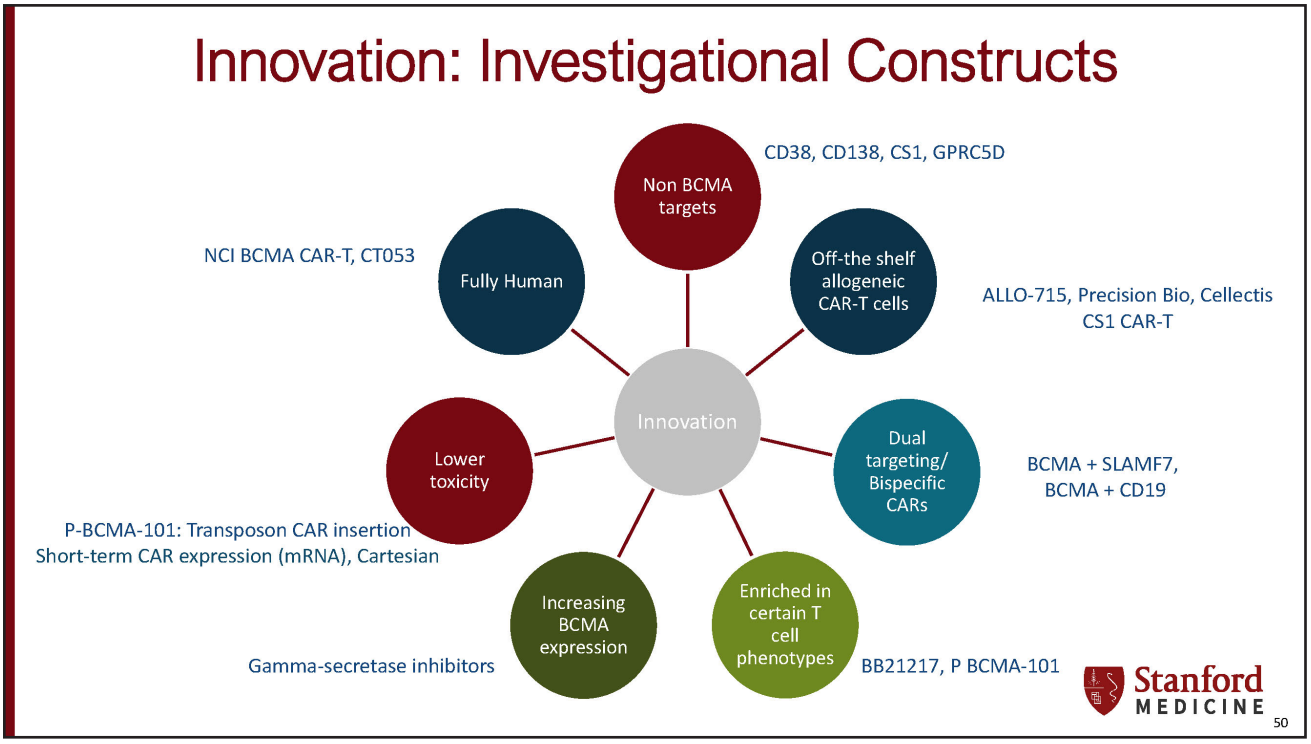
As far as the duration of response, the average duration has not been reached, but at 2 years, 60% of patients were still without progression in this clinical trial.



Slide 49: Cilta-Cel: Safety

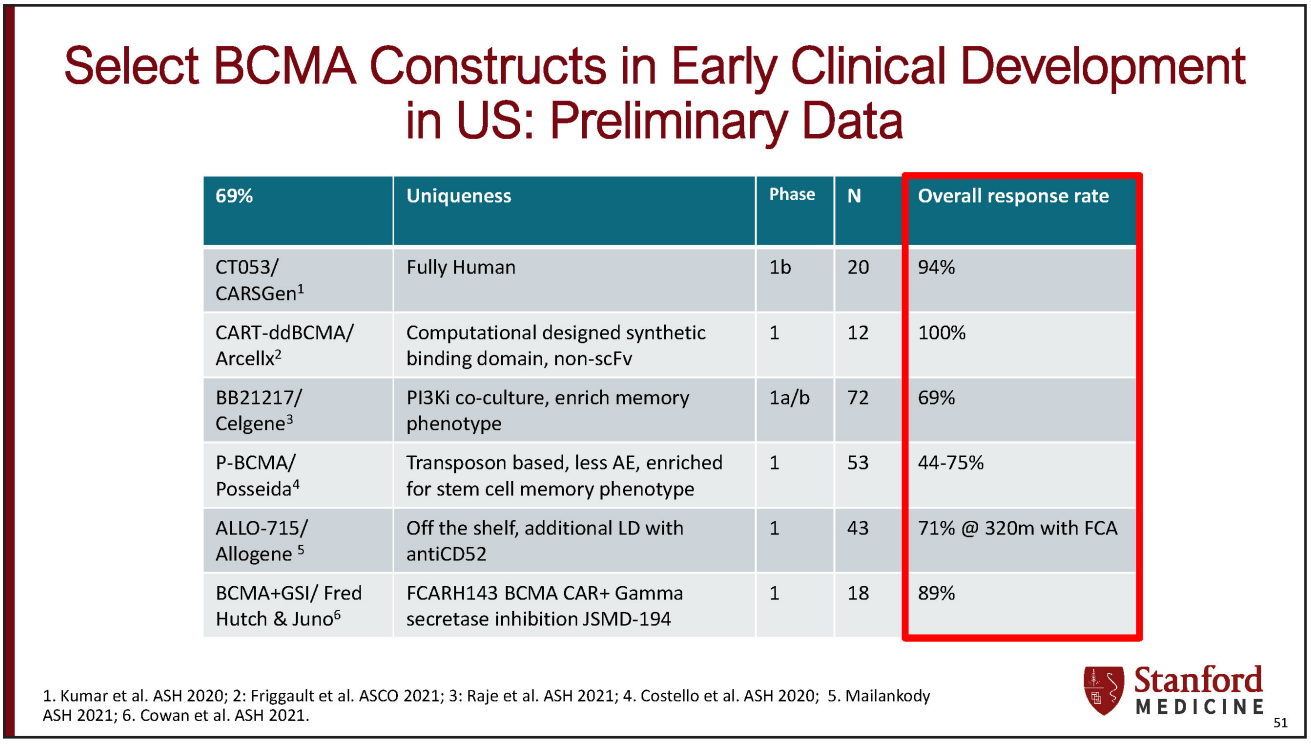
The safety of this drug was this CAR-T cell therapy was very similar to ide-cel. Yes, most of the patients do get cytokine release syndrome, some get neurotoxicity, but it's mild in the majority of patients. Infections and low blood counts are an issue, especially as we go several weeks beyond CAR-T cell therapy.

With this CAR-T construct we also saw that some patients were getting neurotoxicity a month after CAR-T cell therapy, which is quite unusual compared to what we've seen with other CAR-T cell therapies. And so the company looked at it and they saw that okay, there're several risk factors for this and if we eliminate these risk factors this incidence doesn't happen. And so, for the past year we have not seen any of these happen again, which is very reassuring.



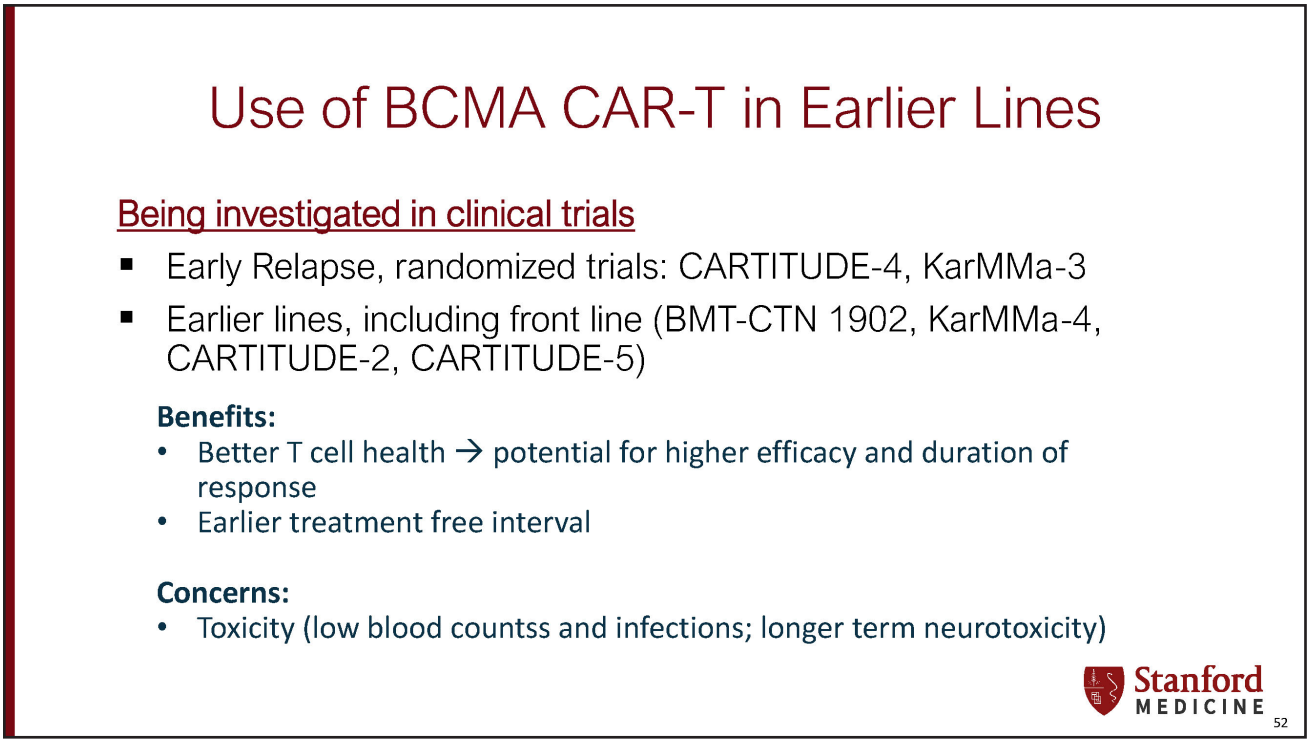
Slide 50: Innovation: Investigational Constructs

Those are the 2 main CAR-T cell therapies, one that's FDA approved, one that is in FDA review. But I want to show you on this slide that there's a lot of innovation happening in CAR-T cell therapy in myeloma. We're targeting non-BCMA targets. We're working on off-the-shelf constructs that are derived from a donor, so that the wait time of 4 to 6 weeks to make the CAR-T cell product, it does not happen. We're trying to make dual-targeted CAR-T cell against BCMA and others. And we're also trying other innovative strategies to make the response better and to make the response last longer. So there's a lot of hope on the horizon and a lot of new therapies that are out there that should be coming to clinic in the next few years.



Slide 51: Select BCMA Constructs in Early Clinical Development in US: Preliminary Data

And this slide is just a summary slide, not to inundate you with data, but to show that in the early trials with these newer CAR-T cell therapy constructs, we are seeing very high response rates, anywhere from 70 to 100% on average. So more to come in the coming years with these newer CAR-T cell therapies.

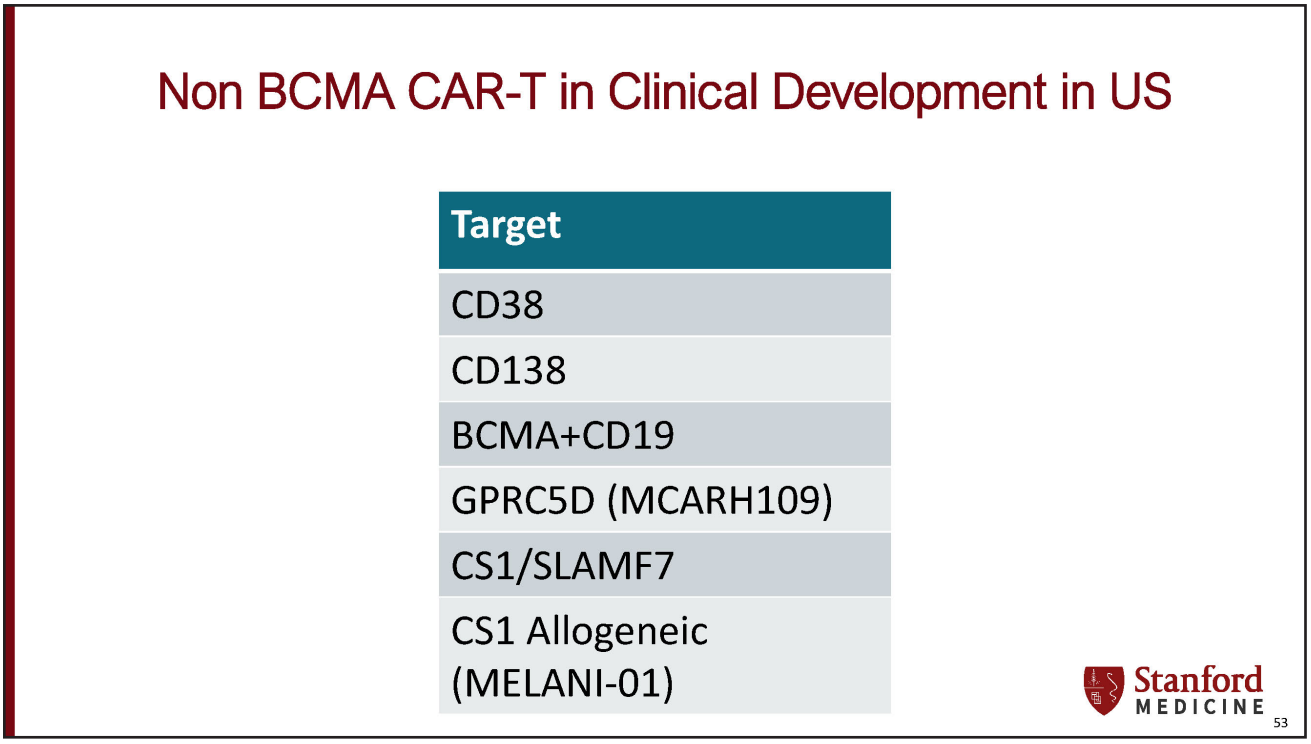


Slide 52: Use of BCMA CAR-T in Earlier Lines

As I mentioned, with any therapy that we have, we first use it in patients who've been more heavily pretreated, but then gradually try to use it in earlier lines of therapy. So BCMA CAR-T cell therapy is being investigated in earlier treatment lines, at first relapse, at newly diagnosed, and others in several clinical trials.

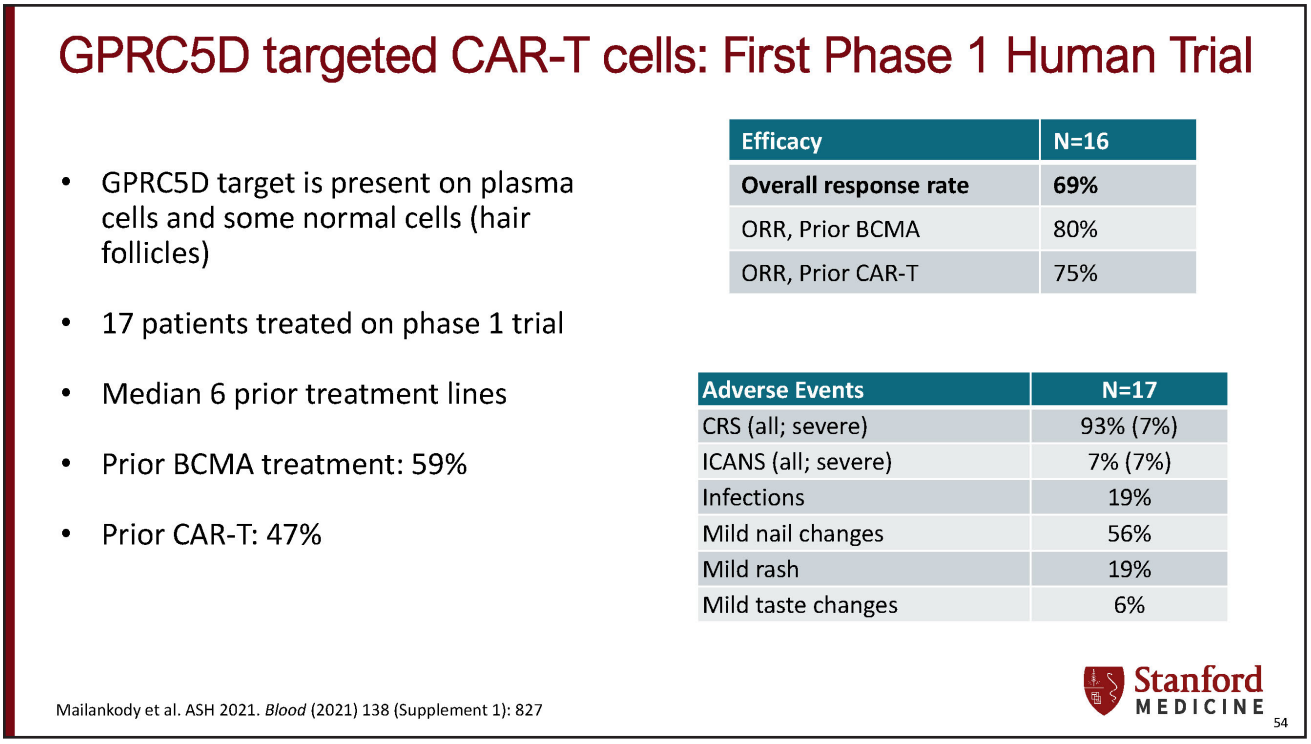
There are some benefits of it and as patients you receive these therapies when your T cells are technically more healthy and perhaps there's an earlier benefit for a treatment-free interval because there's typically no maintenance after CAR-T cell therapy.

The concerns of course are there's some long-term toxicities we don't know about that may happen earlier in the disease course.



Slide 53: Non BCMA CAR-T in Clinical Development in US

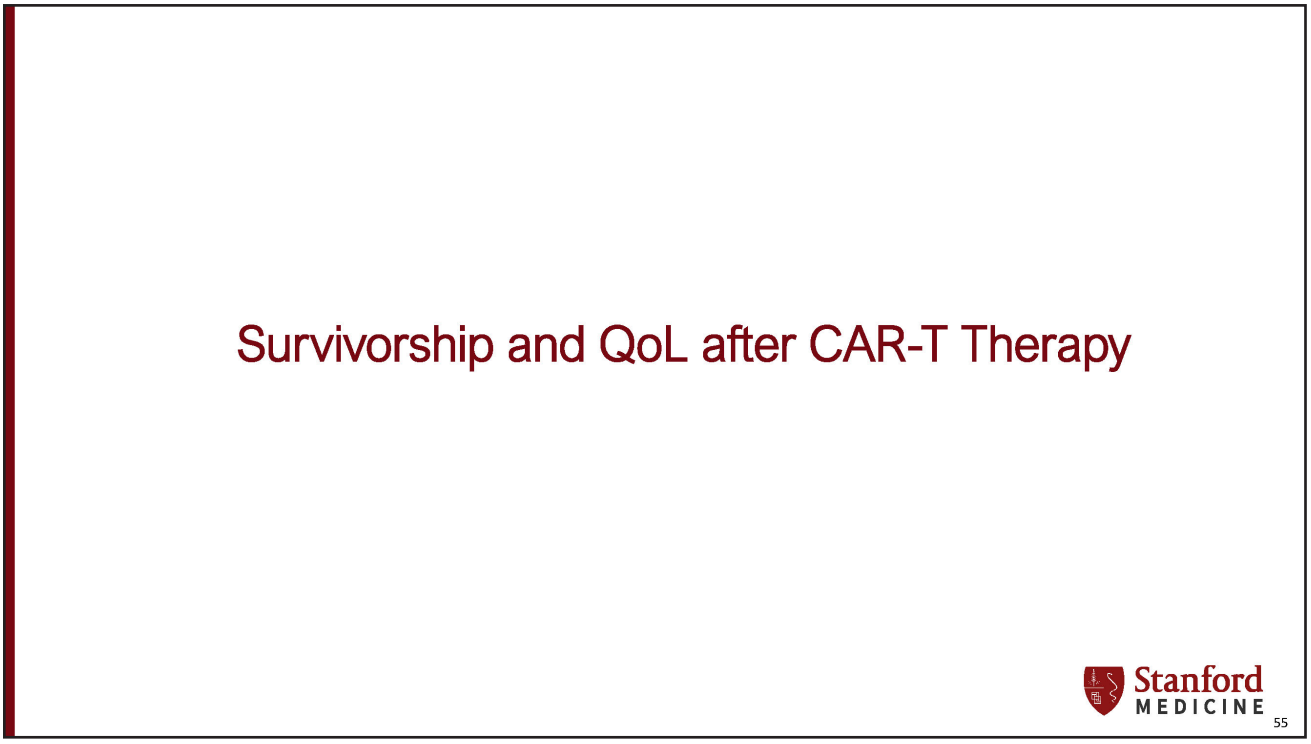
As I mentioned, there are several non-BCMA targets in clinical development in the US and all around the world. And, I will show you 1 slide of a clinical trial that was presented at the American Society of Hematology meeting in 2021, December.



Slide 54: GPRC5D targeted CAR-T cells: First Phase 1 Human Trial

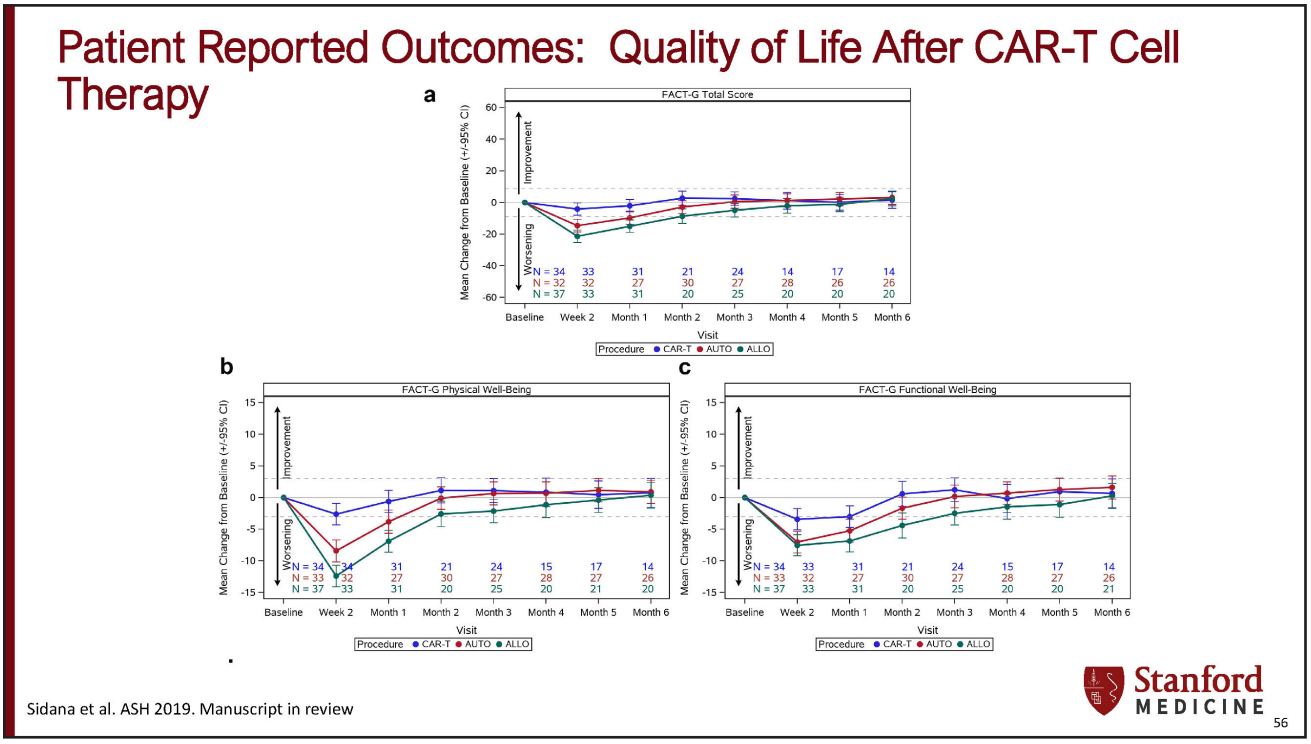
This is targeting GPRC5D, which is also a protein expressed by plasma cells and including both myeloma cells and normal plasma cells, as well as expressed on hair follicles. And so only 17 patients were treated on this early Phase I trial and interestingly, about 60% of them had had prior BCMA treatment and almost 50% had had prior CAR-T cell therapy. And despite that, almost 70% of patients responded. That's very encouraging, including responses after prior BCMA treatment and prior CAR-T cell therapy treatment.

Side effects were very similar, except that because this protein is expressed in the skin and hair follicles, we saw some of those side effects with rash, abnormal taste changes, but those were very mild and manageable.



Slide 55: Survivorship and QoL after CAR-T Therapy

So I want to now focus on what happens after you get CAR-T cell therapy, how does life look like for patients and what things do we need to watch out for?



Slide 56: Patient Reported Outcomes: Quality of Life After CAR-T Cell Therapy

So, this is a study that we conducted in patients who were undergoing both CAR-T cell therapy and transplant. The impact of CAR-T cell therapy shown in the blue line and the line shows the average quality-of-life of patients starting from before CAR-T up to 6 months after CAR-T. And you can see here in the beginning there's a slight dip at 2 weeks after CAR-T, but that continues to go back up to normal after a month or 2 after CAR-T cell therapy, meaning that there's a slight impact on quality-of-life of patients the first month after CAR-T, but that becomes close to normal or their baseline a month or 2 after CAR-T cell therapy, which is very encouraging.

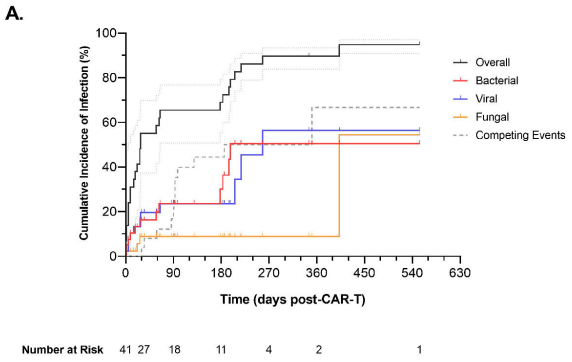
Post CAR-T Cytopenias after Month 1

Severe low blood counts: Very common (50-70%), improve with time

- ANC < 1000
- Platelets < 50,000
- Hemoglobin < 8 g/dL

Treatment: Growth factor medications, transfusions, rarely stem cell boost

Infections: Also common, long-term antimicrobial prophylaxis is necessary



1. Baird J et al, Blood Advances 2021. 2. Jain T et al, Blood Advances 2020

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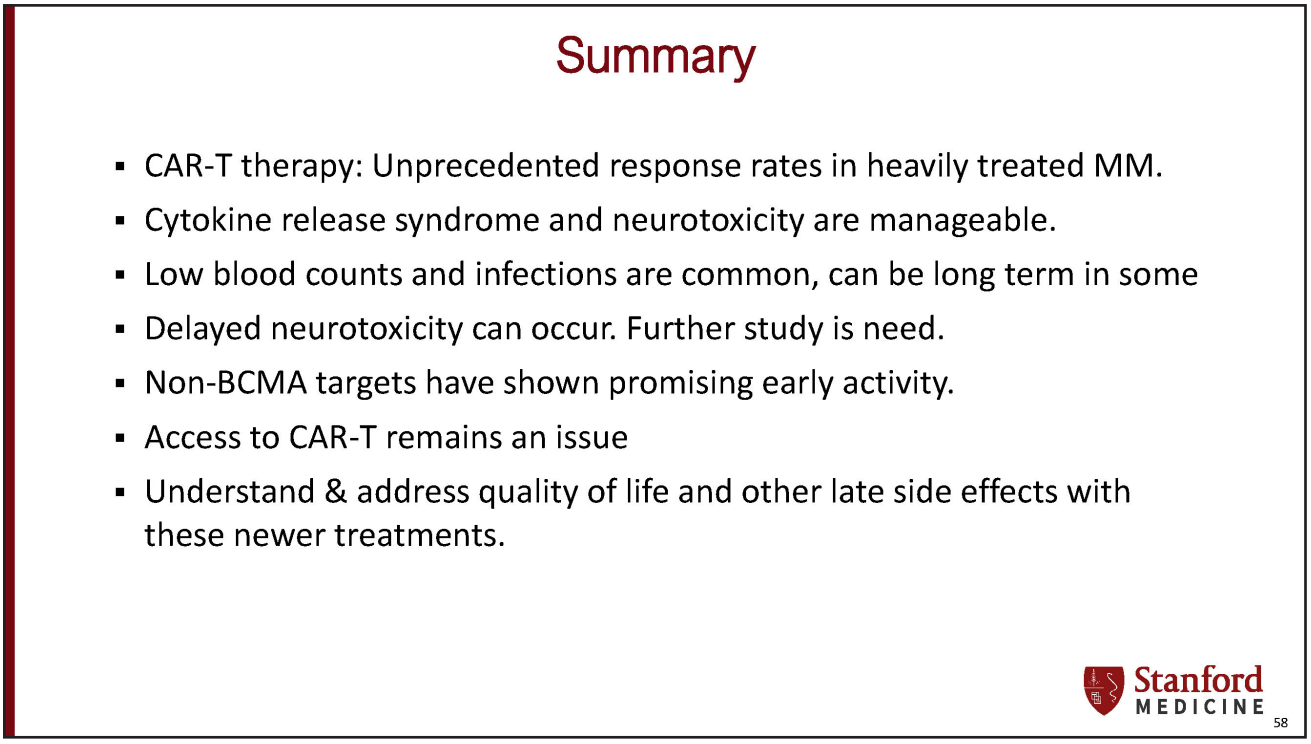
57

Slide 57: Post CAR-T Cytopenia's after Month 1

And lastly, as I mentioned in my several slides before, it's important to look at low blood counts and the risk of infections after CAR-T cell therapy. Severe low blood counts are quite common, even a month after CAR-T cell therapy, but they do improve with time. On the right-hand side of the slide, there's a figure of the risk of infections over time from a study done by one of our outstanding fellows, Dr. John Baird, who showed that over time there are infections, viral infections, bacterial infections, and sometimes even fungal infections that can happen for several months after CAR-T cell therapy. So what does that tell us? It tells us that it's very important, we want to watch out for them, and very importantly to give sometimes antimicrobial medications to prevent some of these that we can prevent.



Slide 58: Summary

So with that, to summarize, CAR-T cell therapy has resulted in unprecedented response rates in patients with multiple myeloma. Cytokine release syndrome and neurological toxicities occur but are very manageable. Low blood counts and infections are common and can be long-term in some patients. Delayed neurotoxicity can occur and we need to keep a very close eye on this and study this further. Non-BCMA targets have shown very promising early activity. However, despite all of this, access to CAR-T cell therapy remains an issue and all of the patients who can benefit from this are not getting this therapy and that's something Dr. Miklos also highlighted. And then, as we go forward, we need to continue to innovate and continue to understand and address quality of life and other late side effects that happen with these newer treatments.

With that, thank you very much for your attention.

Slide 59: ASK A QUESTION

Ms. Figueroa-Rivera:

Thank you, Dr. Miklos and Dr. Sidana. It's now time for our question-and-answer portion of the program.

We'll start with our web audience. Doctors, Barbara's asking if CAR-T will replace stem cell transplant.

Dr. Miklos:

Stem cell transplant can be autologous from one's own stem cells, also known as high-dose chemotherapy with stem cell rescue, and it can be allogeneic. And I think it's really important that we clarify. So far, the benefits of CAR-T are occurring in lymphoid neoplasms and not in the myeloid or AML or MDS. And allotransplant remains the therapy for all the myeloid malignancies. Autologous has a role in patients who are relapsing late after treatment for lymphoma, but I think I showed today some very exciting data that CAR-T is showing benefits for those patients with aggressive lymphoma, large cell in particular, that it is optimal for the patient to receive the CAR-T before considering auto transplant in those patients.

So, the short answer is, it's adding to the benefits of auto and allo transplant and CAR-T is ever showing more benefits to the patients.

Ms. Figueroa-Rivera:

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

Operator:

Richard in Maryland, your line is open.

Richard:

My question is related. I'm wondering about the toxicity. How does the toxicity of the CAR-T cell therapy compare with the toxicity of the stem cell transplant?

Dr. Miklos:

I'll make one comment and I'll pass it to Dr. Sidana. The first comment is, toxicity at its most crude basis is non-relapse mortality, that's patients dying from a therapy without their cancer relapsing. The non-relapse mortality of an auto transplant or a CAR-T at any of these excellent centers across the country is less than 1 to 2%. The toxicities that cause death is controlled. The toxicity nature is different, and I'll pass it to Dr. Sidana.

Dr. Sidana:

Thanks, Dr. Miklos. I think that's an excellent question. The toxicity nature for these 3 therapies are slightly different, so it's hard to compare.

Let me answer this from a patient's perspective. In the study that we did comparing CAR-T to auto to allogeneic transplant, we saw that there is a dip in a patient's quality of life, which is due to increase in side effects in all 3 modalities. It came back quickest to baseline in CAR-T cell therapy, followed shortly after by autologous transplant, and then while the allogeneic transplant patients took a little bit longer, they were also able to come back to near normal baseline for them. So I think the trajectories are different, but patients with CAR-T cell therapy at least in the experience of the patients that they are reporting recover faster.

Dr. Miklos:

And, Richard, I emphasize the importance of the excellence of the care center, the nurses, the pharmacists, the physicians. And, for example, at Stanford our bone marrow transplant program manages the patients side-by-side who are going through allogeneic, autologous, and CAR-T therapy, because the needs for those patients are really overlapping. So, good question, I hope we helped you.

Ms. Figueroa-Rivera:

Thank you so much. Vic and Patricia are asking, do you foresee CAR-T being used as frontline therapy instead of waiting for other treatments to fail?

Dr. Miklos:

I'll take that one real quick. I think that when you have a therapy that can create a cure, such as CHOP has done in large cell lymphoma for 60% of the patients, it will be a very high bar in order to demonstrate that the CAR-T should replace such therapy. I think our opportunities for the next 5 years are to really focus on second-line therapy, improving the numbers of targets, improving the nature of the CAR therapy itself, and we'll take advantage of already established research benefits for the patients in the frontline. I do not expect CAR-T to become frontline therapy in the next 5 years.

Ms. Figueroa-Rivera:

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

Operator:

We'll hear from Teresa in Georgia.

Teresa:

Hi. My sister has just completed CAR-T cell therapy. She came home 2 weeks ago. At the initial ending, after 23 days T cells were reintroduced to her system, they basically said it failed. She had had 2 previously, five years ago she was diagnosed with CLL with a p17 deletion [Del(17p)], which I know that makes it a bigger than normal diagnosis. But she's going to continue with the therapy to see if it carries on, but she's having severe side effects now, lymph nodes are just outrageous, CLL cells are still prevalent, and she's just not responded well. And, we do have a family history that started in 2015 with blood cancer. My mother AML, 83. They just did the best they could with hospice care. My brother had MPN.

Dr. Miklos:

Can I help you? I think what you're going to ask me is, what can your sister take advantage of as possible future therapies.

Teresa:

Yes.

Dr. Miklos:

You identify that chronic lymphocytic leukemia to this point does not have an FDA approved CAR-T cell therapy. It's one of the challenges that we're all working on.

And, as you know, there are really a couple of great drugs out there that work effectively in CLL, but frequently become resistant, especially those patients who have the 17;p mutation that you described your sister having. I'm sorry about that, that's very difficult.

Those therapies at this point, ibrutinib (Imbruvica®), venetoclax (Venclexta®), and then the allogeneic transplant is the one long-term benefit in the 17;p. So, patients who are fit, who have a 17;p mutation, who are progressing after ibrutinib/venetoclax should be looking towards an allogeneic transplant. Or, participating on these clinical trials for the CAR-T advancement. Those are important opportunities.

I hope that your sister can find a clinical trial and I hope that she can recover to the point where she can benefit. It's a very difficult situation she's in. I'm so sorry.

Ms. Figueroa-Rivera:

Yes, thank you so much for the question. And Doctors, many people, as well as John, is asking about insurance coverage for CAR-T. Is CAR-T covered by insurance? And I know that both doctors have also mentioned, CAR-T not being available everywhere. Can you just speak to the availability of CAR-T across the country?

Dr. Miklos:

I guess Surbhi's going to ask me to do that since I'm the Chief. It's important for the audience to recognize that Medicare supports the treatment of FDA indicated CAR-T cells across the entire United States, that the therapies, when offered through Medicare, are also in the provision of the supportive hospitalizations, chemotherapy, and post-care treatment. These are expensive therapies, but they are lifesaving and it's just really important to recognize that a Medicare patient has the right to receive these therapies.

Most of the Blue Cross-Blue Shield and Medicaid organizations also support the indications as FDA approved. Places where you may have more variability are how clinical trials and the support for the clinical trials at individual centers across the country will vary, and that varies by state and even county sometimes.

That is a challenge. This is why The Leukemia & Lymphoma Society is so important. They provide a lot of financial and resource support for the patients, finding clinical trials, and getting them to the docs who have the treatments available. Surbhi, again, the need for the patients and how we support them?

Dr. Sidana:

Thank you, Dr. Miklos. So as both of us have said, there're so many more patients who need it than what's available right now. Especially multiple myeloma. I know last year when the therapy got FDA approved, we had lots of patients express interest and in fact they have the need, but currently we have limitations in manufacturing, there's only so many slots available for commercial CAR-T cell therapy that we're not able to meet the need nationally. I'm hoping with further FDA approvals or other clinical trials that are available for patients that we can meet the needs of more patients, but this is an issue.

Dr. Miklos:

Thank you, Dr. Sidana. That's really important, the ability to provide more therapy is critical right now.

Ms. Figueroa-Rivera:

Thank you. As you said, The Leukemia & Lymphoma Society has Information Specialists, as well as Nurse Navigators, to assist patients in finding either a clinical trial that's appropriate or finding a treatment center that does provide CAR-T cell therapy.

Our next question, Doctors. Is CAR-T cell therapy an inpatient procedure versus a bone marrow transplant (BMT), which can be either inpatient or outpatient?

Dr. Sidana:

I can take that question. I think it depends on the institution you're being treated at. Several institutions do it in the inpatient side just because it's a newer therapy, we are just getting familiar with the side effects. But some institutions, depending on how close patients can live by and what resources are available, may do it as an outpatient. Again in the future, we might try this more in the outpatient, but because it's so new I think we're all playing it safe more or less.

Ms. Figueroa-Rivera:

Thank you. The next question comes from Ray. Ray is asking what measures can prevent CAR-T cell therapy from damaging cognitive functioning? How long does it take for a patient to recover from cognitive decline?

Dr. Sidana:

Thank you. I think that's an excellent question and something that we as clinicians and researchers are still trying to understand. So the study that I showed you, we also asked patients if they perceived any cognitive decline, and of course at the beginning with neurotoxicity there is something, but what about month 1, 2, and 3? Patients didn't actually report any cognitive decline. Now, is it because there is no cognitive decline or do they not perceive it? I think we're doing studies to see if there's any objective cognitive decline that patients don't even realize they have. So far, we haven't seen much of an indication, but I think that it's just too early to tell.

Dr. Miklos:

Ray, I'd emphasize what Dr. Sidana said, that in the first month after CAR-T, there is cognitive deficits that are impacting you, the fatigue and even the just ongoing problems of hospitalization and medicalization do make patients very tired, and it's very rewarding though as a physician to watch how they change from day 28 to day 60. By 2 months afterwards, most people are back to their baseline, and they're just thrilled that they have benefited.

Ms. Figueroa-Rivera:

Great. I know Dr. Miklos you mentioned this, in our last question today, I just want to make sure that we go over it again. A lot of people are asking the age limit for CAR-T cell therapy.

Dr. Miklos:

Wow, this is my favorite question. So, for 50 years we've talked about 3 things being an indication of what lymphoma patients' prognosis might be. It's the amount of disease, it's the performance status of the patient, how fit they are or how beaten up they are from the cancer, and finally, it's the age. And for 50 years we've said age is a negative thing. Now, it turns out that when you look at CAR-T therapy across patients on a variety of trials, that the older patient population is doing just as well, and I say older as in 65 or higher. My own cut of the data shows that women above 70 do better than men under 60 in overall survival and performance in large cell lymphoma. We actually have an abstract coming to ASCO this year, looking at the benefits in that randomized control trial called ZUMA-7, showing the age benefit above 65, especially when compared to auto transplant, was far better for older age.

So I spoke to this, that is what we previously were describing the elderly patients who are transplant ineligible as having limited therapies, I believe we're going to open the therapeutic armamentarium to the older patient population. And since I have a birthday on Monday, I think this is really important news. So, good news, these therapies can be given to patients, and we don't have an upper age limit at Stanford.

Ms. Figueroa-Rivera:

That is really great news and happy birthday to you.

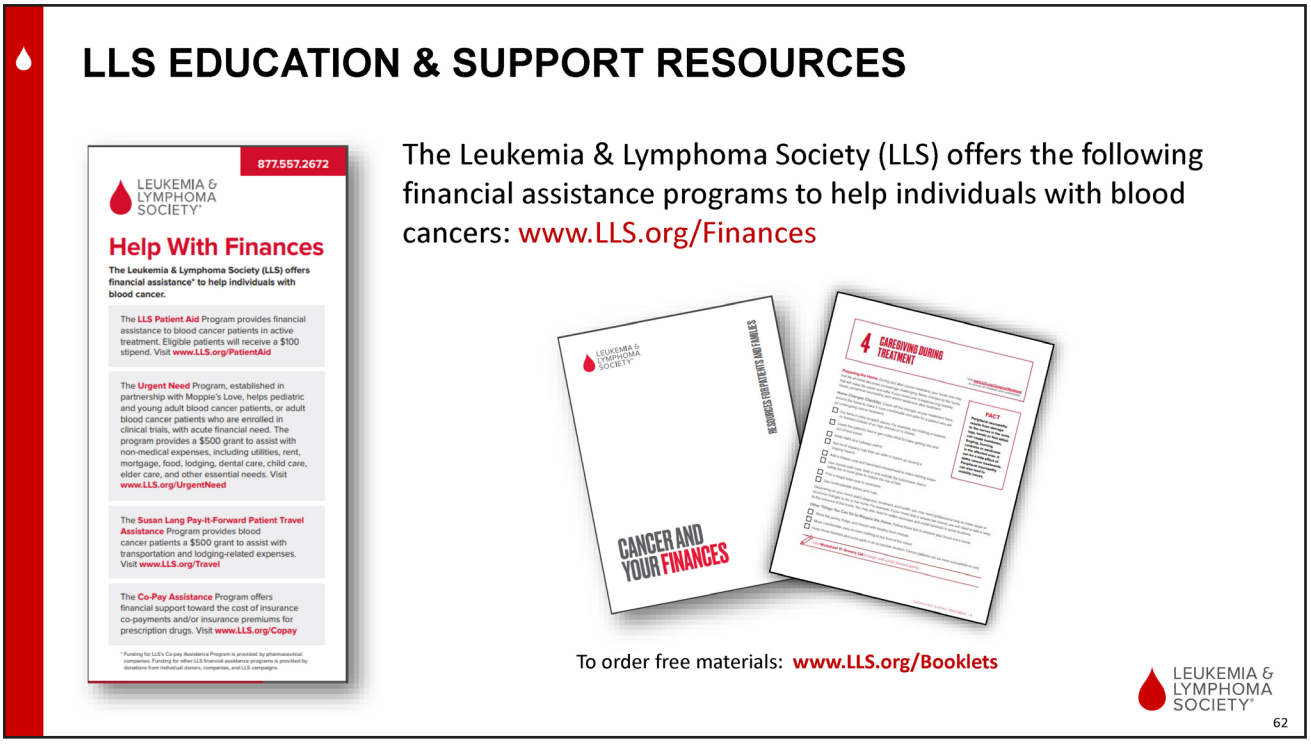
And that was our final question today. Special thanks to Dr. David Miklos and Dr. Surbhi Sidana for volunteering their time and expertise with us today, especially during these busy times. So thank you so much.

Slide 60: LLS EDUCATION & SUPPORT RESOURCES

And 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 by email at LLS.org/ContactUs. Information Specialists are available to answer any of your questions about treatment, about clinical trials, as well as financial assistance. And we also have a Clinical Trial Support Center, where Clinical Trial Nurse Navigators are registered nurses and have an expertise with blood cancers and can assist you in finding a clinical trial if that is right for you. And they could be found at LLS.org/Navigation.

Slide 61: LLS EDUCATION & SUPPORT RESOURCES

As a reminder, you can download and print the slides as well as listen to the audio and visual of today's program from our website at LLS.org/Programs.



Slide 62: LLS EDUCATION & SUPPORT RESOURCES

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

Slide 63: THANK YOU

Doctors Miklos and Sidana, thank you again for volunteering your time and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us today. Goodbye and we wish you well.