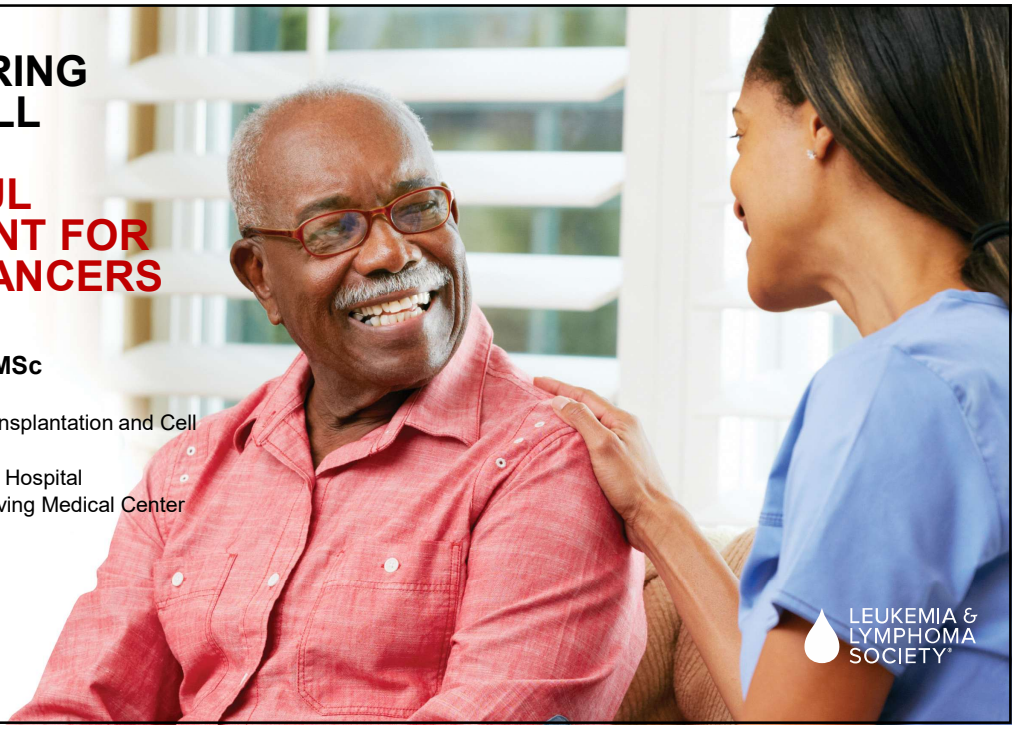
CONSIDERING CAR T-CELL THERAPY: A HOPEFUL TREATMENT FOR BLOOD CANCERS

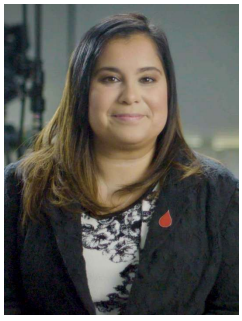


Ran Reshef, MD, MSc
Professor, Medicine
Blood and Marrow Transplantation and Cell Therapy Program
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center
New York, NY

1

WELCOMING REMARKS

CONSIDERING CAR T-CELL THERAPY: A HOPEFUL TREATMENT FOR BLOOD CANCERS



Lizette Figueroa-Rivera, MA
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

LEUKEMIA & LYMPHOMA SOCIETY®

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FACULTY

CONSIDERING CAR T-CELL THERAPY: A HOPEFUL TREATMENT FOR BLOOD CANCERS

Ran Reshef, MD, MSc
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New York, NY

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DISCLOSURES

CONSIDERING CAR T-CELL THERAPY: A HOPEFUL TREATMENT FOR BLOOD CANCERS

Ran Reshef, MD, MSc, has the following disclosures:

Allogene, Gilead Sciences, Incyte, TScan, Orca Bio, Pierre Fabre Pharmaceuticals, CareDx, Quell Biotherapeutics, Sana Biotechnology, Sail Biomedicines, Bayer, Autolus *(Consultant)*; Atara Biotherapeutics, Incyte, Sanofi, Immatics, AbbVie, TCR2, Takeda, Gilead Sciences, CareDx, TScan, Cabaletta, Synthekine, BMS, J&J, Allogene, Genentech, Vittoria Therapeutics, Imugene *(Grant Support)*.

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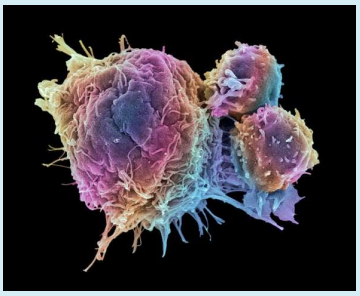
COLUMBIA | COLUMBIA UNIVERSITY HERBERT IRVING COMPREHENSIVE CANCER CENTER

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Considering CAR T-cell therapy: A Hopeful Treatment for Blood Cancers



Ran Reshef, MD MSc
Professor of Medicine
BMT and Cell Therapy Program

Columbia University Irving Medical Center

Discover. Educate. Care. Lead.

5

CAR T Cell Therapy in Blood Cancers

- How do CAR T cells work?
- A touch of history
- What did clinical trials show in blood cancers?
- What are the potential short-term and long-term side effects?
- Is this the right choice for me?

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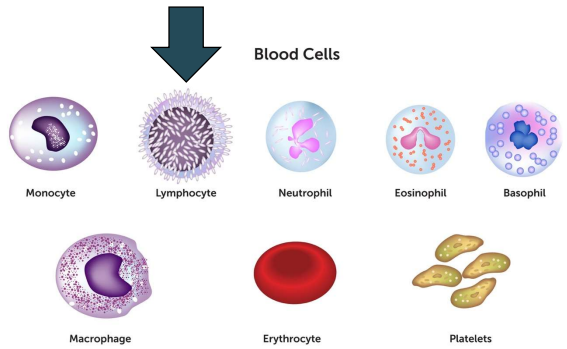
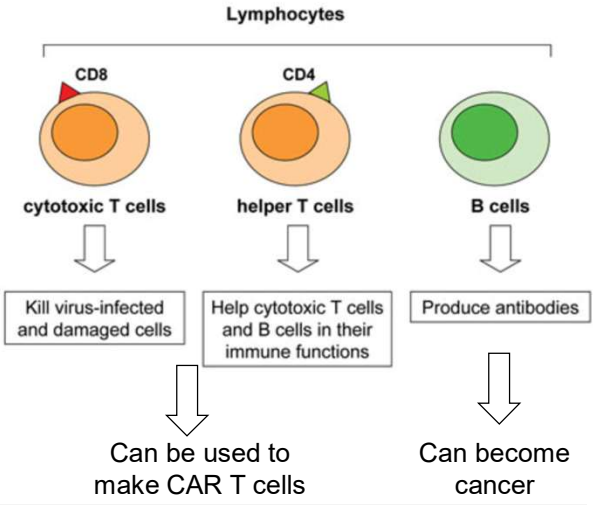
6

T cells and B cells are types of white blood cells





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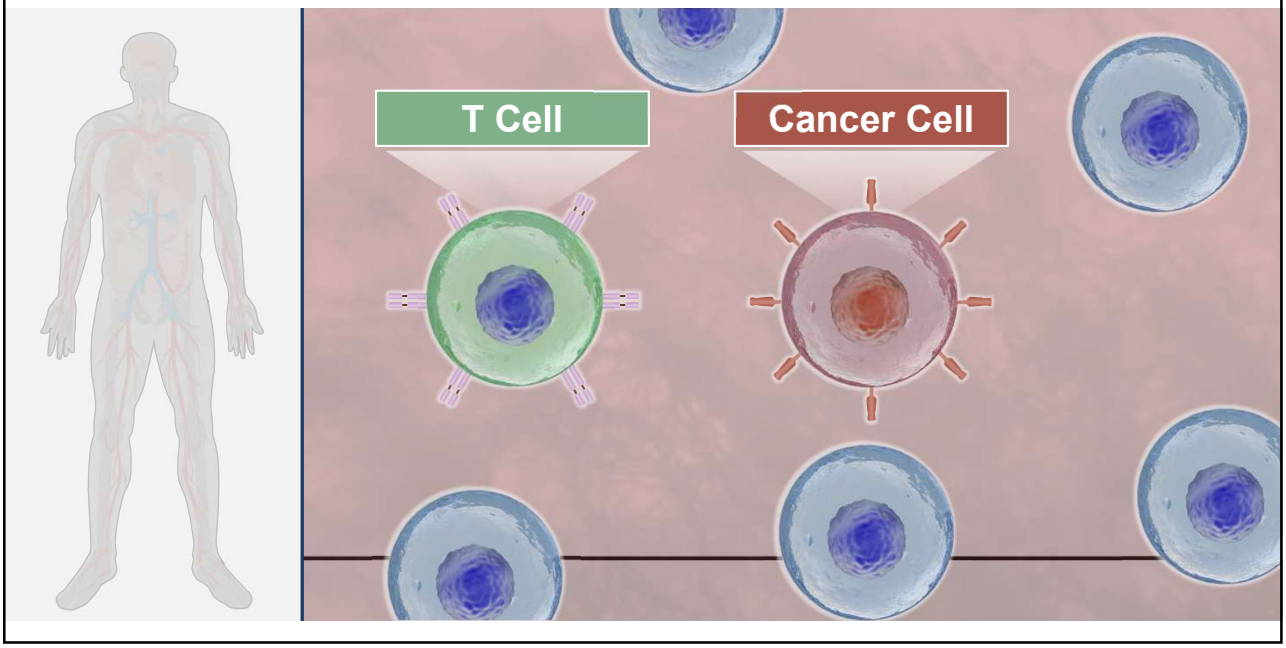
How do CAR T cells work?



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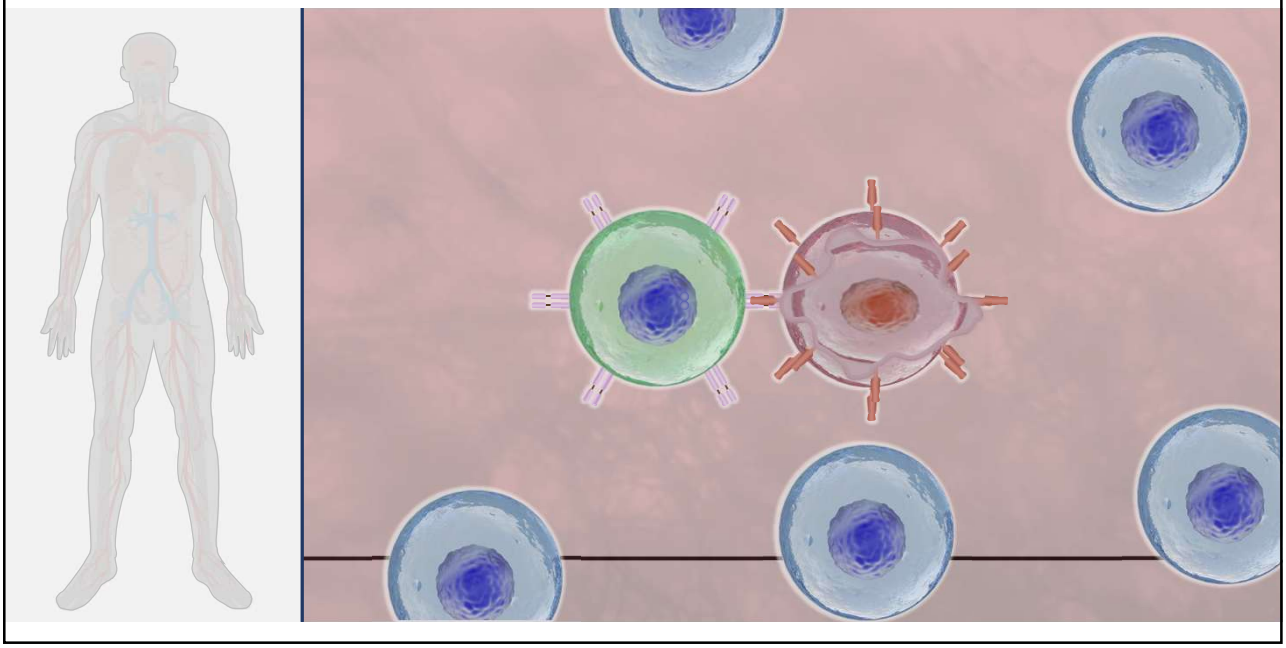
T Cells Can Kill Cancer Cells



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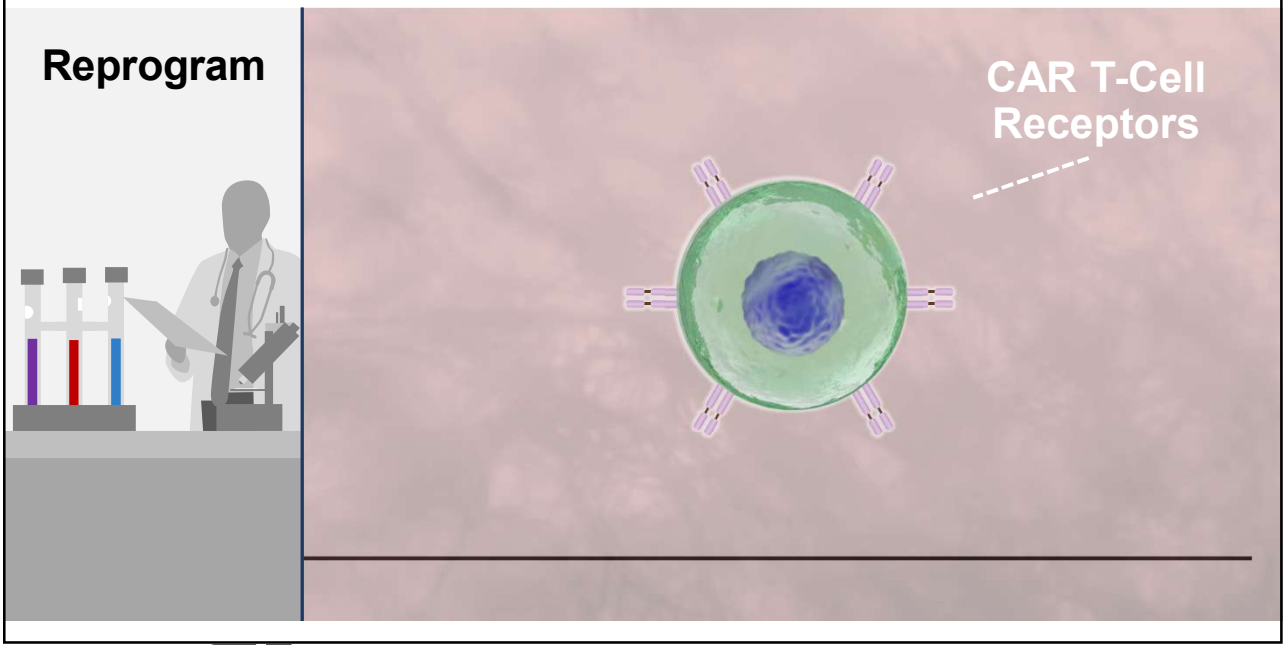
Genetic Modification



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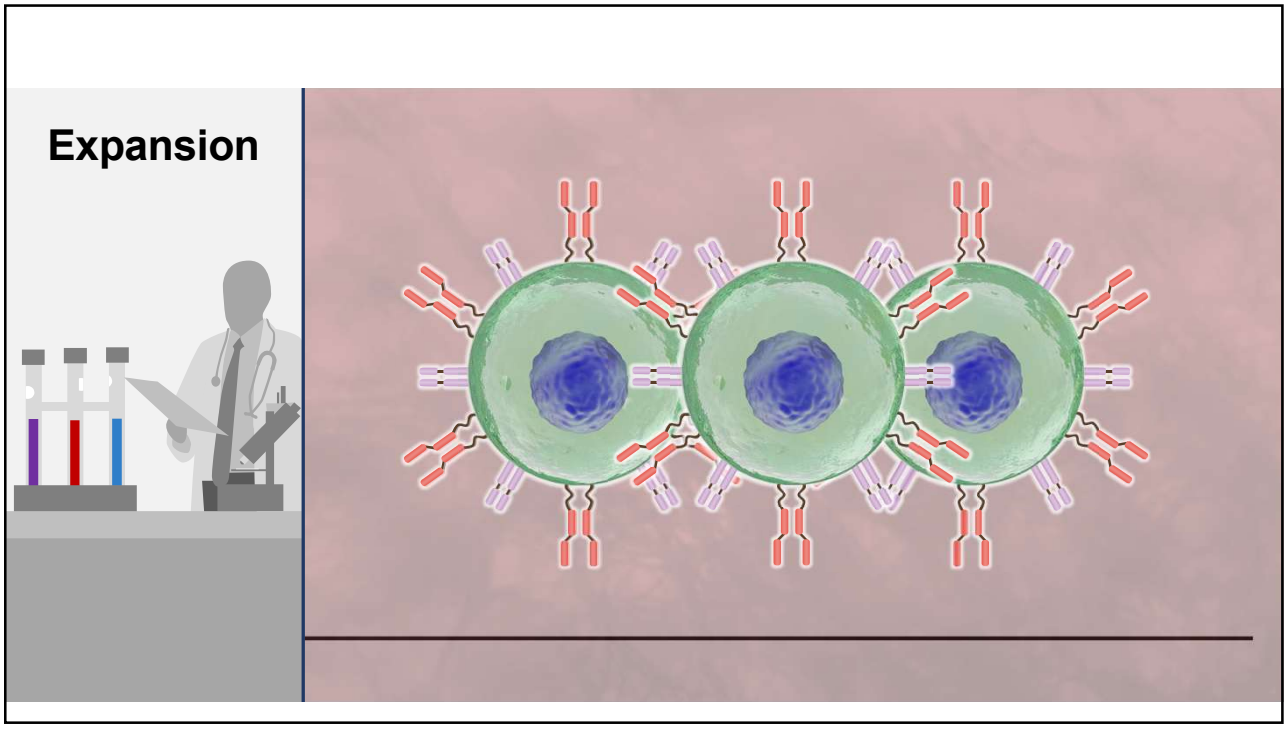

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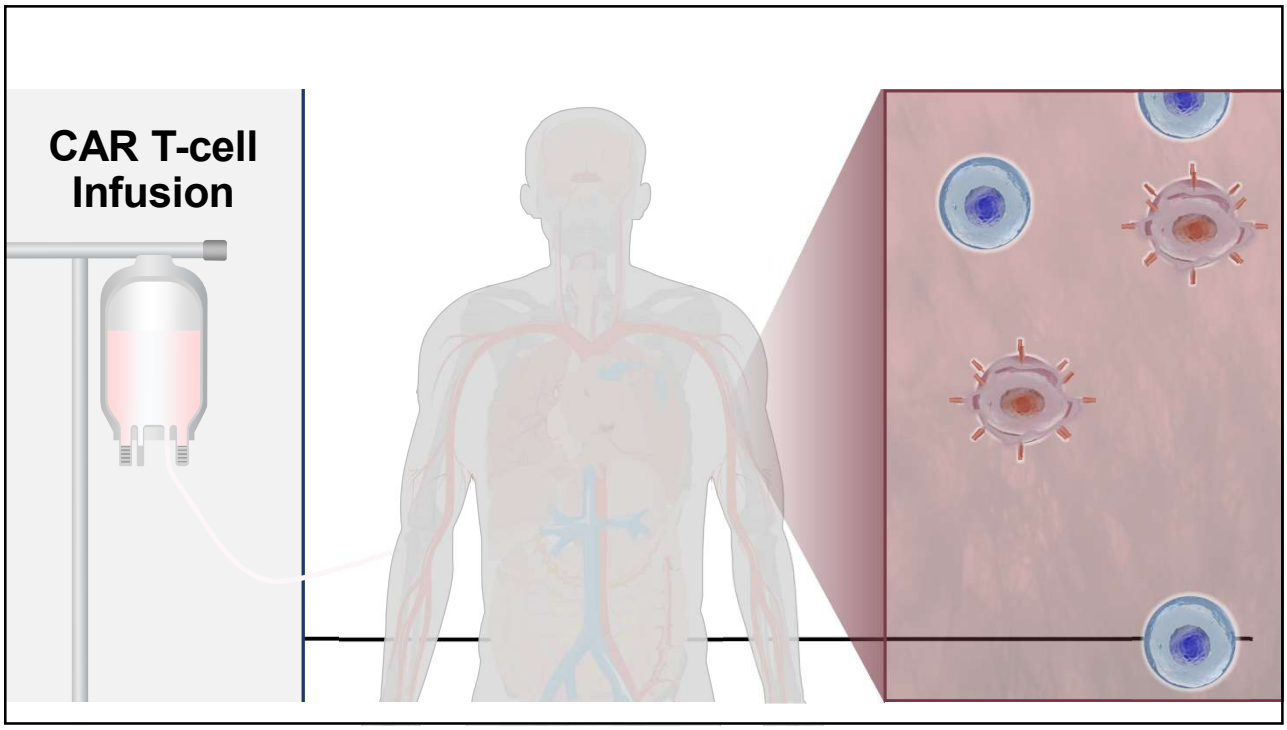
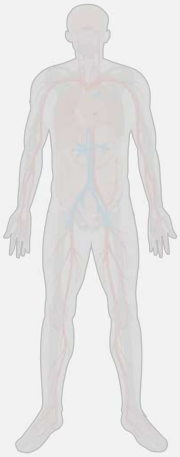
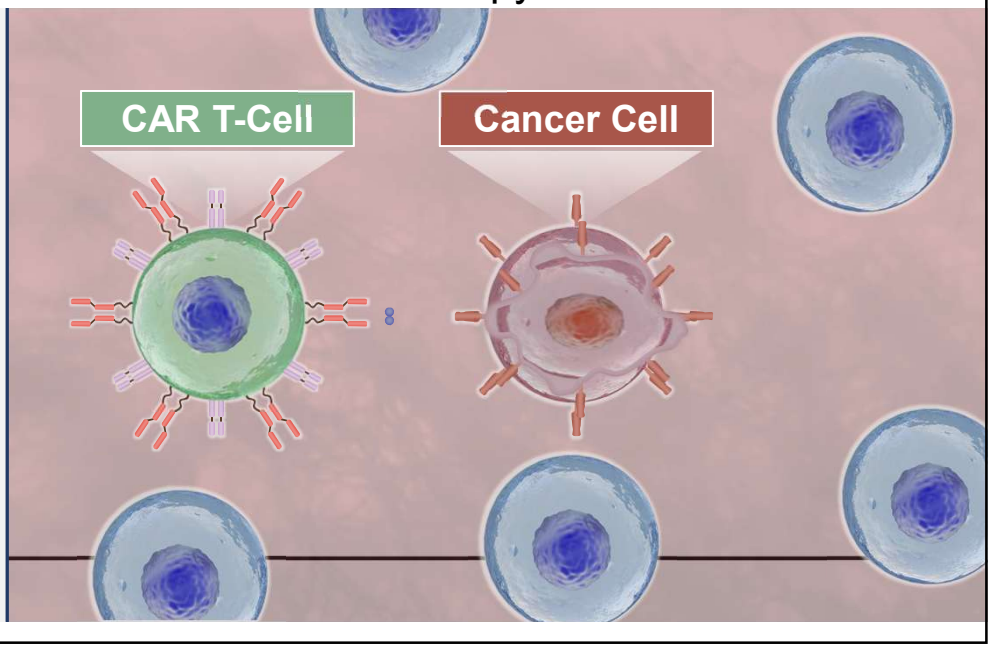


12

CAR T-cell Therapy

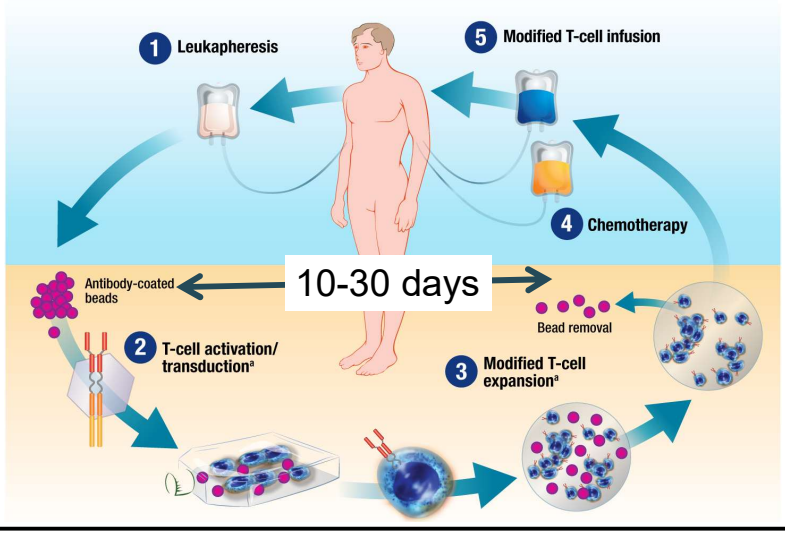
Expansion & Persistence





13

Patient's Journey



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Timeline varies by product and manufacturer

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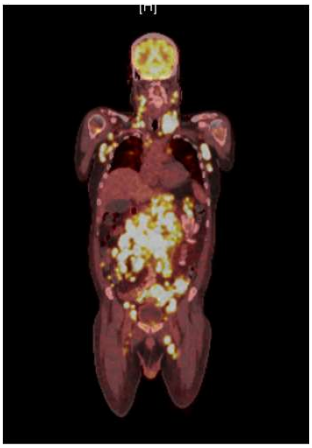
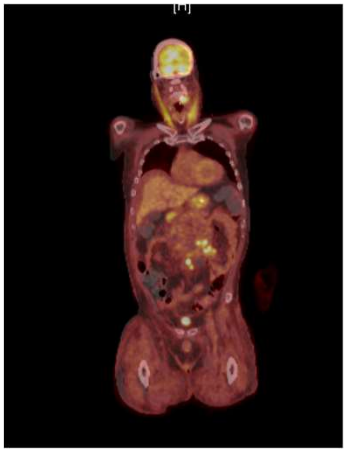
Dramatic Efficacy of CAR T Cells

BEFORE CAR T



Day 28



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CAR T Cells – A Touch of History

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

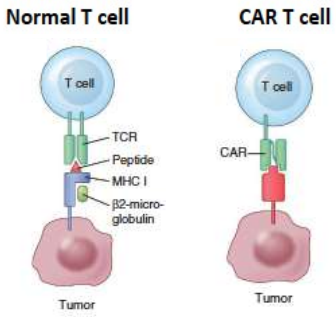
Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Vol. 149, No. 3, 1987 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
December 31, 1987 Pages 960-968

EXPRESSION OF CHIMERIC RECEPTOR COMPOSED OF IMMUNOGLOBULIN-DERIVED V REGIONS AND T-CELL RECEPTOR-DERIVED C REGIONS

Yoshihisa Kuwana[1], Yoshihiro Asakura[1], Naoko Utsumomiya[2], Mamoru Nakanishi[2], Yohji Arata[3], Seiga Itoh[3], Fumihiko Nagase[4] and Yoshikazu Kurosawa[1]*

This approach can be exploited, for example, to direct cytotoxic T lymphocytes to kill tumor or virally infected cells.



Hinrichs et al. Nat Biotech 2013

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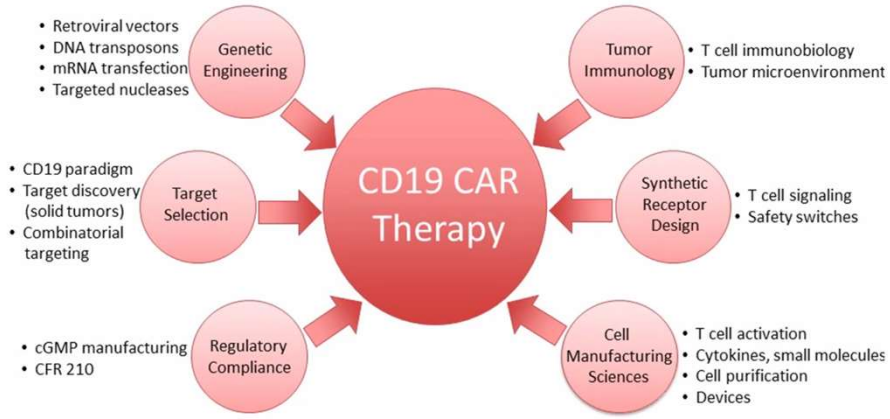
Assembling CARs for T Cell Therapy



Rivière & Sadelain Mol Ther 2017

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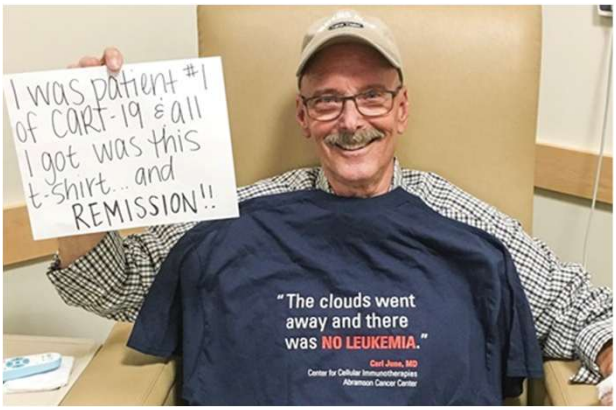
CD19 CAR T Initial Success in CLL

August, 2010

October, 2017



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CD19 CAR T Initial Success

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

NEJM.ORG AUGUST 25, 2011

Decade-long leukaemia remissions with persistence of CD4$^+$ CAR T cells

https://doi.org/10.1038/s41586-021-04390-6
Received: 7 May 2021
Accepted: 29 December 2021
Published online: 02 February 2022
Check for updates

J. Joseph Melenhorst[1,2,3,4,5,16], Gregory M. Chen[6,16], Meng Wang[1,2,3,14], David L. Porter[3,7,15], Changya Chen[8,9], McKensie A. Collins[1,2,3,10], Peng Gao[8,9], Shovik Bandyopadhyay[10], Hongxing Sun[1,2,3], Ziran Zhao[1,2,3], Stefan Lundh[1,2,3], Iulian Pruteanu-Malinici[11], Christopher L. Nobles[12], Sayantan Maji[1,2,3], Noelle V. Frey[3], Saar I. Gill[3], Lifeng Tian[13], Irina Kulikovskaya[1,2,3], Minnal Gupta[1,2,3], David E. Ambrose[1,2,3], Megan M. Davis[1,2,3], Joseph A. Fraietta[1,2,3,12], Jennifer L. Brogdon[11], Regina M. Young[1,2,3], Anne Chew[1,2,3], Bruce L. Levine[1,2,3], Donald L. Siegel[1,2,3], Cécile Alanio[4,5,14], E. John Wherry[4,5,14], Frederic D. Bushman[10], Simon F. Lacey[1,2,3], Kai Tan[2,4,5,9,10,16] & Carl H. June[1,2,3,4,5,16]

Nature | Published online: 02 February 2022

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First Success in ALL – Emily Whitehead

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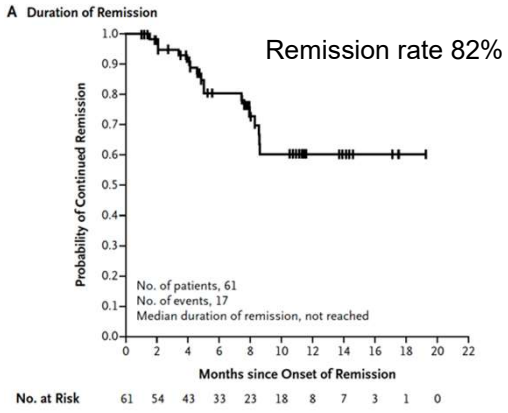
First Success in Acute Lymphoblastic Leukemia (ALL) in Children

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.



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Seven Approved CAR-T Cell Therapies in Lymphoma, Leukemia and Myeloma

AUCATZYL®
obecabtagene autoleucel
suspension for IV infusion

22

Approved Cellular Therapies in Blood Cancers

Target	Indication	Line	
CD19	Large B-cell Lymphoma	**2nd**	**Yescarta - Axicabtagene ciloleucel** **Breyanzi - Lisocabtagene maraleucel** Kymriah – Tisagenlecleucel (3rd line only)
	B-cell Acute Lymphoblastic Leukemia	3rd / Refr. 2nd 2nd	Kymriah - (Age≤25) Tecartus - Brexucabtagene autoleucel Aucatzyl – Obecabtagene autoleucel
	Follicular Lymphoma	3rd	Yescarta, Breyanzi, Kymriah
	Mantle Cell Lymphoma	2nd	Tecartus, Breyanzi (3rd line only)
	Chronic Lymphocytic Leukemia	3rd	Breyanzi
BCMA	Myeloma	**3rd** **2nd**	**Abecma - Idecabtagene vicleucel** **Carvykti - Ciltacabtagene autoleucel**

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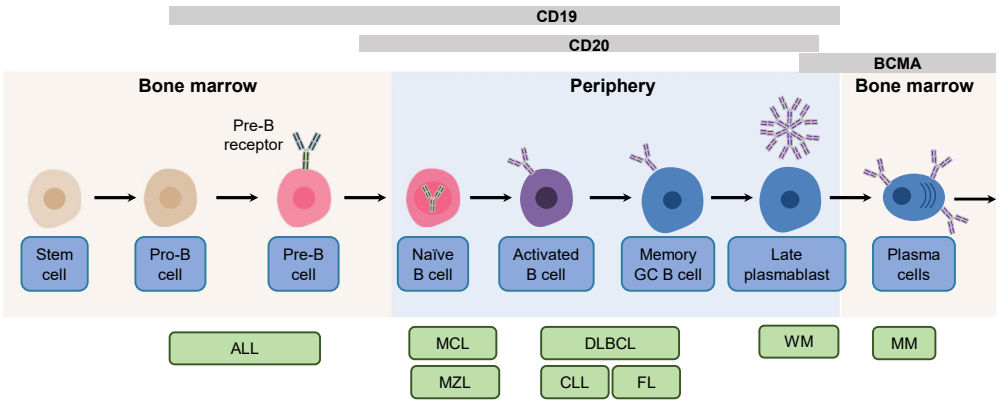
How to pick a target for CAR T cells?



Blanc CCR 2011

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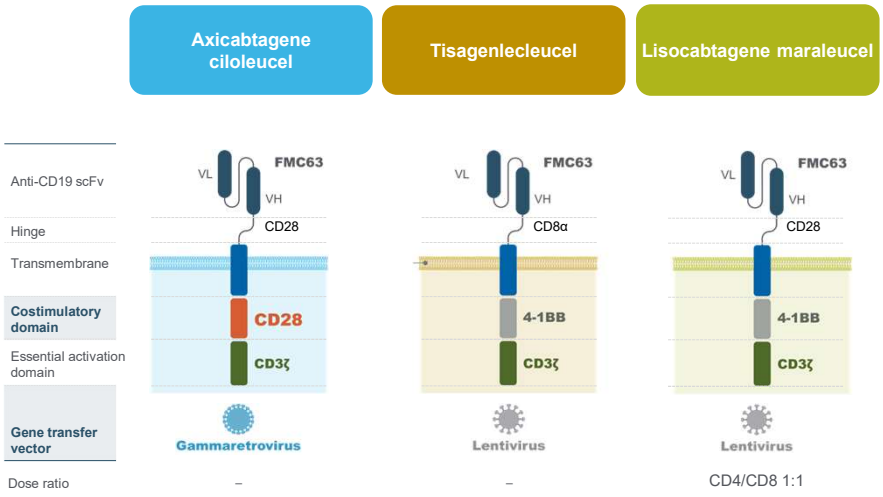
CD19-Targeting CAR T Cells are not all the same



van der Stegen SJ, et al. Nat Rev Drug Discov 2015
Scarfò I & Maus M. J Immunother Cancer 2017

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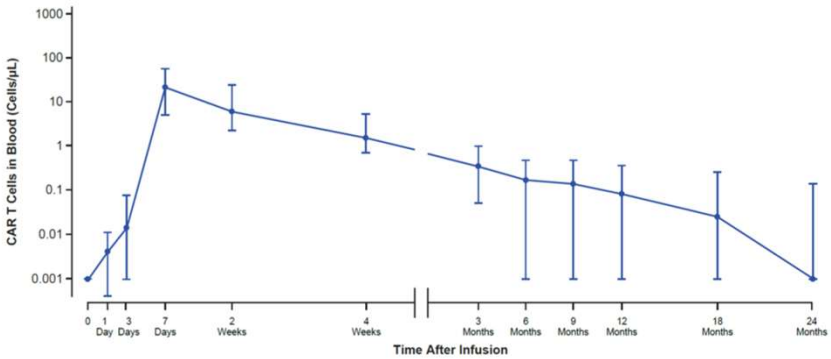
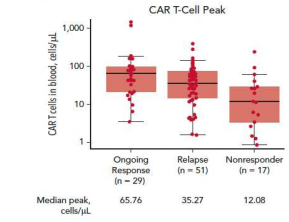
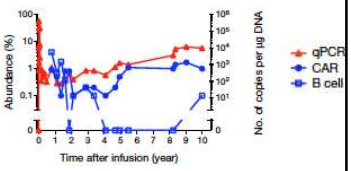
CAR T Expansion is Rapid and Subsides Over Time







Locke NEJM 2022
Neelapu Blood 2023
Melenhorst Nature 2022

Columbia University Medical Center

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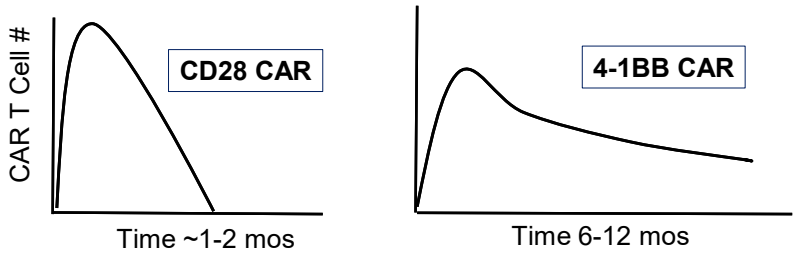
CAR Structure Affects Expansion and Persistence



These differences also determine the side effect profile:

CRS - early and rapid vs. delayed and gradual
Loss of healthy B cells – transient vs. long-standing (possibly indefinite)

Melenhorst Nature 2022

Columbia University Medical Center

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High Success Rate in Manufacturing Personalized Cell Therapies

ZUMA-1	
Manufacturing success rate	99%
Turnaround time from leukapheresis to infusion	Median 17 days

JULIET	
Manufacturing success rate	92%
Turnaround time from enrolment to infusion	Median 54 days

TRANSCEND-NHL-001	
Manufacturing success rate	92%[a]
Turnaround time from leukapheresis to infusion	Median 37 days

[a] Percentage excluded patients for whom product could not be manufactured (n=2) and those who received non-conforming product (n=25)

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What does the clinical trial data show?

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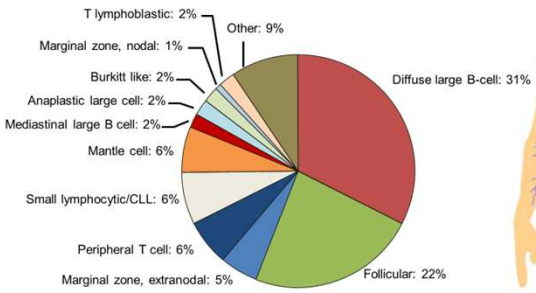
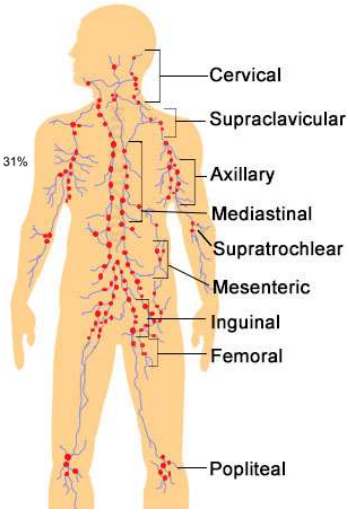
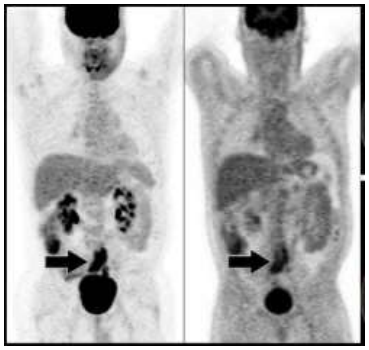
Success in B-cell Lymphoma







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Neelapu NEJM 2017
Locke Lancet Oncology 2019
Schuster Lancet Oncology 2021
Abramson Lancet 2020

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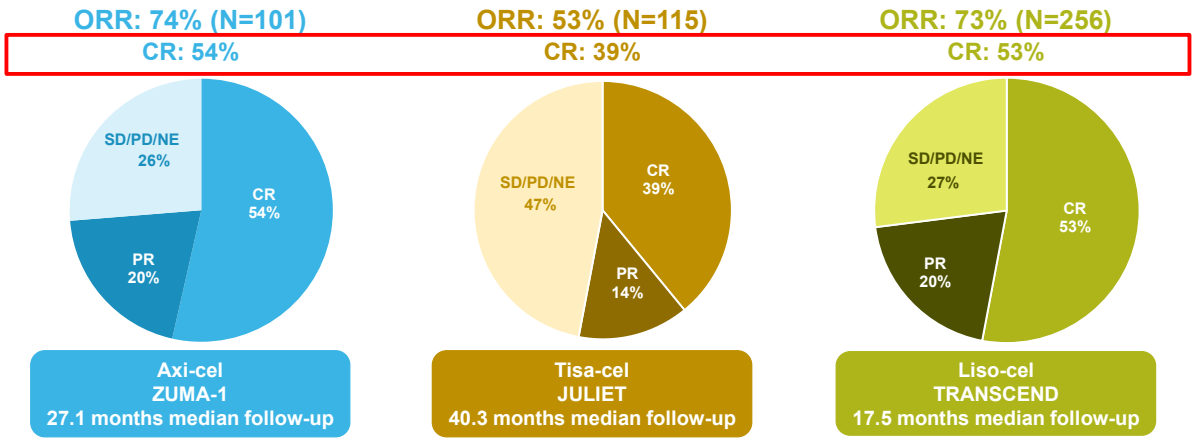
Pivotal CAR T Cell Trials in ≥3rd line Aggressive Lymphomas



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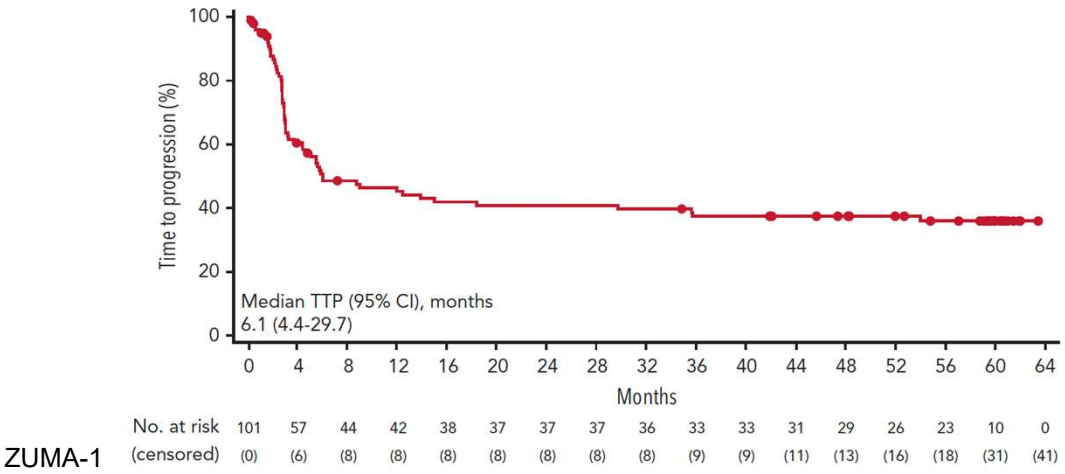
Neelapu NEJM 2017
Locke Lancet Oncology 2019
Schuster Lancet Oncology 2021
Abramson Lancet 2020

31

Two-thirds of complete responses are highly durable



ZUMA-1 Trial

Neelapu Blood 2023

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CD19 CAR T in Aggressive Lymphoma Moving to 2nd Line

Three randomised trials in transplant-eligible patients:

- ZUMA-7: Axicabtagene ciloleucel vs transplant
- TRANSFORM: Lisocabtagene maraleucel vs transplant
- BELINDA: Tisagenlecleucel vs transplant

Two single-arm trials in transplant-ineligible patients:

- ALYCANTE: Axicabtagene ciloleucel
- PILOT: Lisocabtagene maraleucel

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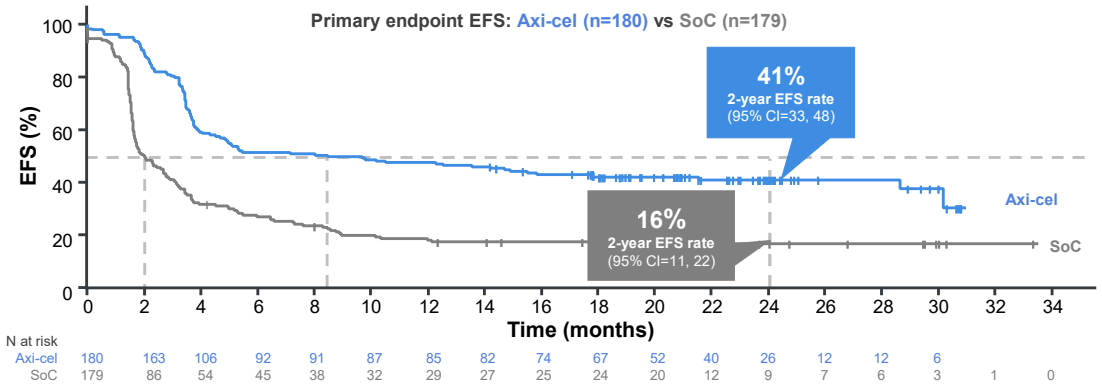
CAR T Cells Win Against Autologous Stem-cell Transplant

ZUMA-7

Phase 3, randomized, multicentre trial of axi-cel vs SoC (ASCT) as 2L treatment in patients with R/R LBCL (N=359)



Locke NEJM 2022

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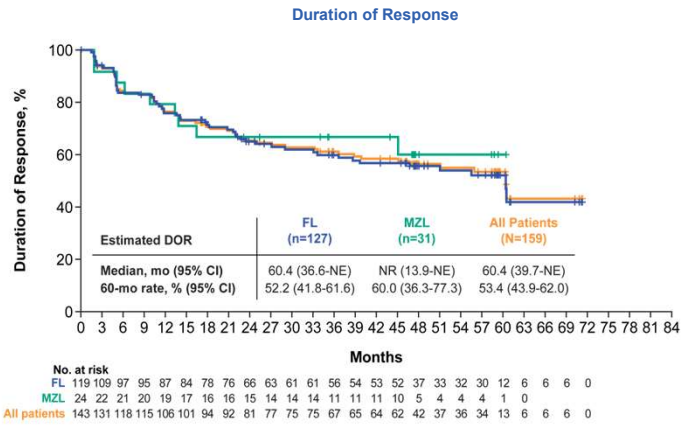
CAR T in Follicular Lymphoma (ZUMA-5)

Efficacy	
Overall Response	90%
Complete Remission	75%

Age range 34-79 (Median 60)
Prior lines of therapy 1-10 (Median 3)

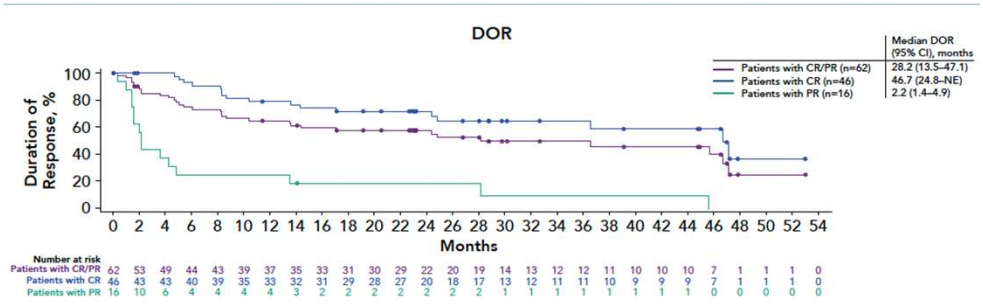


Neelapu et al. ASH 2024

CAR T in Mantle-cell Lymphoma (ZUMA-2)

Efficacy	
Overall Response	93%
Complete Remission	67%

Age range 38-79 (Median 65)
Prior lines of therapy 1-5 (Median 3)

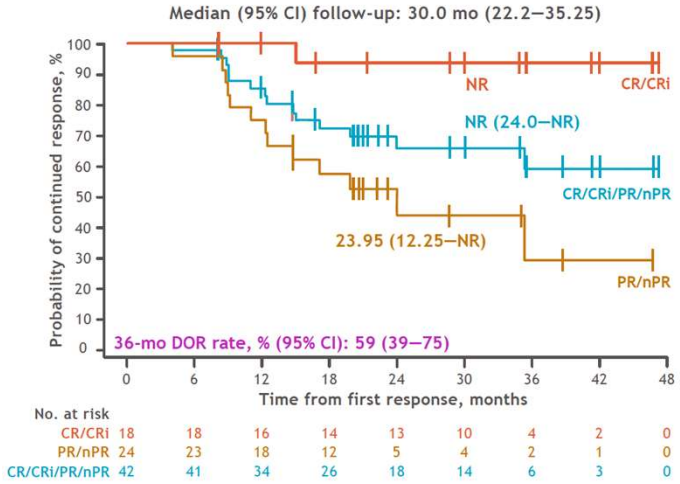


Wang et al. ASCO 2022

CAR T in CLL – TRANSCEND-CLL-004 Trial

Efficacy	
Overall Response	44%
Undetectable CLL (marrow)	60%
Undetectable CLL (blood)	64%

Age range 49-82 (Median 65)
Prior lines of therapy 2-14 (Median 5)
83% had high risk CLL



Siddiqi et al. ASCO 2023

Columbia University Medical Center

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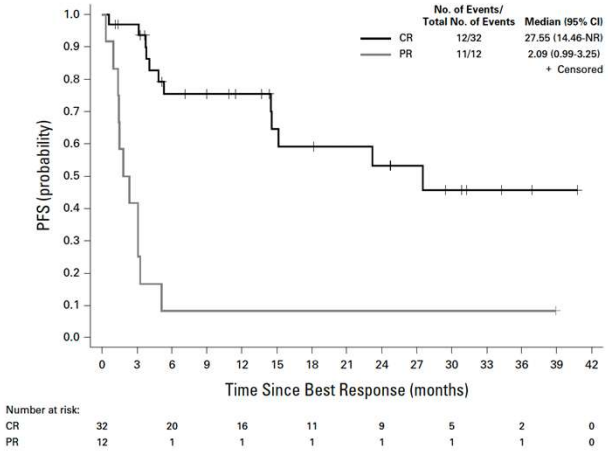
CAR T in Richter's Transformation

Efficacy	
Overall Response	63%
Complete Remission	46%

Age range 27-80 (Median 64)
Prior lines of therapy for CLL 0-10 (Median 2)
Prior lines of therapy for Richter 0-7 (Median 2)



Kittai JCO 2024

Columbia University Medical Center

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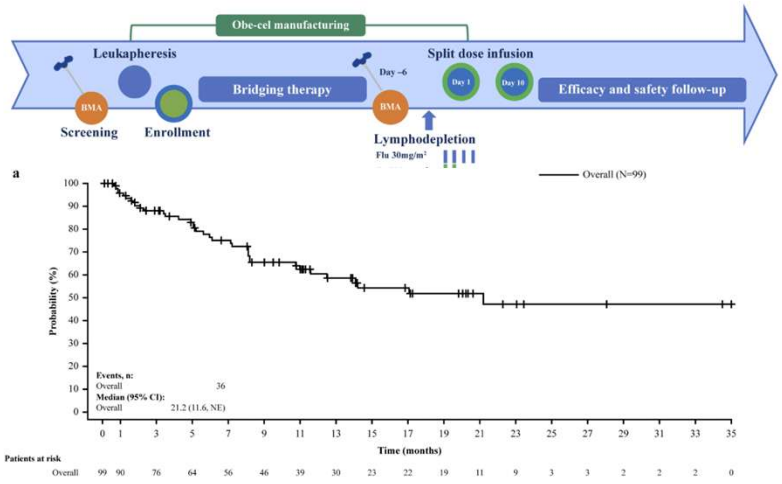
CAR T in Adult ALL – Felix Trial

Efficacy	
Complete Remission	78%

Age range 20-81 (Median 47)
Prior lines of therapy 1-6 (Median 2)
44% had a prior bone marrow transplant



Roddie et al. NEJM 2024

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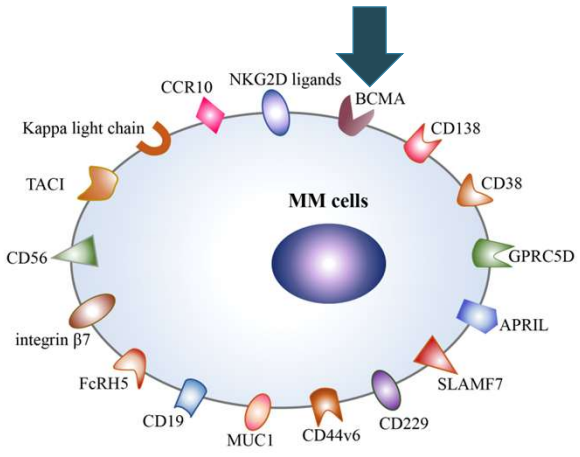
CAR T Cells in Myeloma – Potential Targets



Zhang et al. Front Immunol 2023

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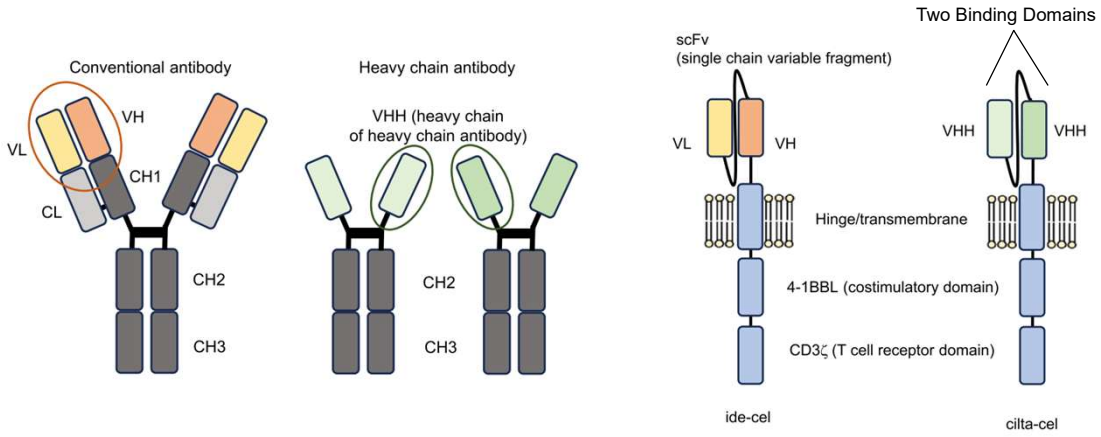
BCMA Targeting CAR T Cells are not the same



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Nakashima & Kagoya Int J Hematol 2024

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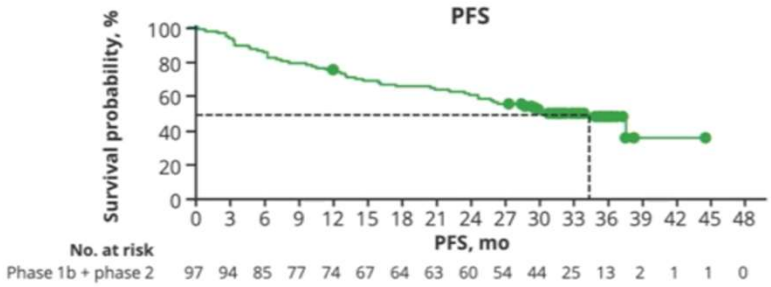
BCMA CAR T in Heavily Treated Patients

CARTITUDE-1 Trial

Efficacy	
Overall Response	98%
Undetectable Minimal Residual Disease	93%

Age range 43-78 (Median 61)
Prior lines of therapy 3-18 (Median 6)



Lin et al. ASCO 2023

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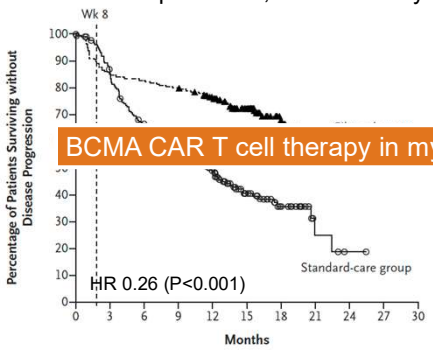
BCMA CAR T in Myeloma Moving to Earlier Lines

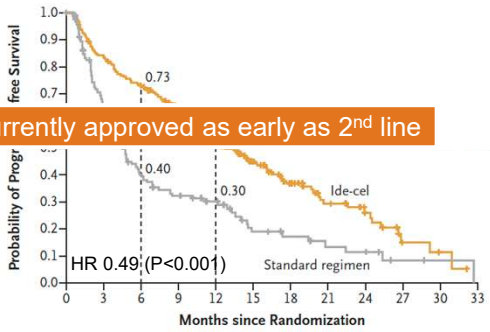
CARTITUDE-4: Ciltacabtagene autoleucel vs. physician's choice

Patients with 1-3 prior lines, Len refractory



karMMa-3: Idecabtagene vicleucel vs. physician's choice

Patients with 2-4 prior lines, triple exposed



BCMA CAR T cell therapy in myeloma is currently approved as early as 2nd line

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San Miguel NEJM 2023
Rodriguez-Otero NEJM 2023

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BCMA CAR T in Myeloma Moving to 1st line?

Newly diagnosed patients:

- CARTITUDE-5: Cilta-cel vs. maintenance in transplant ineligible patients – **completed enrolment (n=743). Primary results 2026.**
- CARTITUDE-6: Cilta-cel vs. transplant in transplant eligible patients – **ongoing (n=750). Primary results 2033.**

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CAR T Cell Therapy: Side Effects

Cytokine Release Syndrome (CRS)

- Common (40-95%) ; requires careful monitoring
- Management Approach – observation & supportive care. Medications if needed.

Neurologic Symptoms - Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- Common (10-65%); requires monitoring and sometimes treatment

Infections

- Effect on blood counts - Reversible but sometimes prolonged
- B-cell depletion leading to low antibody production and interfering with vaccines
- T-cell decrease due to lymphodepleting chemotherapy (typically Flu/Cy)

Second Cancers

- Rare

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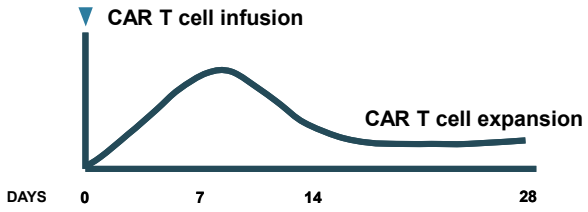
Typical Onset and Resolution of CRS and Neurologic Symptoms



CRS

Neurologic events

Median time to CRS onset:

LBCL	**Myeloma**
Tisa-cel – 3 days	Ide-cel – 1 day
Axi-cel – 2 days	Cilta-cel – 7 days
Liso-cel – 5 days	

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Case - John, A 52-Year-Old Man with Diffuse Large B-cell Lymphoma (DLBCL)

- Presented in December 2022 with epigastric pain and fatigue.
- Imaging showed enlarged lymph nodes, 18cm mass in the abdomen and bone marrow involvement.
- Biopsy - DLBCL
- Received R-CHOP (combination chemo-immunotherapy) and did not go into remission.
- Cells collected for CD19 CAR-T cells.
- CAR-T cells infused on June 6th, 2023 after standard lymphodepleting chemotherapy.

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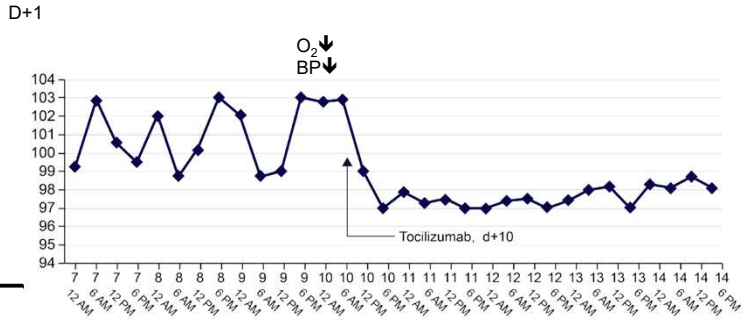
Case – Post-infusion Course

- CAR-T infusion well-tolerated.
- On day +1 new onset of high fevers. Infectious workup negative and antibiotics started. Around-the-clock acetaminophen started.
- On day +4 fevers ongoing. Oxygen level drops to 89% and BP 90/50 without good response to fluids.



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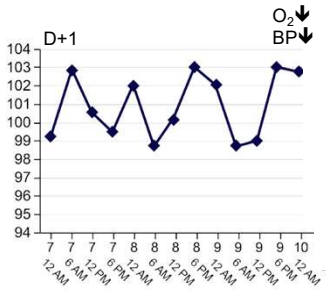
Case – Post-infusion Course

- Tocilizumab (antibody against IL-6) is administered for grade 2 **Cytokine Release Syndrome (CRS)**.
- Resolution of symptoms within several hours.



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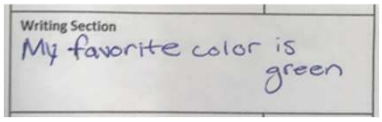
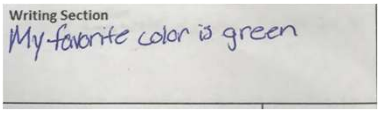
Case – Post-infusion Course

- On Day+5 the patient appears sleepy.
- Slight tremor on exam.
- On Day+6 unable to name certain objects, operate smartphone, write a sentence.
- On exam no neurologic signs, MRI brain and EEG without findings.
- Steroids started for **Immune Effector Cell-Associated Neurotoxicity (ICANS)**.
- On Day+7 neurological exam back to baseline.
- Discharged on D+12.

Day 0

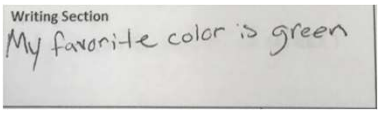


Day +5



Day +6

Day +7



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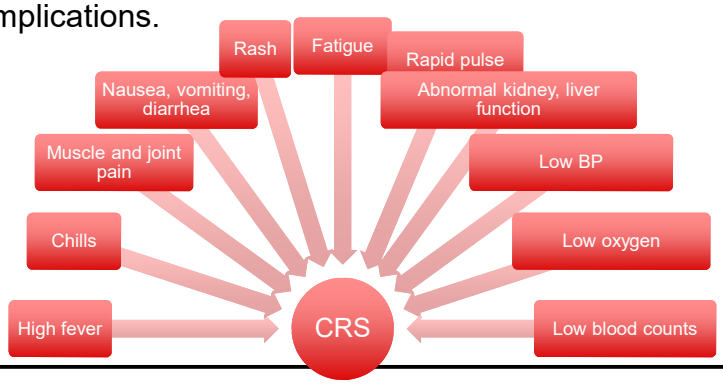
What is Cytokine Release Syndrome?

- A systemic inflammatory response triggered by the massive release of cytokines following immunotherapy.
- CRS has a spectrum of severity, ranging from mild flu-like symptoms to severe complications.



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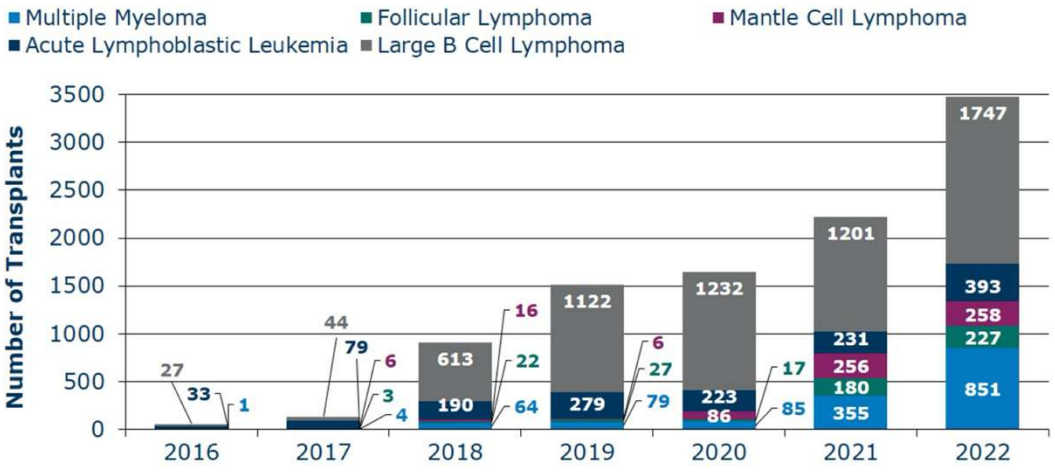
Revolutionary, but... Only A Fraction of Eligible Patients Are Treated



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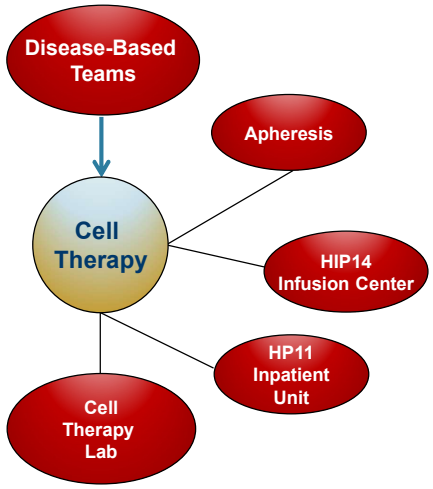
Challenges – Logistics and Resources



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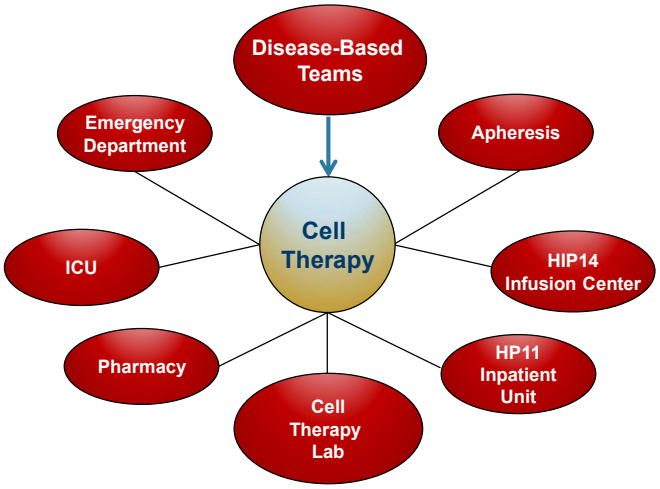
Challenges – Logistics and Resources



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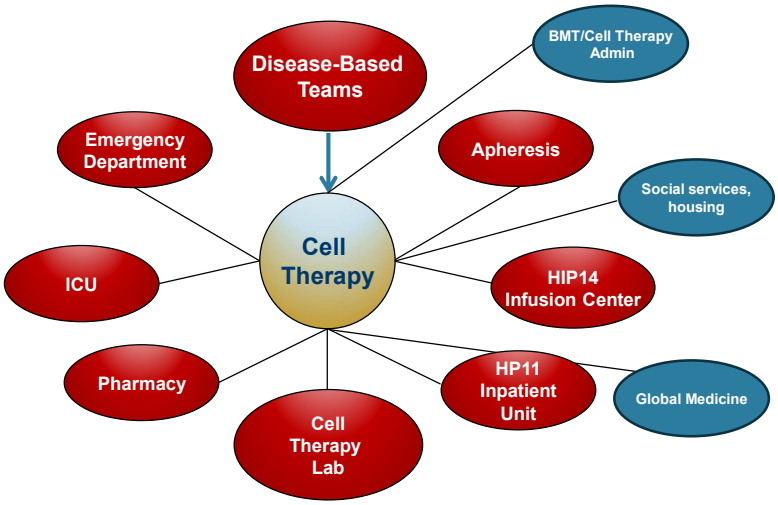
Challenges – Logistics and Resources



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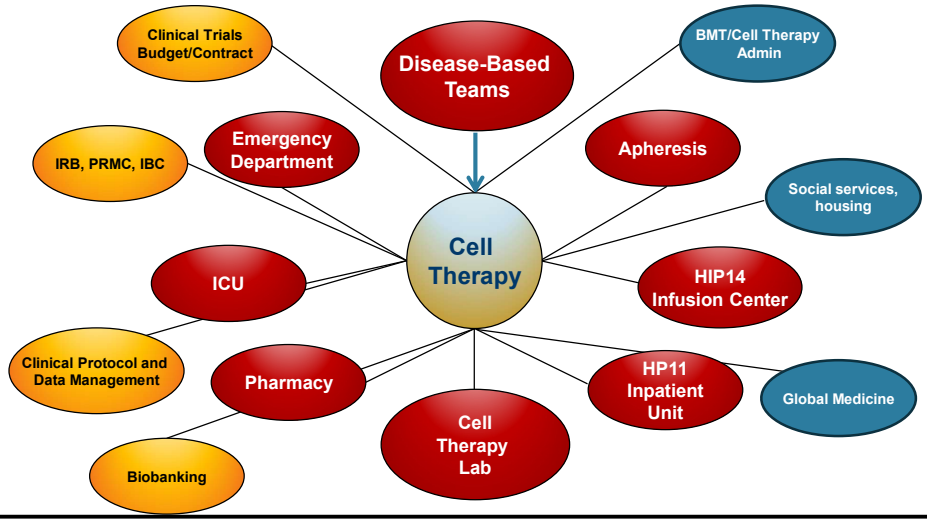
Challenges – Logistics and Resources



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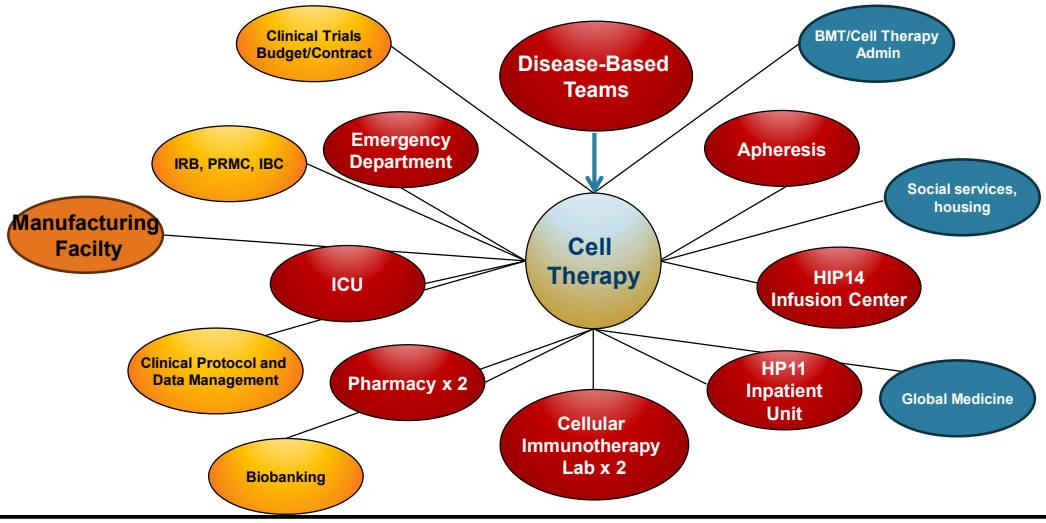
Challenges – Logistics and Resources



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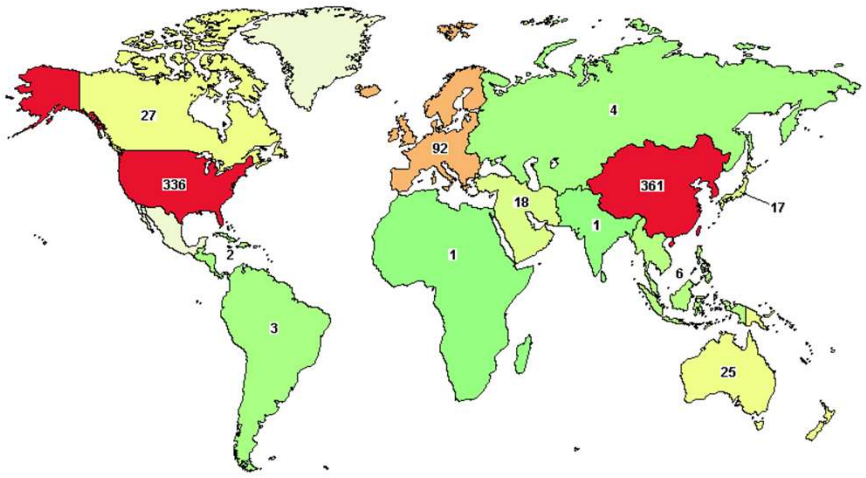
The Future - Experimental CAR T-cell Trials



Clinicaltrials.gov March 28, 2022

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Is CAR T cell therapy the right choice for me?

- Not all CAR T are the same
- Different diseases have different efficacy and side effect profile
- Age, past medical history and “performance status” don’t have hard cutoffs.
  - Patients up to age 91 were treated with CAR T.
- Alternative options should always be discussed
  - Sequencing therapies that use the same target (CD19, BCMA) may not be ideal. Use the most potent therapy first!
- Smart use of bridging therapy may improve efficacy and reduce side effects

Thank you!

ran.reshef@columbia.edu

ASK A QUESTION

CONSIDERING CAR T-CELL THERAPY:
A HOPEFUL TREATMENT FOR BLOOD CANCERS

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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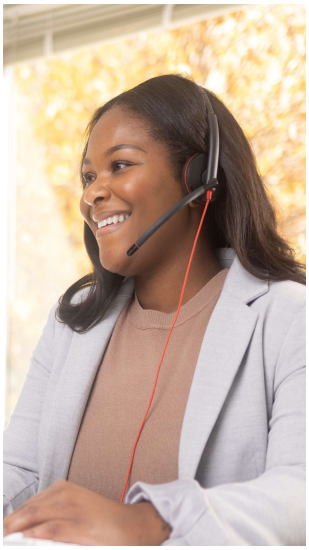
LLS EDUCATION & SUPPORT RESOURCES

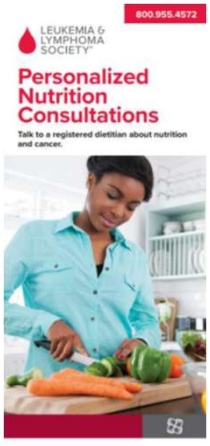


HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:
www.LLS.org/InformationSpecialists

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation



NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLSNutrition.org

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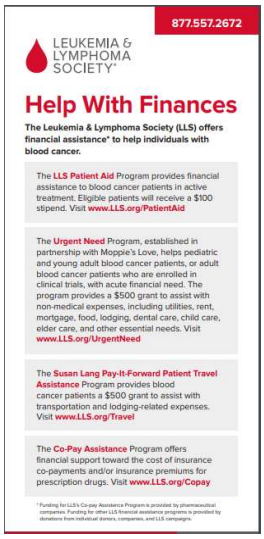
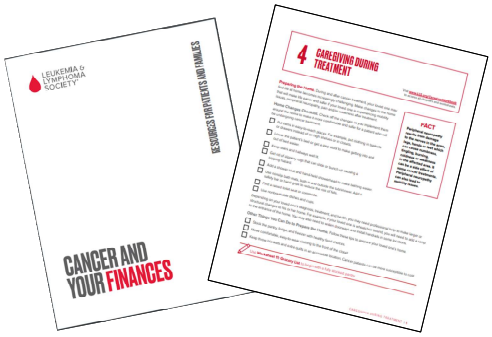


The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**



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

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