ADVANCES IN CAR T-CELL THERAPY

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DISCLOSURES

Advances in CAR T-cell Therapy

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

BEATING CANCER IS IN OUR BLOOD.

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Objectives

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

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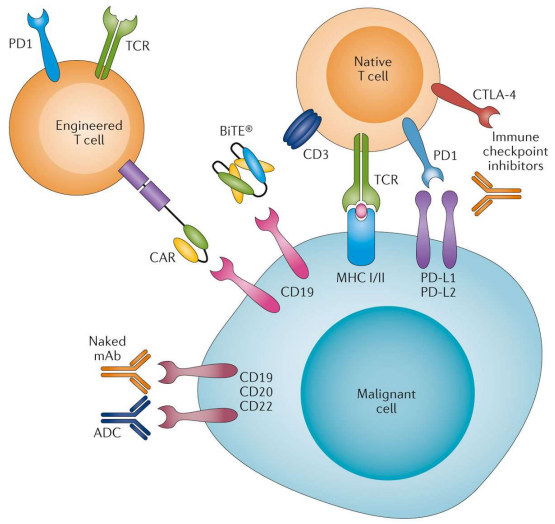
Multiple Mechanisms of Modulating Immune System to Treat Cancer

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



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

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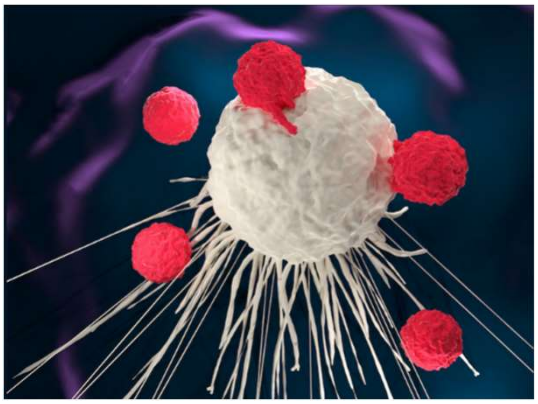
What is CAR T-cell therapy?

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



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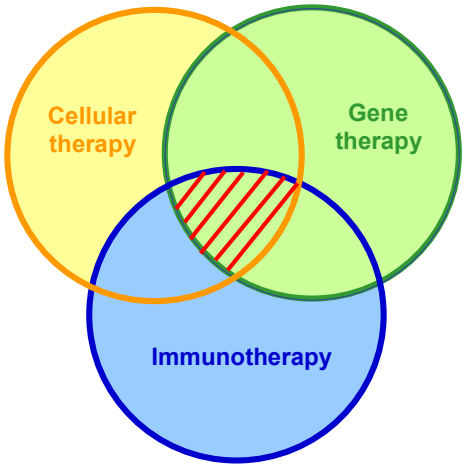
CAR T-Cells are at The Intersection of Three Innovative Technologies



Cellular therapy
Using the patient's own T- cells as therapy

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

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

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

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

Lisa Rosenbaum, M.D.

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

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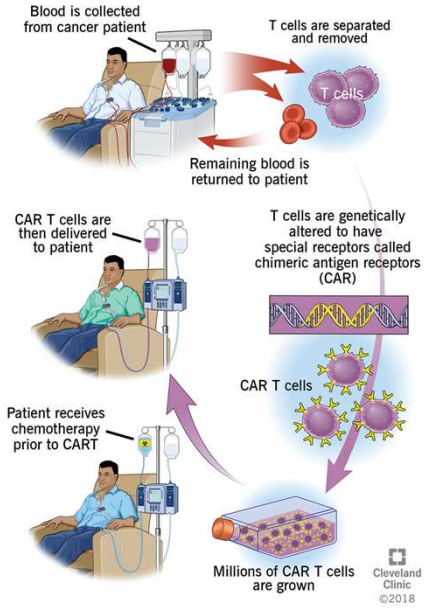
From Manufacturing of CAR T-Cells to Infusion



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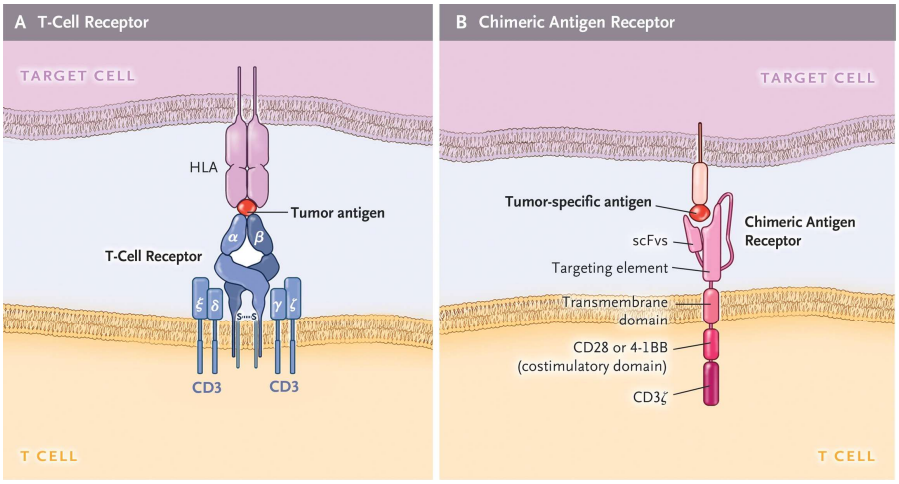
Structure of T-Cell Receptors and CAR Modified T-cells



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

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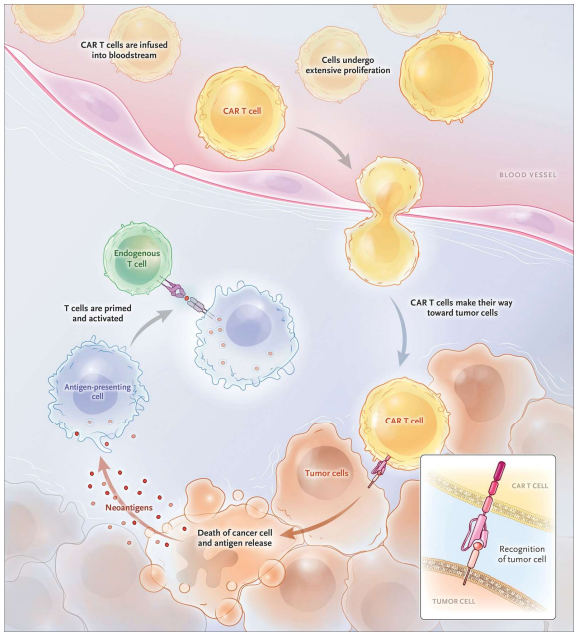
CAR T Cells Traffic to Tumor and Proliferate Extensively after Infusion



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

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Ideal CAR Target

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

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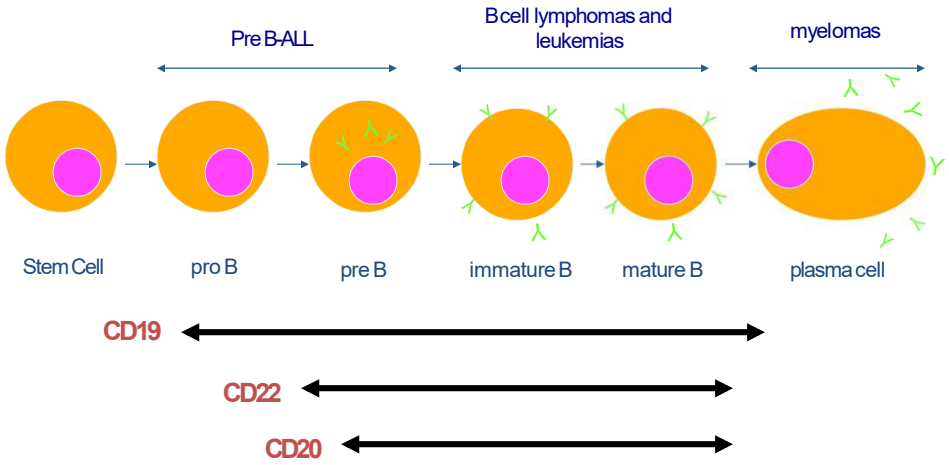
CD19 as a Target of B-Cell Malignancies



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

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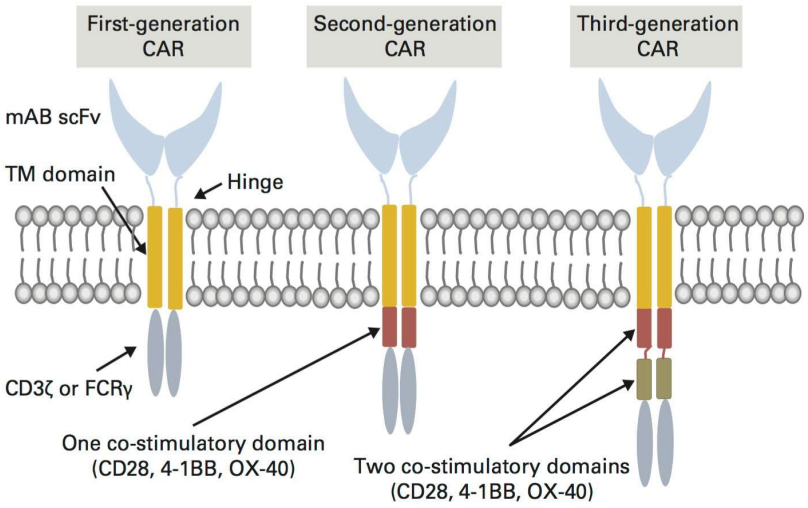
Evolution in CAR Design



Park Jet al. *JClin Oncol.* 2015;33(6):651-653.

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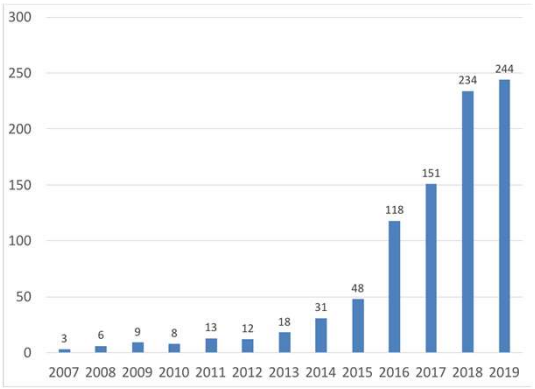
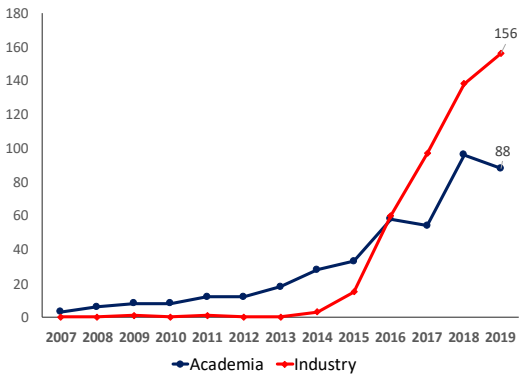
Total Registered CAR-T Trials Worldwide





Industry is Taking Over CAR T-Cell Development

Data source: CellTrials.org

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Selected Approved or Late-Stage CAR T Therapies

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

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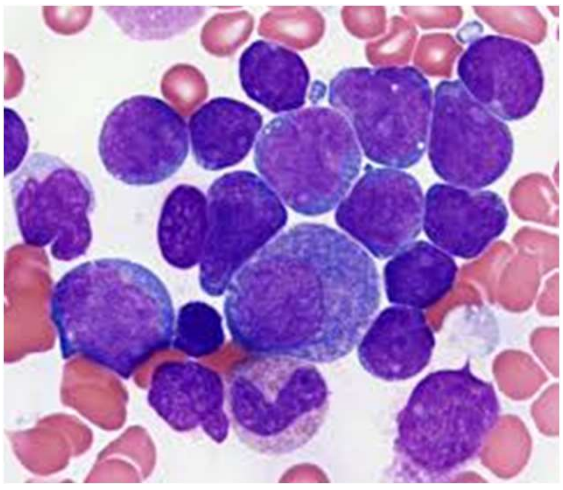
CAR T- Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)



Atlas of Genetics and Cytogenetics in Oncology and Hematology

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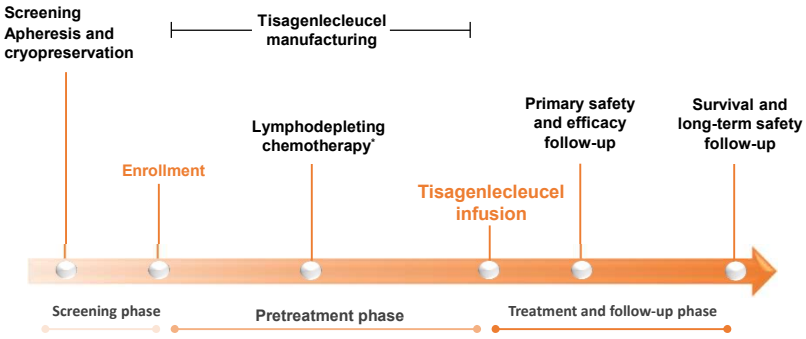
Pediatric Relapsed/Refractory (R/R) B-ALL: ELIANA Study Design

- ELIANA (NCT02435849) is a phase 2, open-label, single-arm study in pediatric and young adult patients with r/r B-cell ALL[1-2]



B-cell ALL, B cell acute lymphoblastic leukemia.

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

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

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ELIANA Study in B-ALL

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

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

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ELIANA: Patient Demographics and Baseline Clinical Characteristics

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

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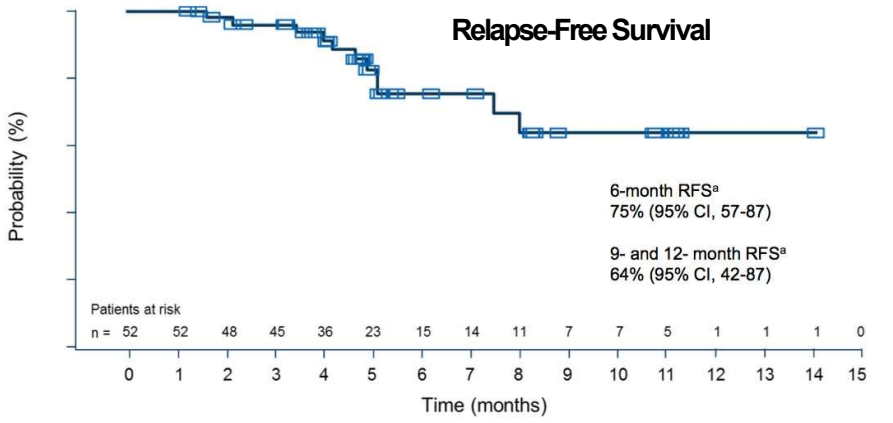
Duration of Remission: ELIANA



Patients (N = 52) Number of events (n = 11) Median follow-up, 4.8 mo **Median DOR, not reached**

Buechner J et al. *EHA 2017*, Abstract S476

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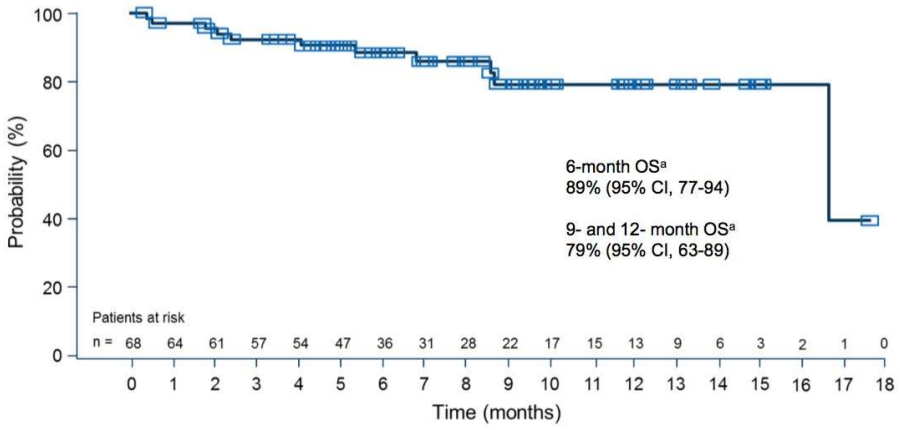
Overall Survival: ELIANA



Patients (N = 68)

Number of events (n = 11)

Median follow-up, 6.2 mo (max, 17.6 mo)
Median OS, 16.6 mo

Buechner J et al. *EHA 2017*, AbstractS476

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ELIANA: Overall safety of Tisagenlecleucel

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

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

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

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

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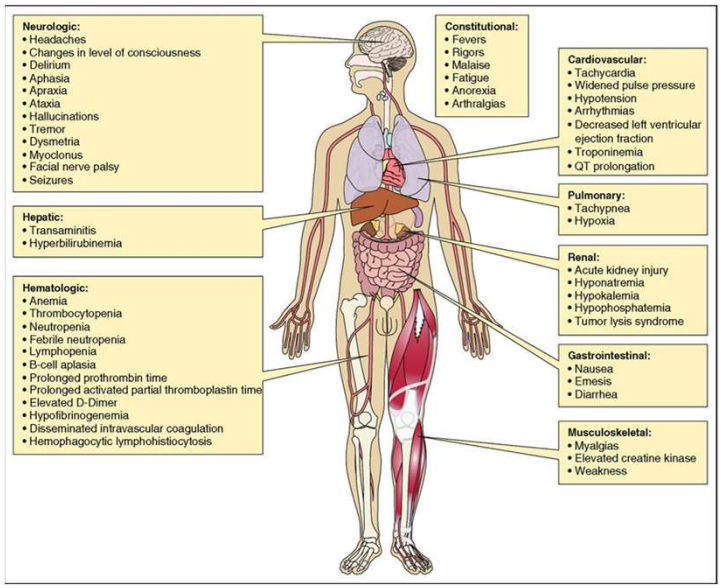
CAR-T 19 Associated Toxicities



Professional illustration by Patrick Lane, ScEYEnce Studios

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CAR-T 19 Associated Toxicities

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

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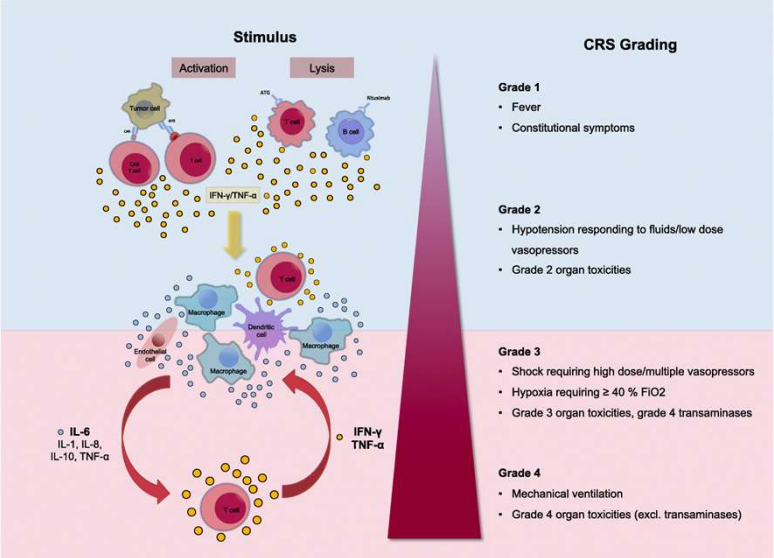
Mechanism of Cytokine Release Syndrome (CRS)



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

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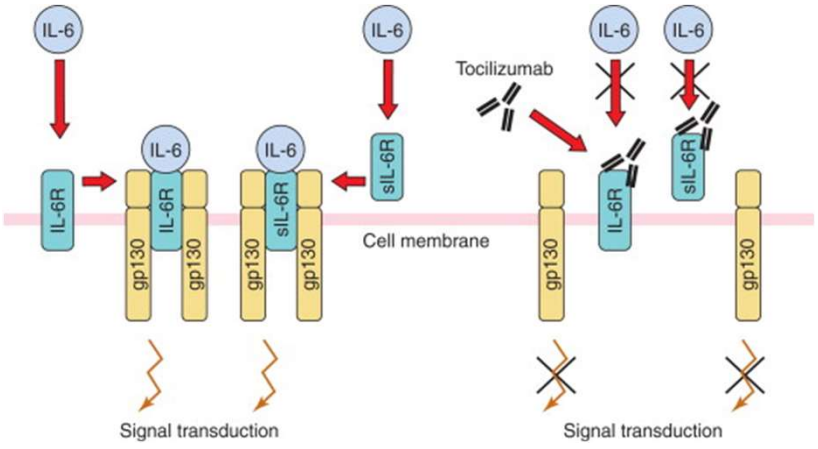
Inhibitory Action of Tocilizumab in IL-6 Signaling



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

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Neurologic Toxicity with CAR T-Cells

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

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

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Mechanism of Neurotoxicity

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

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

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Tools for Grading Neurotoxicity

Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [12]	ICE
• **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points	• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points	• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point	• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point	• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
	• **Attention:** ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

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

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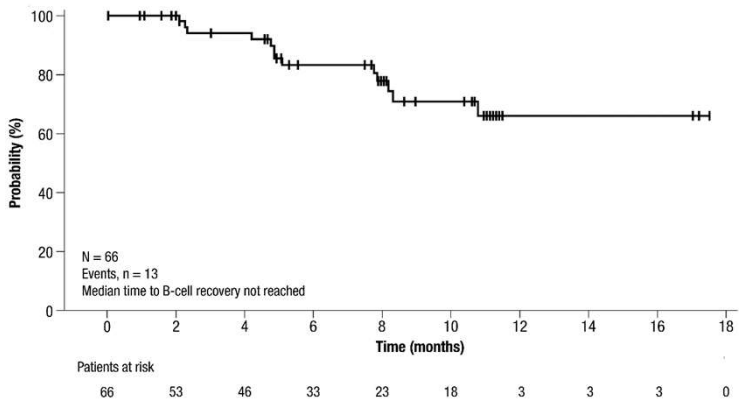
B-Cell Aplasia Following CAR-T



- All patients with a response to treatment had B-cell aplasia.
- The median time to B-cell recovery was not reached.
- The probability of maintenance of B-cell aplasia at 6 months after infusion was 83% (95% CI, 69 to 91).

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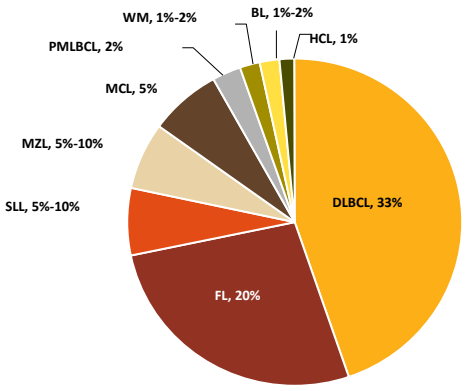
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

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

Relative Incidence of the Most Prevalent NHL Subtypes in the United States[1]



T-cell lymphomas constitute < 15% of all NHL cases.

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Treatment of Aggressive DLBCL

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

   ***These regimens may induce remission but response is generally short-lived due to lymphoma stem cells that are resistant to "standard doses" of chemotherapy**
3. Autologous stem cell transplant (ASCT)

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Autologous Stem Cell Transplant (ASCT)

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

  -This helps prevent toxicity of the "high dose chemotherapy."

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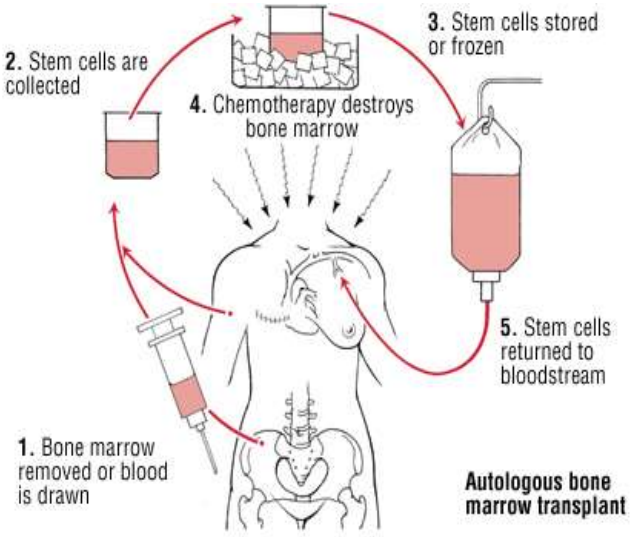
Autologous Stem Cell Transplant

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



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Treatment Challenges

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

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Three Large Multicenter CAR T Studies for DLBCL

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

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

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

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

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

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

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CART 19 Therapy Outcomes in R/R LBCL

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

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

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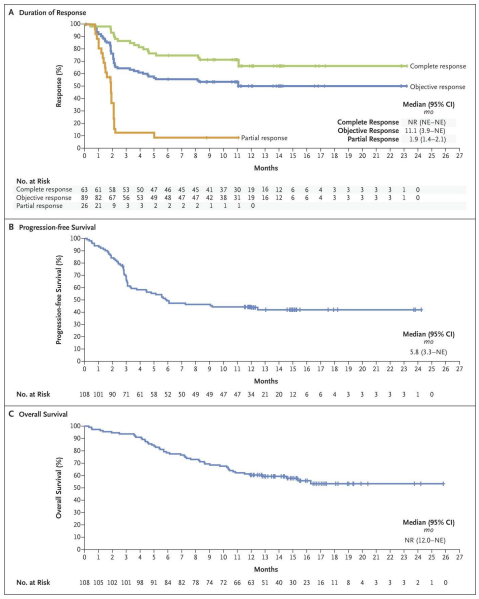
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory LBCL



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

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

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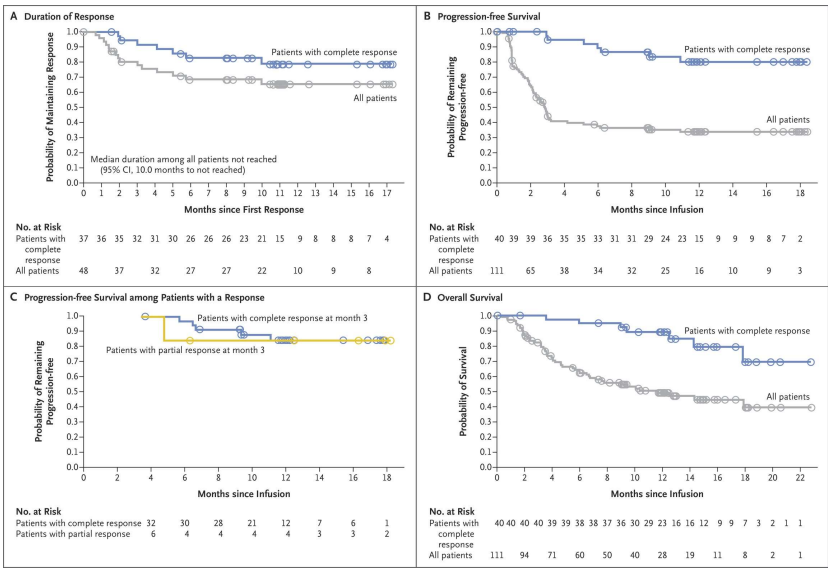
Tisagenlecleucel in Adult Relapsed or Refractory DLBCL



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

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

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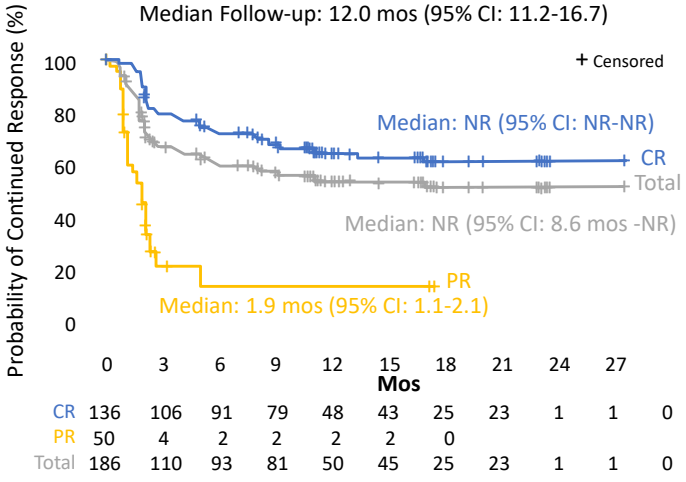
Lisocabtagene Maraleucel in Adult R/R LBCL

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

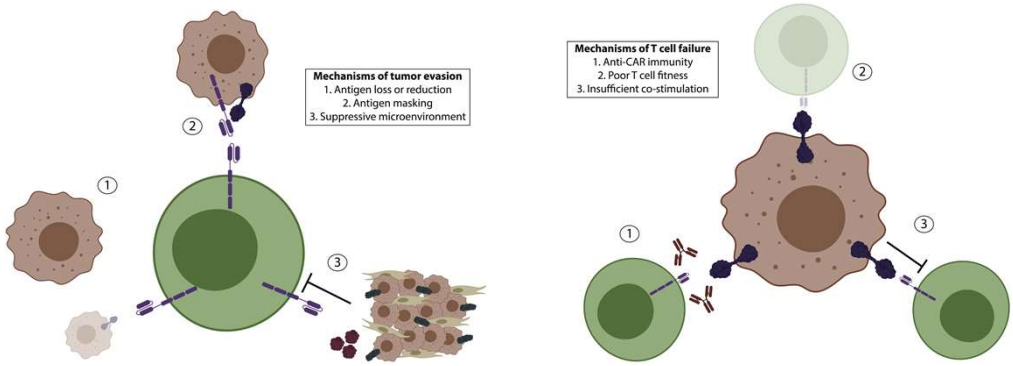


Abramson. ASH 2019. Abstr 241.

42

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

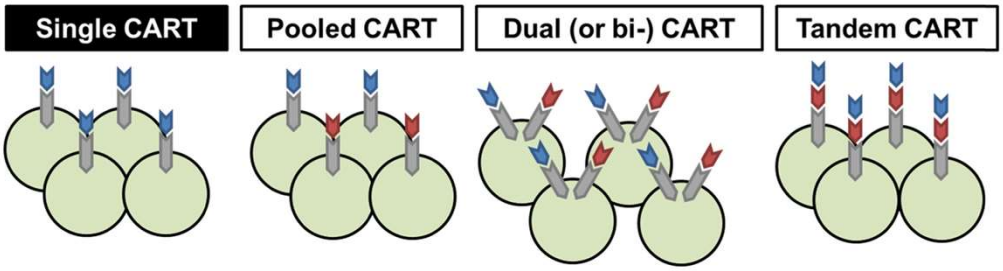
- Leukemia relapse after CAR T-cells could be classified into 2 distinct types:
  - Loss of the CD19 target antigen on the surface of leukemia cells
  - Loss of CD19 CAR T-cells in blood (short persistence)



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

43

Strategies to Avoid Antigen-Loss Relapses

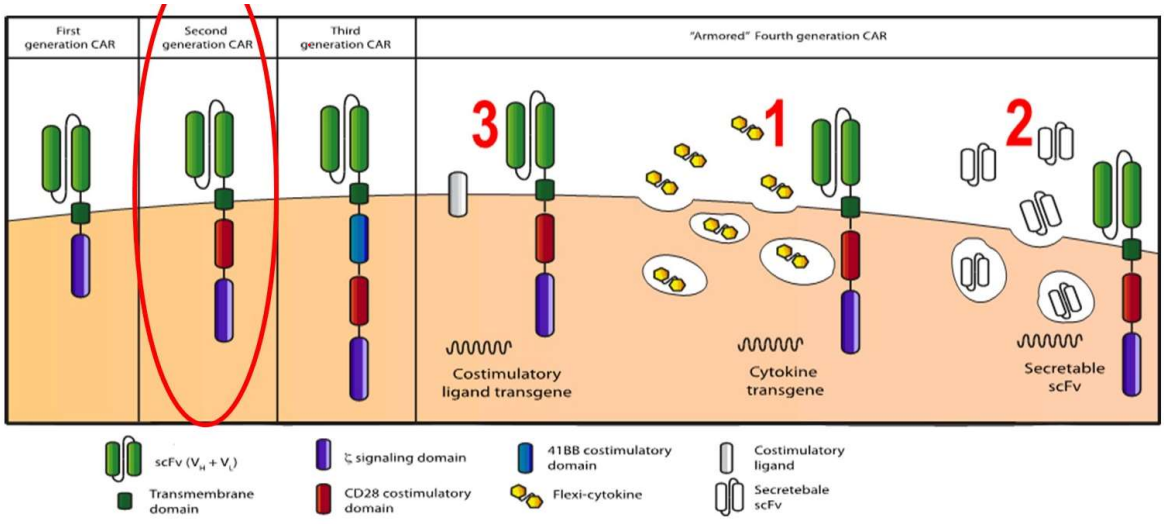


Single CART – CAR T cells of same specificity (i.e. CD19)
Pooled CART – 1:1 mixture of single–specificity CART: each cell remains able to recognize only one target (i.e. one with specificity for CD19, and one with specificity for CD22)
Dual (or bi-) CART – every T cell bears 2 distinct CAR structures able to recognize 2 different targets (i.e. one for CD19 and one for CD22)
Tandem CART – every T cell bears 1 CAR structure where 2 scFvs are built in series and are able to recognize 2 different targets

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

44

Evolution of CAR Design



Maria Lia Palomba ASCO 2019 Annual Meeting

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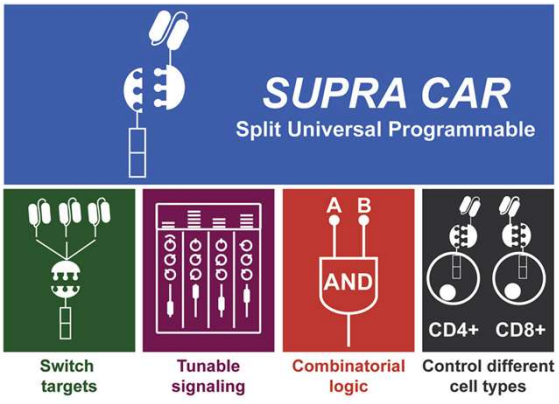

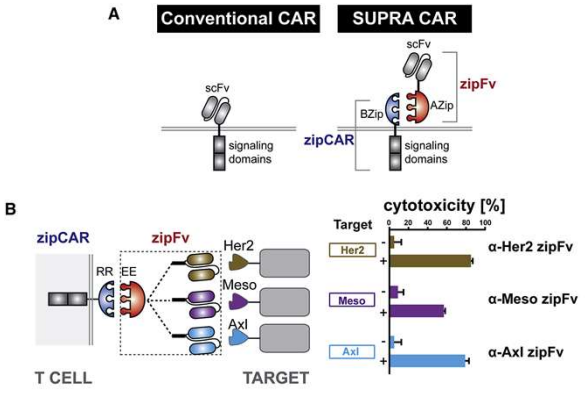

- Programmable system: universal receptor expressed on T cells and a tumor-targeting scFv adaptor molecule
- Targets multiple tumor antigens using different zipFvs
- SUPRA CARs can be finely regulated via multiple mechanisms to limit overactivation
- Variables manipulated: (1) the affinity between leucine zipper pairs, (2) the affinity between tumor antigen and scFv, (3) the concentration of zipFv, and (4) the expression level of zipCAR
- Effect on IFN-γ production by primary CD4+ T cells expressing RR zipCAR

Cho JH, et al. Cell 2018; 173 (6):1316-1317

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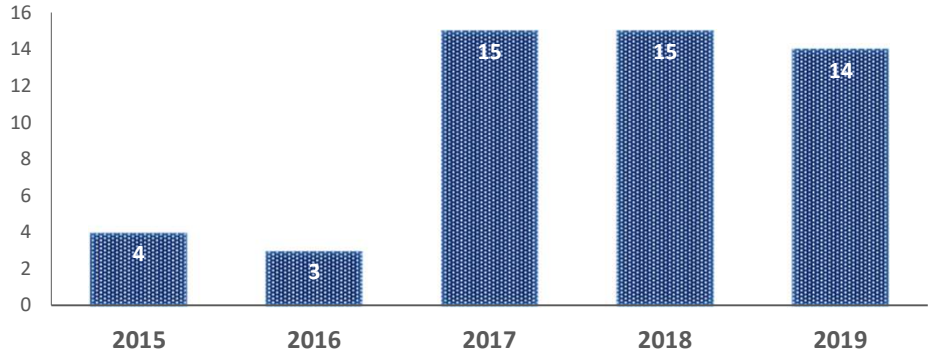
Why "humanize" CARs?

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



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

47

Autologous CAR-T Cells vs Allogeneic CAR-T Cells

Patient Derived Limitations

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

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

Donor derived

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

Donor Derived Advantages

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

Donor Derived Barriers

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

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

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

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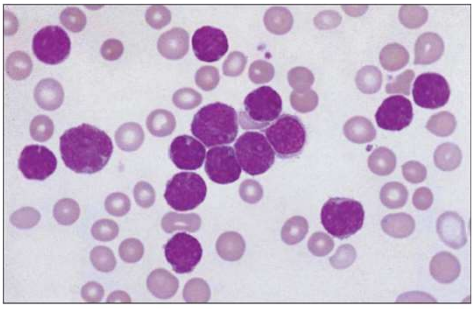
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

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



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

Peripheral blood film in mantle cell lymphoma showing pleomorphic cells

50

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

- Mantle cell lymphoma is an uncommon, aggressive B-cell NHL subtype with hallmark chromosomal translocation t(11;14)(q13;q32)
- KTE-X19: autologous CD19-targeted CAR T-cell therapy comprising a CD3ζ T-cell activation domain and a costimulatory CD28 domain
- The phase II ZUMA-2 study sought to evaluate efficacy and safety of KTE-X19 in patients with relapsed/refractory MCL
- First CAR T-cell therapy, brexucabtagene autoleucel, FDA approved in 2020 for treatment of adults with R/R MCL

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

51

ZUMA-2: Study Design

- Multicenter, global phase II trial

Patients with relapsed/refractory mantle cell lymphoma; 1-5 prior therapies; ≥ 1 measurable lesion; ECOG PS 0-1 (N = 74)

Optional Bridging Therapy
Dexamethasone 20-40 mg/d x 1-4 d, *or*
Ibrutinib 560 mg/d, *or*
Acalabrutinib 100 mg BID
(n = 25)

Conditioning Chemotherapy
Fludarabine 30 mg/m^2 +
Cyclophosphamide 500 mg/m^2
Days -5, -4, -3
(n = 69)

CAR T-Cells
KTE-X19
2 x 10^6 cells/kg, Day 0
(n = 68)

↓

F/U begins with first tumor assessment on Day 28; BM biopsy may be required to confirm CR

Primary endpoint: ORR (IRRC-assessed per Lugano classification)

Secondary endpoints: DoR, PFS, OS, safety, ORR (investigator assessed), QoL (EQ-5D), CAR T-cell levels in blood and cytokines in serum

- KTE-X19 was successfully manufactured in 96% of patients and administered to 92% of patients
- Median time from leukapheresis to KTE-X19 delivery was 16 days

Wang. ASH 2019. Abstr 754.

Slide credit clinicaloptions.com

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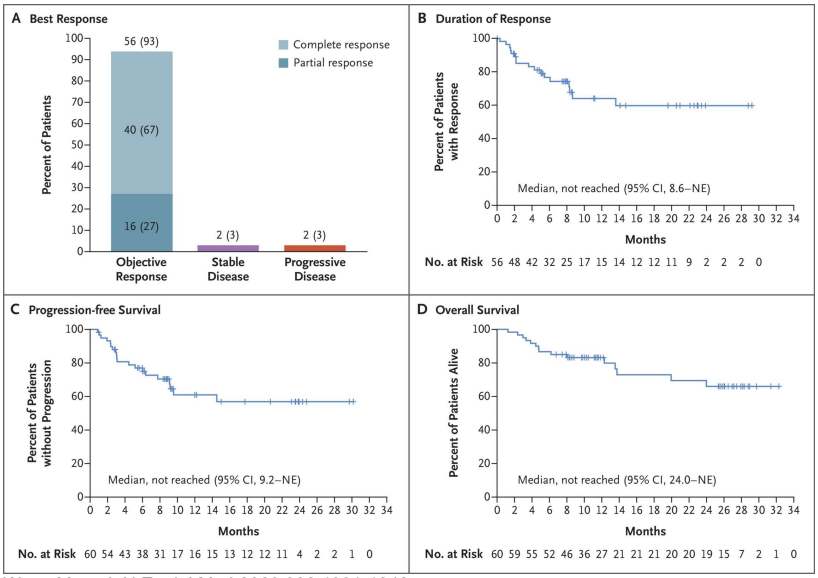
ZUMA-2: Baseline Characteristics

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

Wang. ASH 2019. Abstr 754.

53

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



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

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

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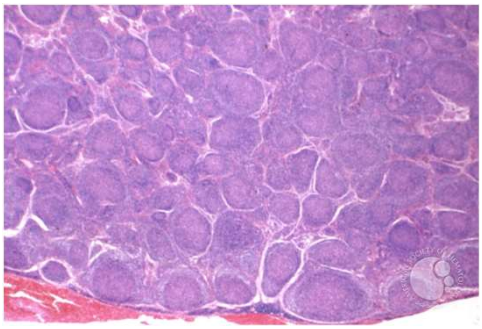
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

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

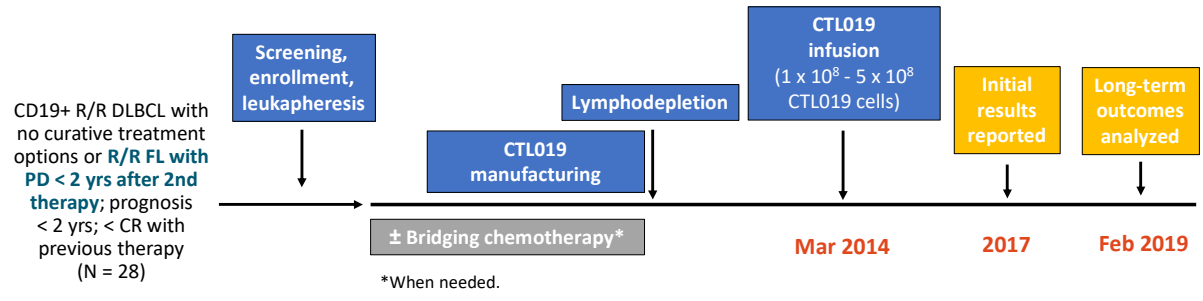


ASH Image Bank – American Society of Hematology

55

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

- Single-center trial at University of Pennsylvania; CTL019 construct: α-CD19-4-1BB-CD3ζ



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

Schuster. NEJM. 2017;377:2545. NCT02030834

Slide credit: clinicaloptions.com

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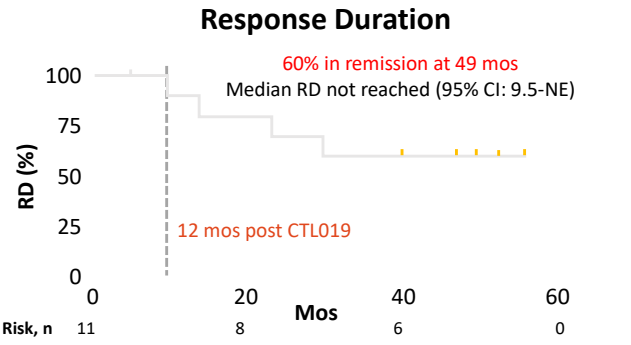
UPenn CTL019 in Follicular Lymphoma: 4-Yr Follow-up

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

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



Chong. ICML 2019. Abstr 090.

Slide credit: clinicaloptions.com

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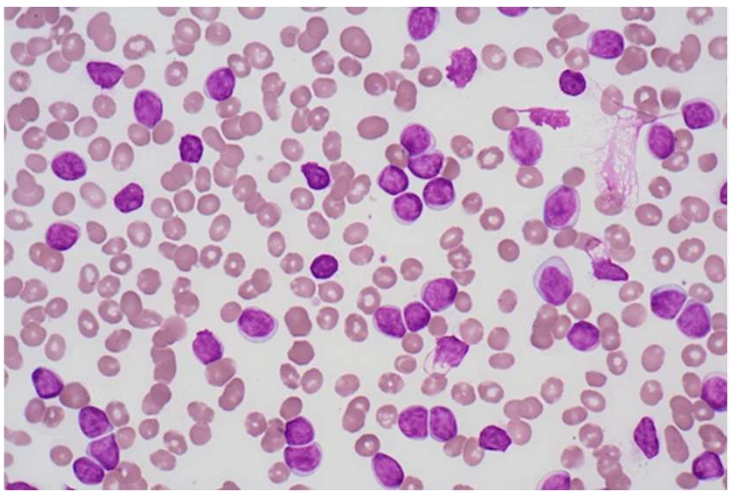
CAR T-Cell Therapy in Chronic Lymphocytic Leukemia (CLL)



Increased numbers of mature lymphocytes in peripheral blood

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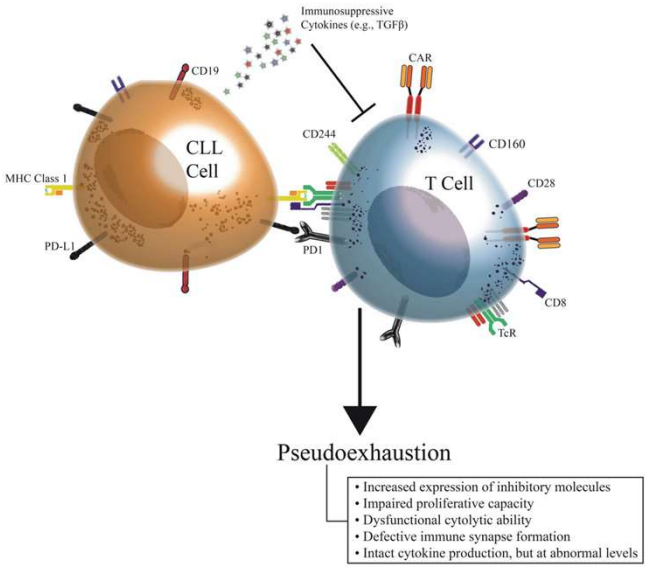
Improving CLL Therapy with CAR T-cells



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

59

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

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

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

Gauthier et al., Blood, 2018

60

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

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

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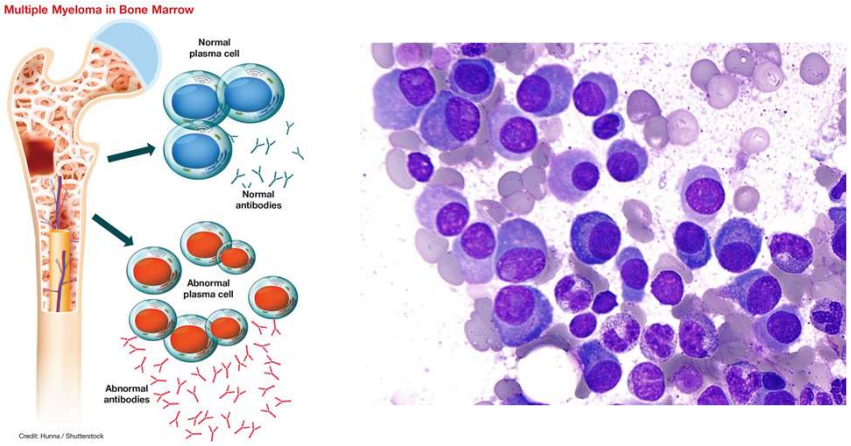
CAR T- Cell Therapy in Multiple Myeloma (MM)



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

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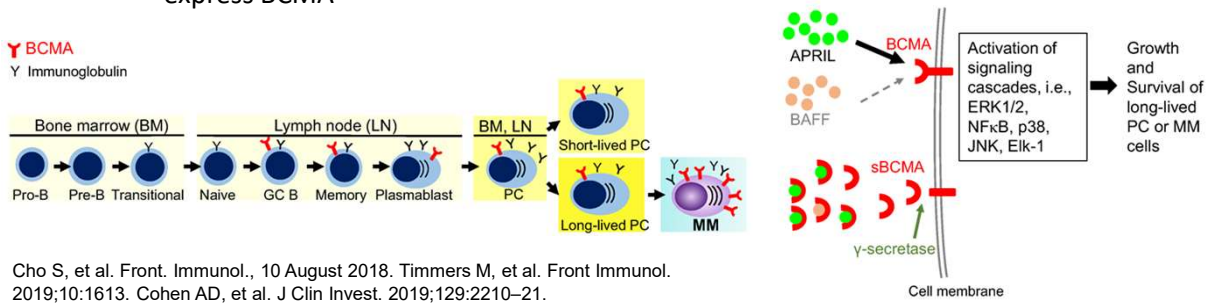
B-cell Maturation Antigen (BCMA)

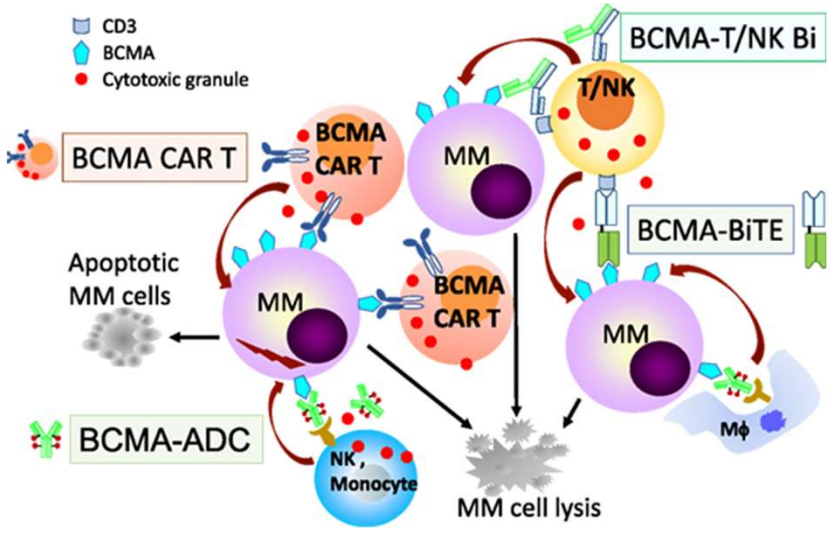
- Functions to maintain long-lived plasma cell homeostasis
  - Essential in regulating B-cell maturation and differentiation
- Highly expressed on malignant plasma cells in MM
  - Increased expression associated with progression of disease
- BCMA shed from the surface of plasma cells leads to soluble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



Cho S, et al. Front. Immunol., 10 August 2018. Timmers M, et al. Front Immunol. 2019;10:1613. Cohen AD, et al. J Clin Invest. 2019;129:2210–21.

63

B-Cell Maturation Antigen (BCMA)-Based Immunotherapies



Cho S., Anderson KC., Tai Y. Front. Immunol., 10 August 2018.

64

Phase I NCI BCMA CAR

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

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

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

65

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

	BB2121 (BLUEBIRD) Idecabtagene vicleucel	LCAR-B38M (LEGEND)	JCARH125 (JUNO)
Population	33	57	44
# Prior Tx	7	3	7
CART Dose	50-800 x 106	0.07-2.1 x 106/kg	50-450 x 106
ORR	85%	88%	82%
CR	45%	74%	27%
CRS All Grades (Grade 3/4)	76% (6%)	89% (7%)	80% (9%)
Med Onset of CRS	2d	9d	3d
Neurotox All Grades (Grade 3/4)	42% (3%)	2% (0%)	25% (7%)
Med PFS	11.8 months	15 months	-

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

66

Future Directions of Most Advanced CAR T Products in Multiple Myeloma

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

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Investigational Allogeneic CAR T-cells in Hematologic Malignancies

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

www.clinicaltrials.gov. Accessed December 12, 2020

DLT: Dose limiting toxicity

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Conclusions

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

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Q&A SESSION

Advances in CAR T-cell Therapy

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

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

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www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: infocenter@LLS.org
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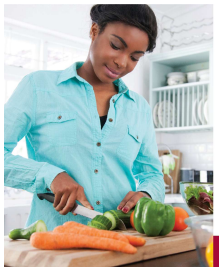

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Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.

www.LLS.org/Consult.

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LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**.

Augmented Reality CAR T-Cell Therapy Process

Use your smartphone, tablet, or other mobile device to see the CAR T-cell therapy process in action, please visit **www.LLS.org/CART**.

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**.

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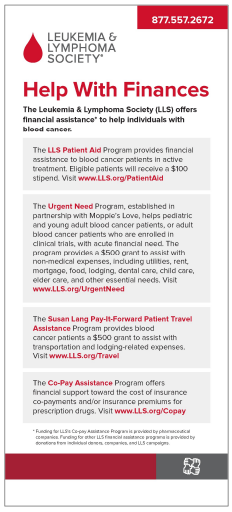
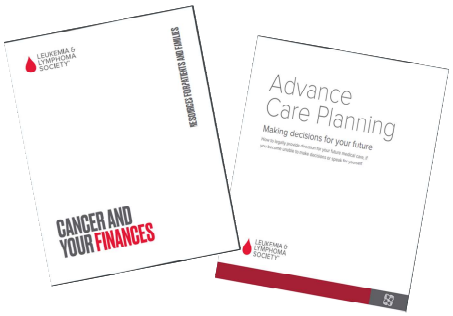
LLS EDUCATION & SUPPORT RESOURCES



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



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

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®

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