WELCOME & INTRODUCTIONS

Car T-Cell Therapy in Children and Adults with Blood Cancers

To register or to view the BCC schedule, visit www.LLS.org/bcc.

Southern California Blood Cancer Conference Anaheim, CA **March 2, 2019**	Florida Blood Cancer Conference Fort Lauderdale, FL **March 30, 2019**

Program will begin shortly

BEATING CANCER IS IN OUR BLOOD.

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CAR T-CELL THERAPY IN CHILDREN AND ADULTS WITH BLOOD CANCERS

Speakers
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CAR T-Cell Therapy in Children with Blood Cancers

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CENTER FOR CELL & GENE THERAPY

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Dr. Rayne Rouce has affiliations with Kite Pharma, A Gilead Company, Novartis and Tessa Pharmaceuticals.

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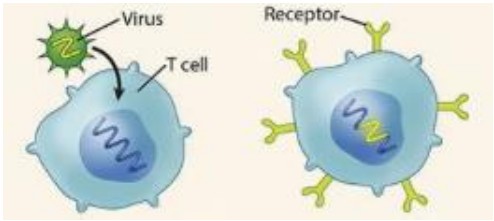
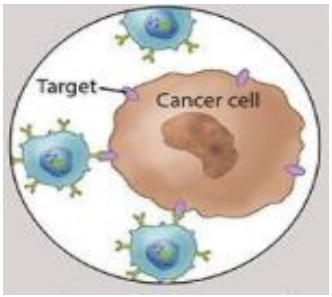
What exactly *is* a CAR T-cell?

- **C**himeric **A**ntigen **R**eceptor T-cell: a **T cell** engineered in the lab to express **artificial receptors** that specifically **target a protein** on the surface of a **cancer cell**.





LLS Website, 2019; Fran Miner 2017

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Pediatrics: Who qualifies for CD19 CAR T-cell therapy?

- Initially CD19 CAR T cells only available on a clinical trial (research study)
  - various trials across the country & world available for relapsed patients
- Different criteria for each trial, BUT common features
  - CD19 must be expressed on surface of malignancy
    - Most commonly ALL, but also lymphomas
  - not available for upfront "initial" therapy, only in case of **relapse** or **refractory** tumor

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Major discoveries from preclinical and early clinical trials

- CAR T cells require additional "help" to expand and endure in the body
- Some of this help comes from "within" the CAR T-cell
  - additional stimulatory molecules that can be added to the cell
- Some of the help comes from "outside"
  - lymphodepleting chemo

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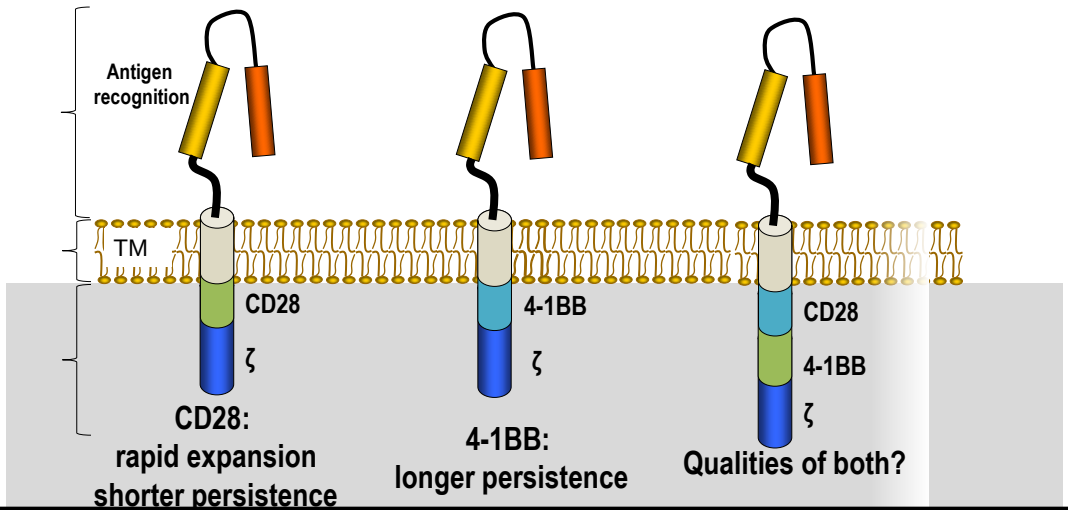
CAR T-cell structure can affect performance in the body



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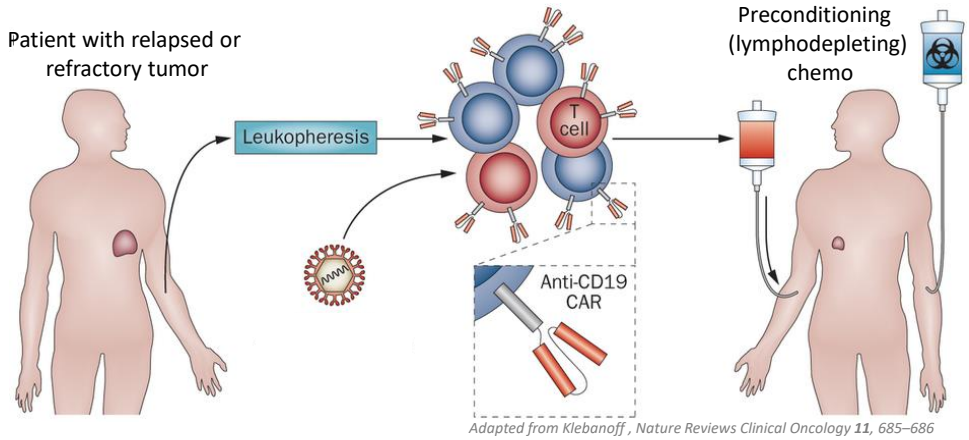
What does CAR T-cell therapy involve?



*Adapted from Klebanoff , Nature Reviews Clinical Oncology **11**, 685–686 (2014)*

Collect white cells from patient → Introduce new gene carrying **CAR (designed to attack protein on tumor cells)** into T cells → **Expand CAR+ T cells** and **give** back through an IV or central line

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CD19 CAR T-cell therapy in 2019

- High complete remission rates in multiply relapsed patients across most studies
  - overall response between 65 and 90%
  - some patients remain in remission for years
- Larger trials, longer follow-up and high remission rates led to partnerships with industry
- Efforts to make widely available & “prescribable”
- August 2017: First FDA approval of a CAR T cell therapy!!

KYMRIAH® (tisagenlecleucel)

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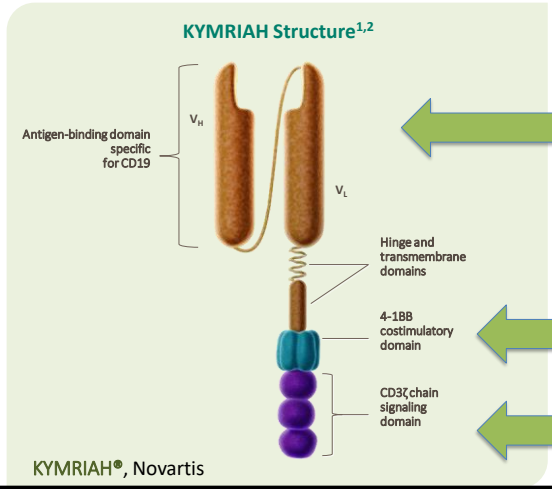
August 2017: First FDA approval of a CAR T-cell therapy!!

KYMRIAH® (tisagenlecleucel)



CD19-recognizing portion

"additional helper" molecule

T-cell killing component

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KYMRIAH® (tisagenlecleucel) Indications

Which Patients Should Be Considered for KYMRIAH?

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

ALL

Consider KYMRIAH for pediatric and young adult patients with any of the following clinical characteristics:

- Have not gone into remission following frontline treatment (**primary refractory**)
- Have relapsed and cannot achieve remission (chemorefractory)
- Have had **second or subsequent relapse following complete remission or HSCT**

Please see Important Safety Information throughout deck and full Prescribing Information, including Boxed WARNING, and Medication Guide.

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

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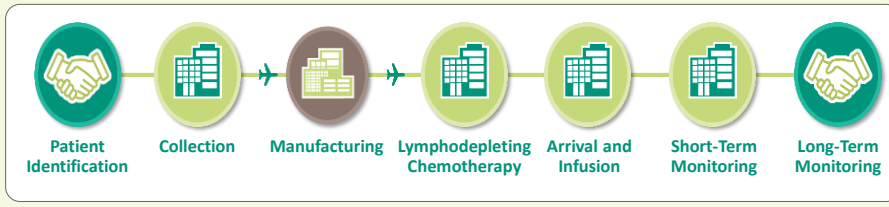
Process Overview: Patient and Cell Journey



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KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

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The Future of CAR T-cell therapy for children with cancer

- CD19 CAR Therapy
  - Moving therapy earlier
    - treating patients in first relapse
    - treating patients with persistent measurable disease (even small amounts aka “minimal residual disease”) early on in treatment
  - Targeting multiple antigens in addition to CD19
  - Combination therapy to enhance benefit
  - “off-the-shelf”options
  - Extending approval to CD19+ lymphoma in pediatric patients

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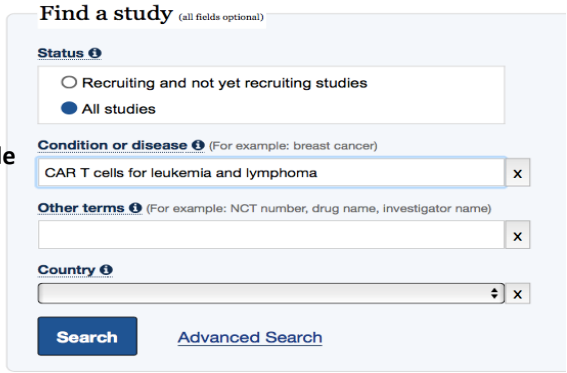
Beyond CD19: other CAR T cells in clinical trials

Step 1: Go to clinicaltrials.gov

Step 2: Type in "CAR T cells for…."
-be as specific or general as possible
-can even search by hospital, city, whether trial actively recruiting or not



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CAR T cell therapies for leukemia and lymphoma in clinical trials

B-ALL, B-NHL
-CD19
-CD22
CD19/22

AML
-CD123
-CD33
-CLL-1
-NKG2D

T-ALL/T-cell lymphoma
-CD5
-CD7

Hodgkin Lymphoma/ALCL
-CD30

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Making Cancer History®

CAR T-Cell Therapy for NHL: Current and Future Directions

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Disclosures

- Research support: Celgene, Genentech, Janssen, Karus, Merck, TG Therapeutics
- Honorarium: Celgene, Genentech, Gilead, Janssen, Novartis

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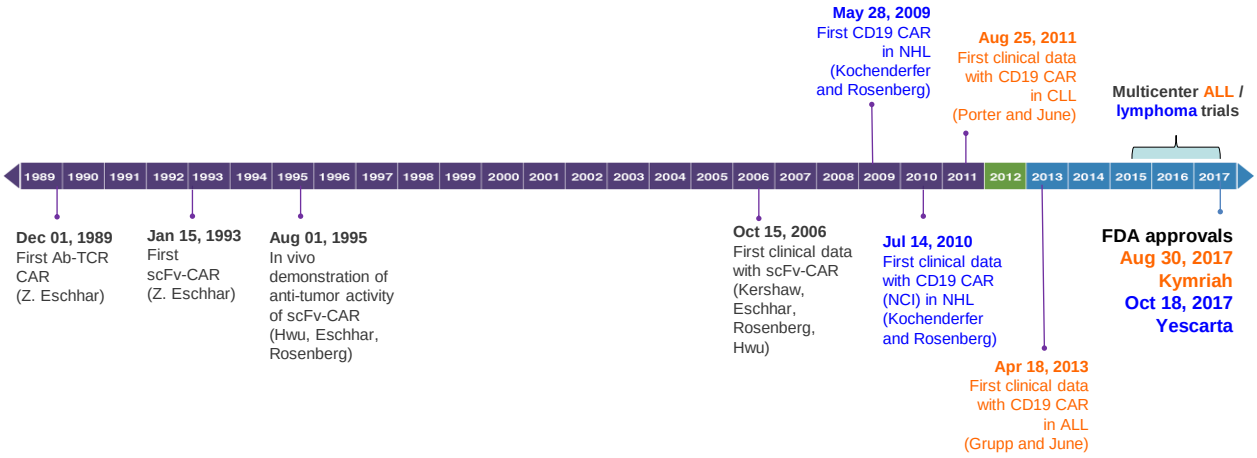
CAR T-cell Development: From Discovery to FDA Approval

Discovery to FDA approval ~25 years



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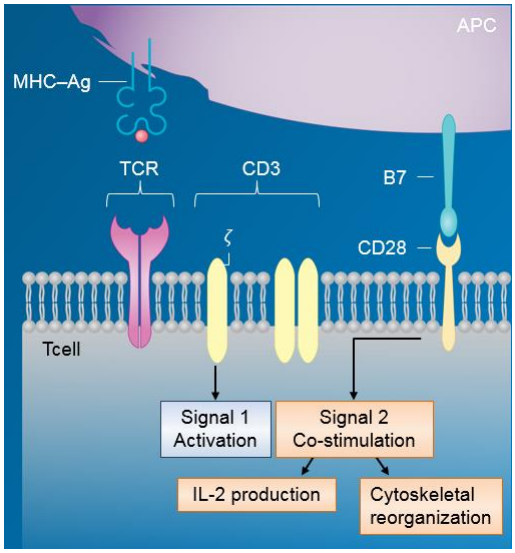
T Cell Activation Requires 2 Signals



APC, antigen-presenting cell; MHC-Ag, major histocompatibility antigen; TCR, T cell receptor.
Adapted from Sadelain et al. *Nat Rev Cancer 2003*

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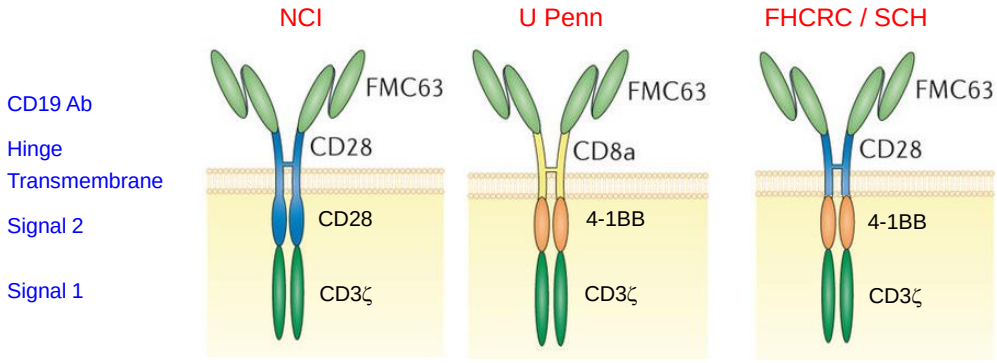
CD19 CAR T-cell Products in Pivotal Trials in NHL



Gene transfer	Retrovirus	Lentivirus	Lentivirus
	Kite Pharma	**Novartis**	**Juno Therapeutics**
	KTE-C19	**CTL-019**	**JCAR017 (CD4:CD8 = 1:1)**
	Axicabtagene ciloleucel	**Tisagenlecleucel**	**Lisocabtagene maraleucel**
	Axi-cel		**Liso-cel**

Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

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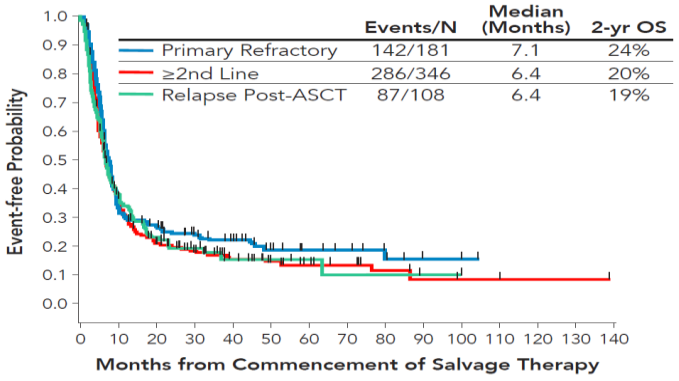
Unmet Need in Chemorefractory Aggressive B-cell NHL

(SCHOLAR - Retrospective Non-Hodgkin Lymphoma Research)

- Meta-analysis to evaluate the outcomes in chemorefractory DLBCL
- CORAL, CCTG-LY12, MDACC, Mayo-Iowa
- Chemorefractory patient population
  - ✓ SD/PD after primary or later-lines of therapy
  - ✓ Relapse ≤12 months after ASCT
- N = 635
- ORR = 26%; CR rate = 8%
- Median OS = 6.6 months

Overall survival



	Events/N	Median (Months)	2-yr OS
Primary Refractory	142/181	7.1	24%
≥2nd Line	286/346	6.4	20%
Relapse Post-ASCT	87/108	6.4	19%

Crump et al, SOHO 2016

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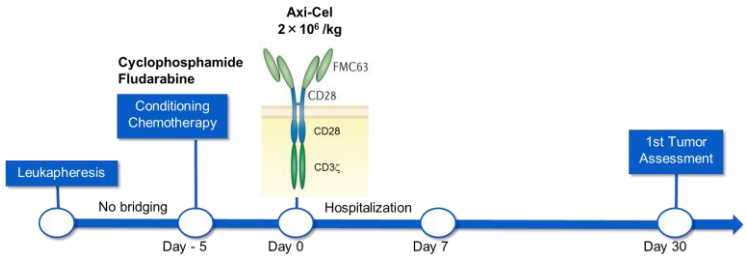
ZUMA1: Phase I/II Study Design



Phase 1 (N = 7)

Refractory DLBCL/PMBCL/TFL (n = 7)

Phase 2 (N = 101)

- Cohort 1 Refractory DLBCL (n = 77)
- Cohort 2 Refractory PMBCL/TFL (n = 24)

Key eligibility criteria

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

- **N = 108**
- **Data cutoff: August 11, 2017**
- **Median follow-up: 15.4 months**

Conditioning regimen

- Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² for 3 days

Axi-cel: 2 × 10^6 CAR+ cells/kg

- 99% enrolled were successfully manufactured
- 91% enrolled were dosed
- 17-day average turnaround time from apheresis to delivery to clinical site

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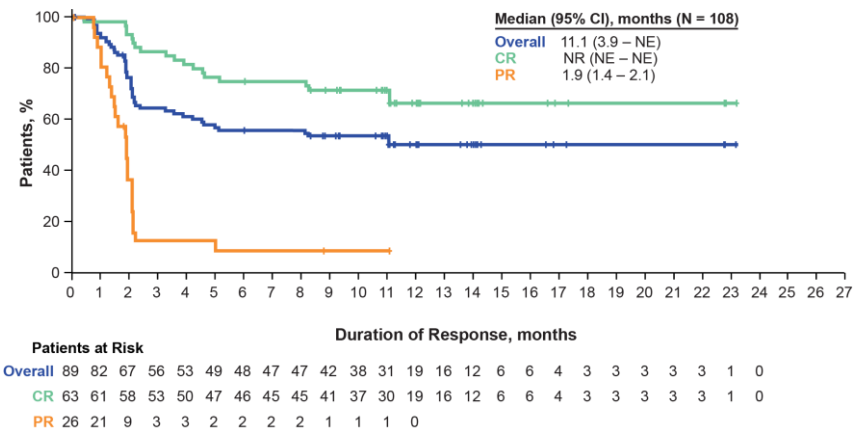
ZUMA1: Duration of Response by Best Objective Response



Patients at Risk

Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0											

- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients have ongoing CR at 24 months

CR, complete response; NR, not reached; PR, partial response.

Neelapu et al. N Eng J Med 2017

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ZUMA1: Safety

	Pivotal cohort (N=101)	
	CRS	**NE**
All grades	93%	64%
Grade ≥3	13%	28%
Time to onset [Median (Range)]	2 (1-12) days	5 (1-17) days
Time to resolution (Median)	8 days	17 days
Tocilizumab usage	43%	
Corticosteroids usage	27%	

- 3 deaths due to AEs – 1 cardiac arrest, 1 HLH, 1 pulmonary embolism
- Lee criteria used for CRS grading
- CTCAE criteria used for neurological event (NE) grading

Neelapu et al. N Eng J Med 2017

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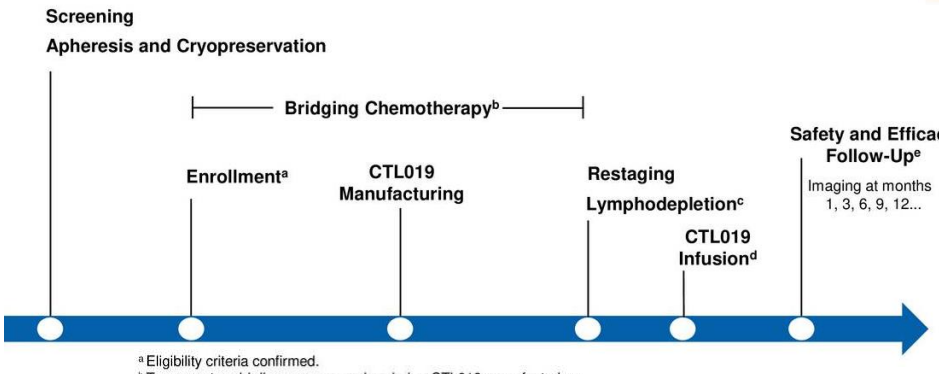
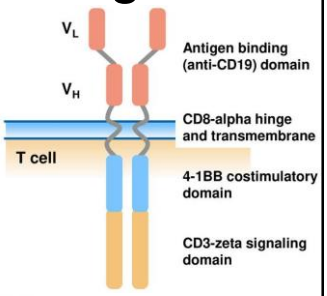
JULIET: Tisagenlecleucel Study Design

JULIET is a single-arm, open-label, multicenter, global phase 2 trial of CTL019 in adult patients with r/r DLBCL (NCT02445248)



[a] Eligibility criteria confirmed.
[b] To prevent rapid disease progression during CTL019 manufacturing.
[c] To be completed 2 to 14 days prior to CTL019 infusion.
[d] Infusion conducted in- or out-patient at investigator discretion.
[e] Long-term follow-up for 15 years (NCT02445222).



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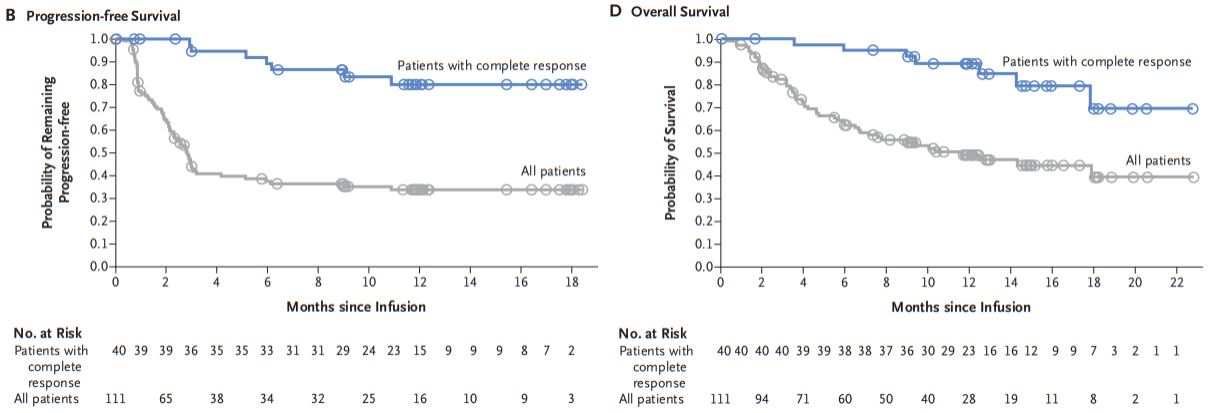
JULIET: Survival



Schuster et. al. *NEJM.* 2018

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Multicenter CD19 CAR T-cell Trials in Aggressive NHL

Study / Sponsor	ZUMA1 / Kite	JULIET / Novartis	TRANSCEND / Juno
Reference	Neelapu et al, NEJM 2017	Schuster et al, NEJM 2018	Abramson et al, ASH 2017
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	0.6-6 x 10^8	0.5-1 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL Gr 3B
Treated/Enrolled	101/111 (91%)	111/165 (67%)	108/140 (77%)
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	21%	49%	42%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	93%	98%
ORR / CR (%)	82 / 54	52 / 40	80 / 55

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Cytokine Release Syndrome and Neurotoxicity: Multicenter CD19 CAR T trials in adult NHL

Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Ref
ZUMA1 / Kite	CD19/CD3ζ/CD 28	101	93%	13%	64%	28%	Neelapu et al, NEJM 2017
JULIET / Novartis	CD19/CD3ζ/4-1BB	111	58%	22%	21%	12%	Schuster et al, NEJM 2018
TRANSCEND / Juno	CD19/CD3ζ/4-1BB	67	36%	1%	21%	15%	Abramson et al, ASH 2017

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

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Outcomes with Standard of Care Axi-Cel

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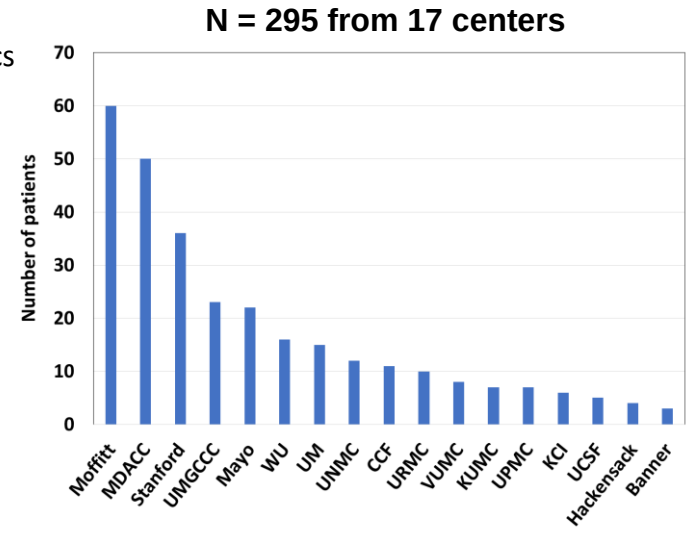
Study Design: Outcomes with SOC Axi-Cel

- **Objective:** Delineate the characteristics and real world outcomes of patients undergoing standard of care axi-cel.
- Retrospective analysis of data from **17 US academic centers**.
- All patients **leukapheresed as of August 31, 2018** with intention to manufacture commercial axi-cel were included in these analyses.



 Nastoupil, ASH 2018 Abstract 91

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Characteristics Differentiating Patients in the Real World from ZUMA-1

- 124 of 286* (43%) patients would not have met eligibility for ZUMA-1 at the time of leukapheresis.

Criteria Excluded from ZUMA-1	N=124 N (%)
Platelets < 75	37 (13)
Active DVT/PE	27 (9)
Prior CD19 or CAR T cell therapy	24 (8)
GFR < 60	22 (8)
History of CNS lymphoma	22 (8)
Symptomatic pleural effusion	11 (4)
LVEF < 50%	10 (4)
Prior allogeneic SCT	7 (2)

* Missing data on 7 subjects enrolled on ZUMA 9

 Nastoupil, ASH 2018 Abstract 91

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Safety of Axi-Cel in the Real World

	SOC Axi-cel N = 274 (mITT)	ZUMA-1[1] N = 108
All Grades of CRS*, N (%)	240 (92%)	100 (93%)
Grade ≥ 3 CRS, N (%)	18 (7%)	14 (13%)
Median time to onset of CRS	3 days	2 days
All Grades of NT**, N (%)	181 (69%)	70 (65%)
Grade ≥ 3 NT, N (%)	85 (33%)	33 (31%)
Median time to onset of NT	6 days	5 days

* Lee criteria used for grading CRS
** CTCAE or CARTOX criteria used for grading neurotoxicity

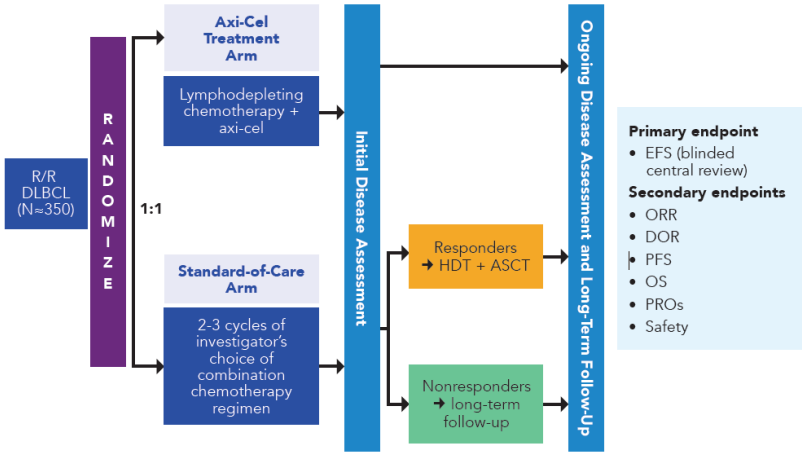
[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

Ongoing Clinical Trials

ZUMA 7: Axicabtagene Ciloleucel vs. Standard of Care in Subjects with R/R DLBCL

Eligible patients:
First relapse of DLBCL including tFL
- primary refractory
- SD
- PR with relapsed ≤ 12 months

Candidate for HDT/ASCT



No chemotherapy bridging is allowed.
ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; DOR, duration of response; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; HDT, high-dose therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

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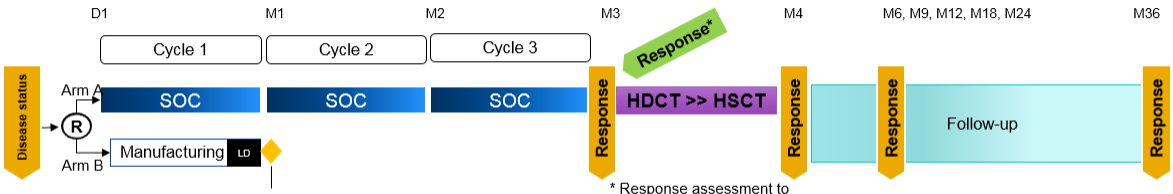
TRANSFORM Study Design: JCAR017



* Response assessment to confirm eligibility for HSCT in responding patients not in PR/CR at M2

- Subjects from Arm A may be allowed to cross over and receive JCAR017 upon confirmation of an EFS event
- JCAR017 will be manufactured once the investigator confirms the request for a cross over and the and the IRC confirm the EFS event (Progression; Start of new antineoplastic therapy [for subjects with SD after 2 cycles of SOC, for subjects with PR after 3 cycles of SOC]; Relapse)
- Subjects who cross over will be followed up for 1 year

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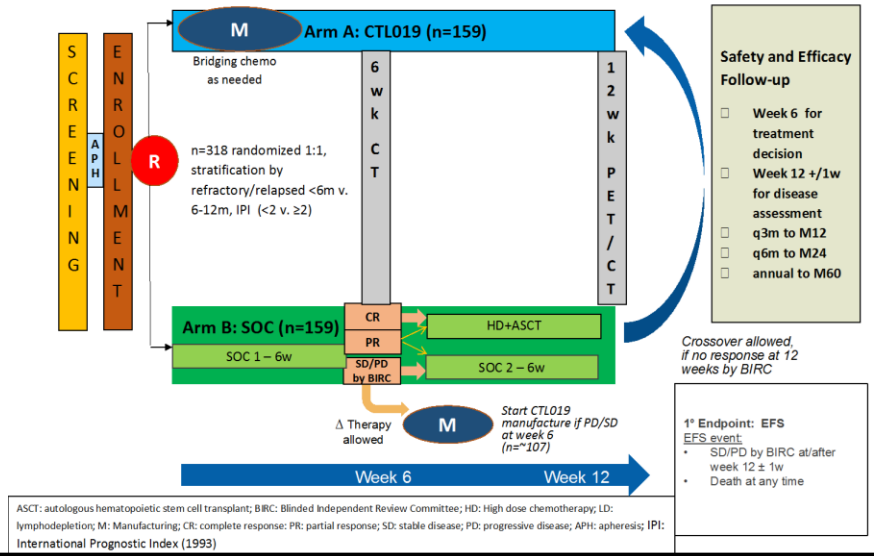
BELINDA: Study Design

CTL019H2301 Amended Design Proposal

Randomization upfront at time of 1st relapse (<12 months from R-CHOP)



ASCT: autologous hematopoietic stem cell transplant; BIRC: Blinded Independent Review Committee; HD: High dose chemotherapy; LD: lymphodepletion; M: Manufacturing; CR: complete response: PR: partial response; SD: stable disease; PD: progressive disease; APH: apheresis; IPI: International Prognostic Index (1993)

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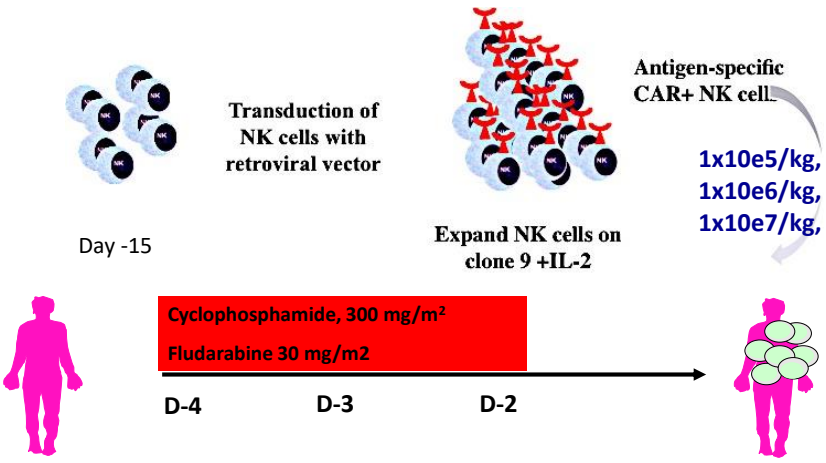
Phase I/II Study of Umbilical Cord Blood-derived CAR-engineered NK cells in Patients with Relapsed/refractory B-lymphoid malignancies



- Patients with relapsed/refractory ALL, CLL or NHL

Outcomes:
Safety
Efficacy

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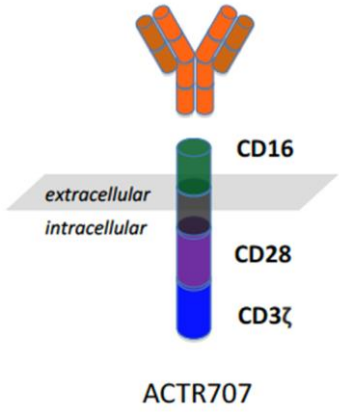
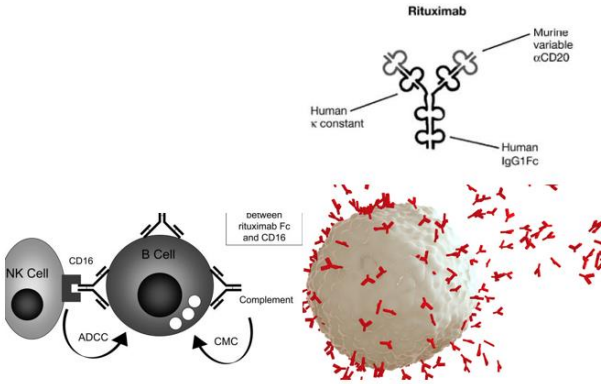
ACTR707, an Autologous T Cell in Combination with Rituximab



ACTR707



- Autologous T cells with chimeric antigen receptor
- CD16 binds Fc
- Results in a CAR T with rituximab as target
- Potential use in CD19- B cell NHL
- Potential use to titrate potency of CAR T

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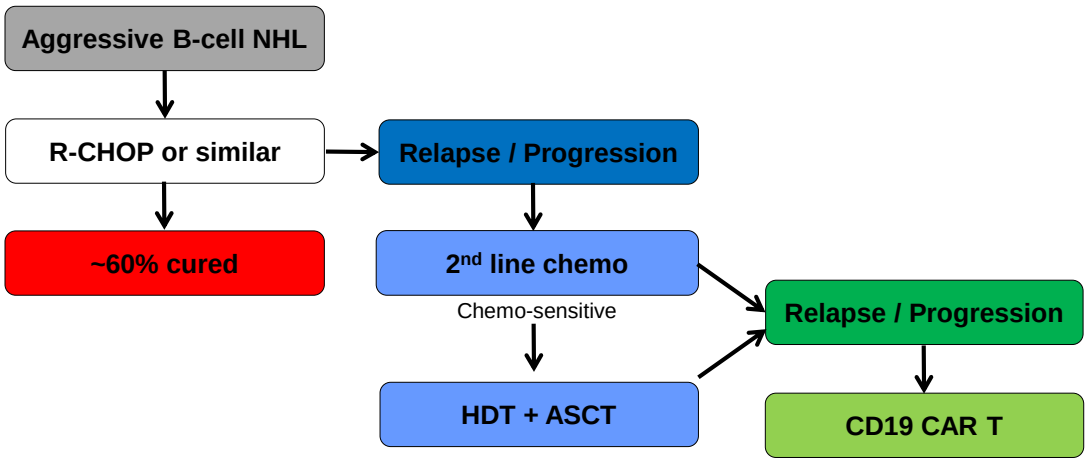
CD19 CAR T in NHL: Current Management of DLBCL



Future Directions:

CD19 CAR T in high-risk aggressive B-cell NHL	Randomized trials of CD19 CAR T vs. ASCT	CD19 CAR T in high-risk indolent B-cell NHL, MCL

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CAR T-cell in Multiple Myeloma

	Bb21217	JCARH125	MCARH171	FCARH143	LCAR-B38M	Native TCR
Center/Sponsor	Celgene/Bluebird bio	Juno/Celgene	MSKCC	Fred Hutch	Nanjing Legend Biotech	Baylor
Donor	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous
scFv	anti-BCMA scFv, cultured in pan PI3K inhibitor bb007 (less differentiated)	Human anti-BCMA scFv	Human anti-BCMA scFv	Human anti-BCMA scFv	llama anti-BCMA non-scFv, 2 variable heavy chain domains = 2 diff epitopes	MAGEA4, PRAME, Survivin, NYESO-1, SSX2 TCRs (enriching native specificity)
Co stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	n/a
Transduction	Lentivirus	Lentivirus	Retrovirus	Lentivirus	Lentivirus	n/a
Lines of therapy	6 (4-17)	7 (3-23)	6	11	3 (1-9)	2-10
High risk pts	58%	77%	64%	73%	?	?
CRS/CRES	CRS 67% (1 gr 3) CRES 24% (1 gr 4)	9% CRS 3/4 (80% all gr) 7% neuro 3/4 (25% all)	6/11 CRS (Gr3/4 – 4) 1 gr 2 neuro	10/11 (<= gr 2) 1 gr 3 neuro	90% (grade 3=7%) Grade 1 neuro = 1	none
ORR >= PR	83% (150x10^6, 11 pts) 25% sCR/CR 4/4 MRD neg	82%, 48% >= VGPR CR/sCR 27%	64% ORR	100% ORR 4 CR, 5 VGPR, 2 PR	88% in 74 patients 74% CR mDOR 16 mo mDOR (MRD-) 22 mo	3 PR, 1 CR/12 pts with active disease

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Q&A SESSION

Car T-Cell Therapy in Children and Adults with 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

- **Information Specialists**

  Master's level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: 1-800-955-4572**
- **CAR T-cell Immunotherapy: www.LLS.org/cart**
- **Caregiver Support: www.LLS.org/caregiver**
- **Free Education Booklets: www.LLS.org/booklets**
- **Free Telephone/Web Programs: www.LLS.org/programs**
- **Live, weekly Online Chats: www.LLS.org/chat**
- **LLS Community: www.LLS.org/community**

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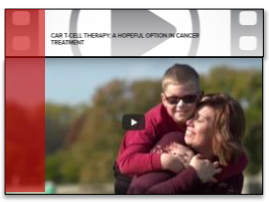
LLS EDUCATION & SUPPORT RESOURCES



- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**
- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: **www.LLS.org/educationvideos**
- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**
- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: **www.LLS.org/nutrition**
- **LLS Copay Assistance Program:**

  Provides financial assistance towards copayments and insurance premiums: **www.LLS.org/copay**
- **Financial Assistance Programs for approved CAR T-cell therapies:**
  - **Kymriah®-** 1-844-459-6742
  - **Yescarta®-** 1-844-454-5483

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THANK YOU
We have one goal: A world without blood cancers
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