The Future of  in Cancer

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5/15/19

A National Cancer Institute Designated Cancer Center

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Disclosures

Research Support	**Amgen; BMS; Celgene; Curis; Juno; Janssen; Pharmacyclics; TG Therapeutics**
Consultancy	**AbbVie/Pharmacyclics; Bayer; Cardinal Health; Celgene/Juno; Dava; Janssen; Gilead/Kite; Novartis; Portola; Seattle Genetics; Spectrum; TG Therapeutics; Vanium; Verastem**
Employment	**NONE**
Major Stock Holder	**NONE**
Speaker Bureau	**NONE**

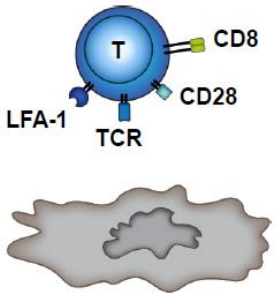
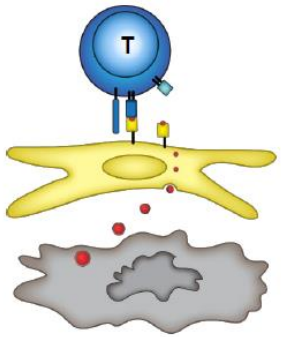
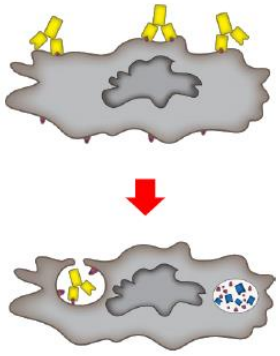
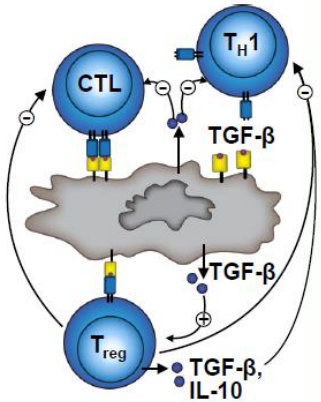
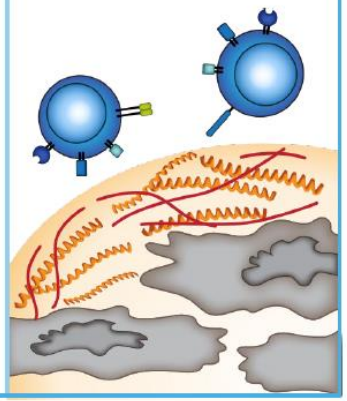
Objectives

1. **Discuss the safety, efficacy, and role of chimeric antigen receptor (CAR) T-cell therapy in cancer treatment**

2. **Outline guideline recommendations for patient selection, administration of treatment, and monitoring and management of toxicities with regard to CAR T-cell therapy**

3. **Discuss current and future strategies for applying CAR T-cell therapy and managing treatment-related complications**

Cancer is Smart!

Low Immunogenicity	Tumor Treated as Self Antigen	Antigenic Modulation	Tumor-Induced Immune Suppression	Tumor-Induced Privileged Site
No peptide:MHC ligand; No adhesion molecules; No co-stimulatory molecules	Tumor antigens taken up and presented by APCs in absence of co-stimulation tolerize T cells	Antibody against tumor cell-surface antigens can induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants	Factors (eg, TGF-β) secreted by tumor cells inhibit T cells directly. Induction of regulatory cells by tumors	Factors secreted by tumor cells create a physical barrier to the immune system
				

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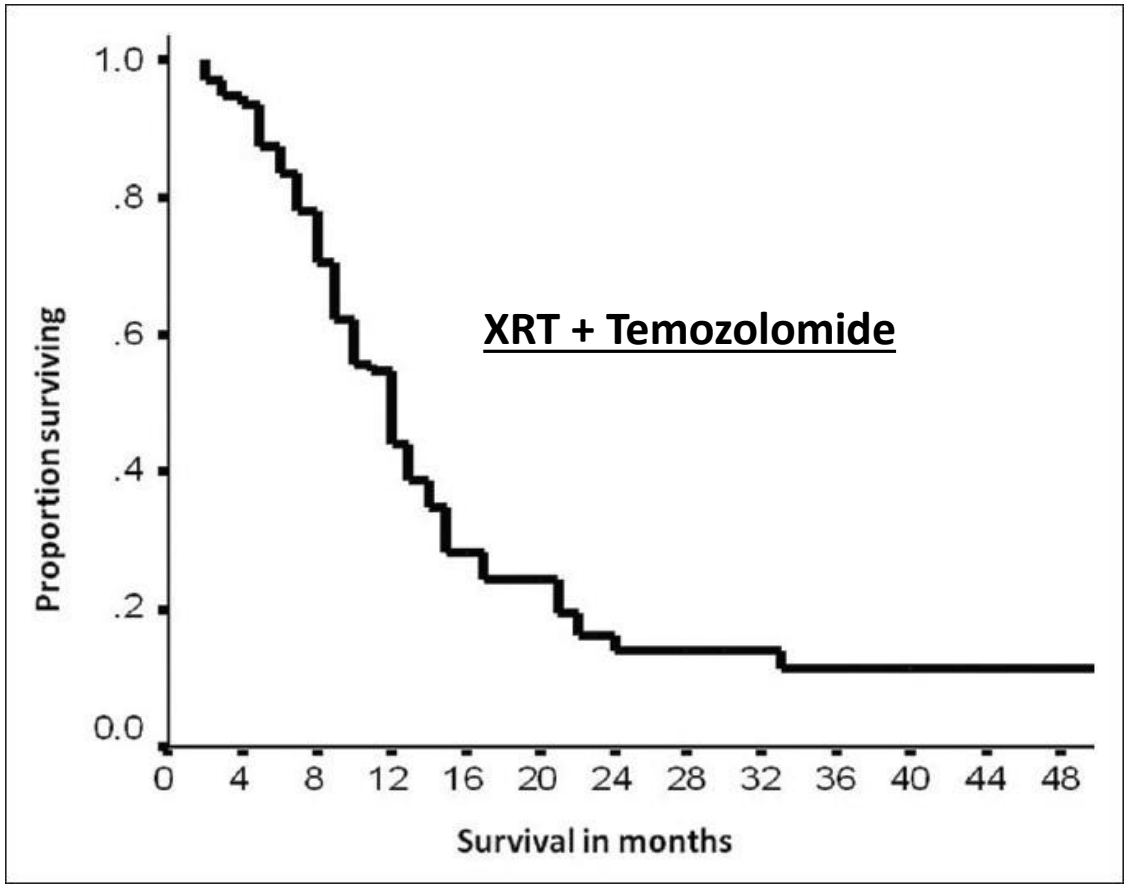
Immunobiology (7th edition). 2008. Garland Science

Glioblastoma



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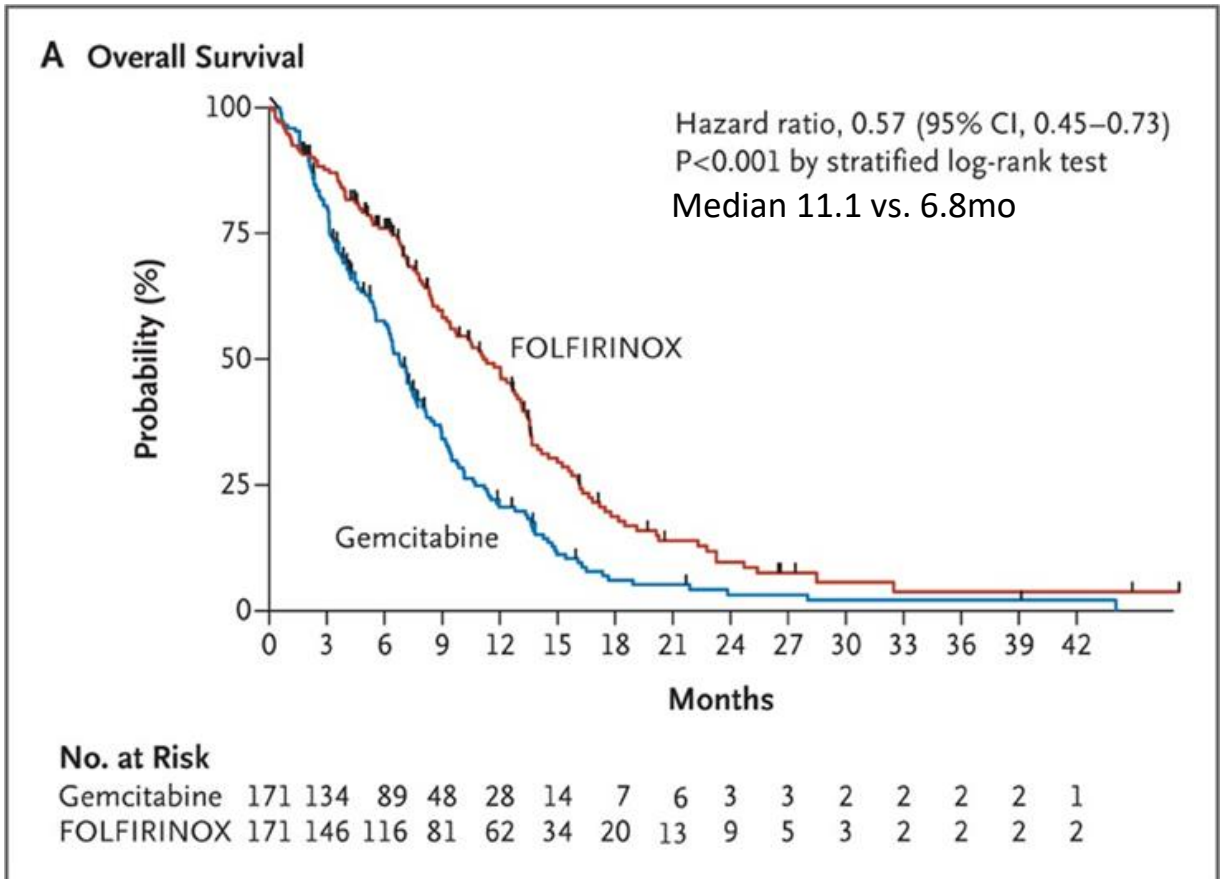
Julka JK et al. J Clin Res & Therapeutics 2013

Metastatic Pancreatic Cancer



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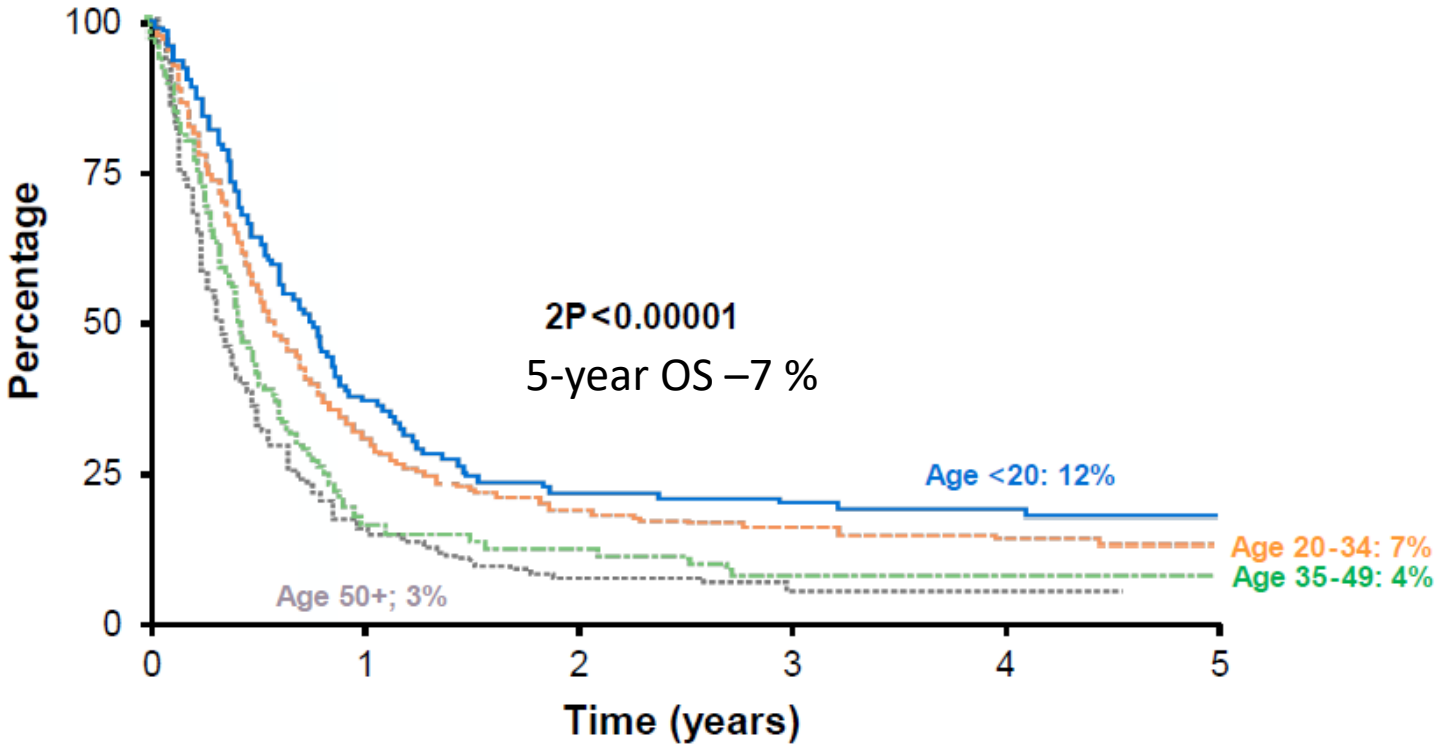
Conroy T et al. NEJM 2011.

1st Relapsed Acute Lymphoblastic Leukemia



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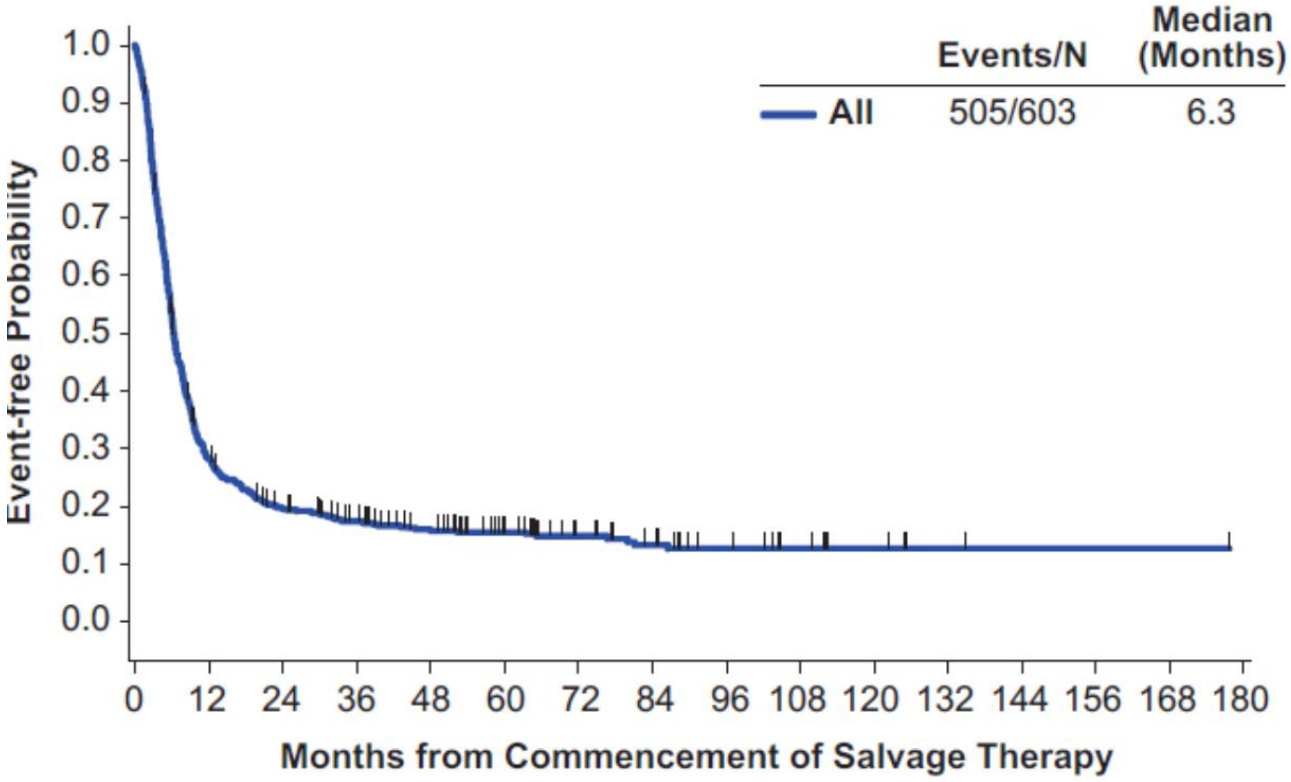
Fielding A et al. Blood 2007

Relapsed or Refractory Diffuse Large B-cell Lymphoma



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Crump M. et al. Blood 2017

Risk of Disease Equals Potential Reward

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Can we Get Smarter?

Target the Tumor

- Chemotherapy and AutoHCT
- Monoclonal Antibodies
  - Rituximab and Herceptin
- Antibody-Drug Conjugates
  - Brentuximab
- Tumor Checkpoint Blockade – PD-L1

Target the Host

- Vaccination
  - Gardasil (anti-HPV16&18)
  - Sipuleucel-T (anti-PSA)
- Immune Modulators
  - Lenalidomide
- Immune Checkpoint Blockade
  - PD1, CTLA4

Target Both Tumor & Host

- Allogeneic HCT
- Bispecific Antibodies
  - Blinatumomab
- **CAR T Therapy**

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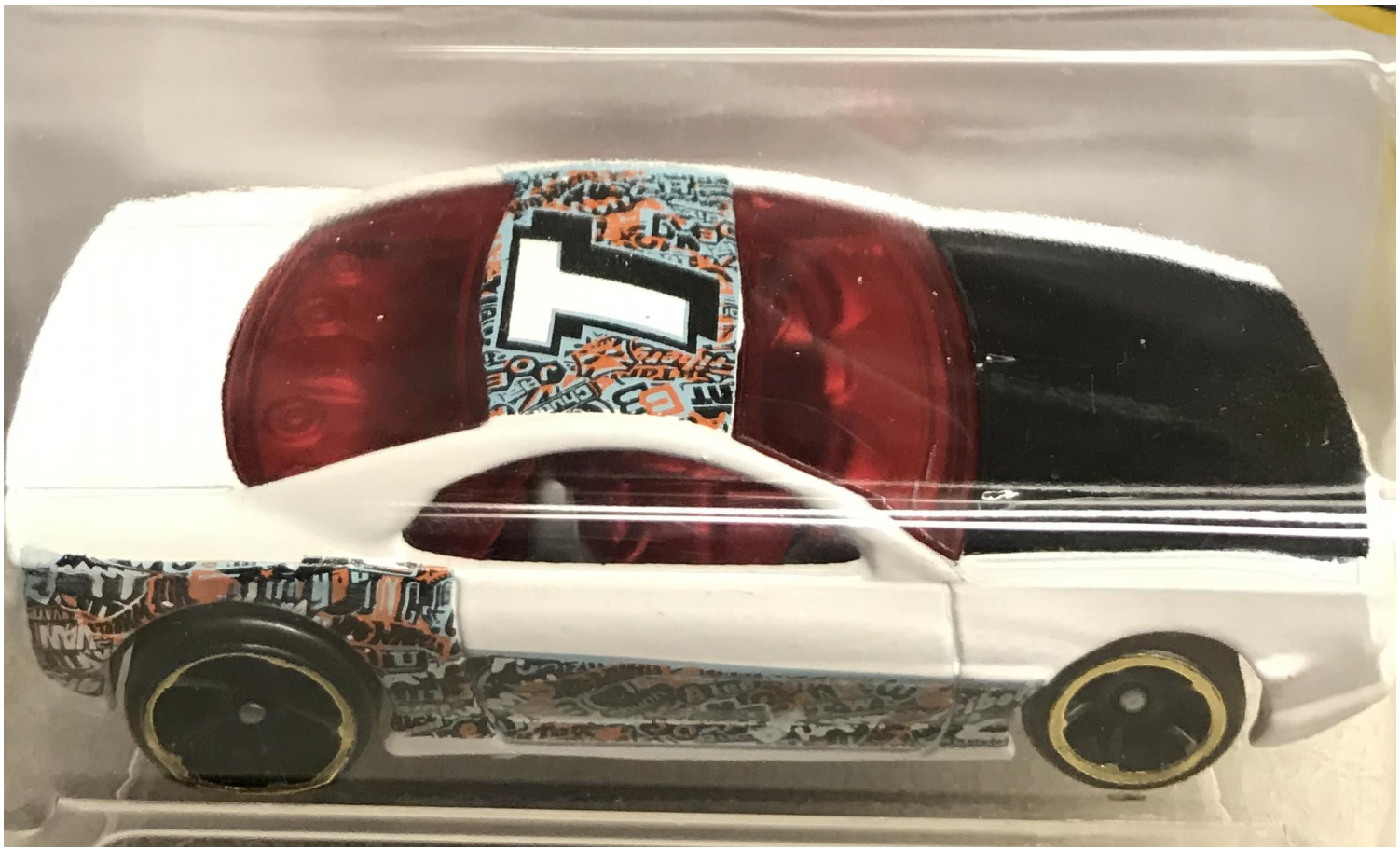
Shifting Gears: What is a CAR T-cell?



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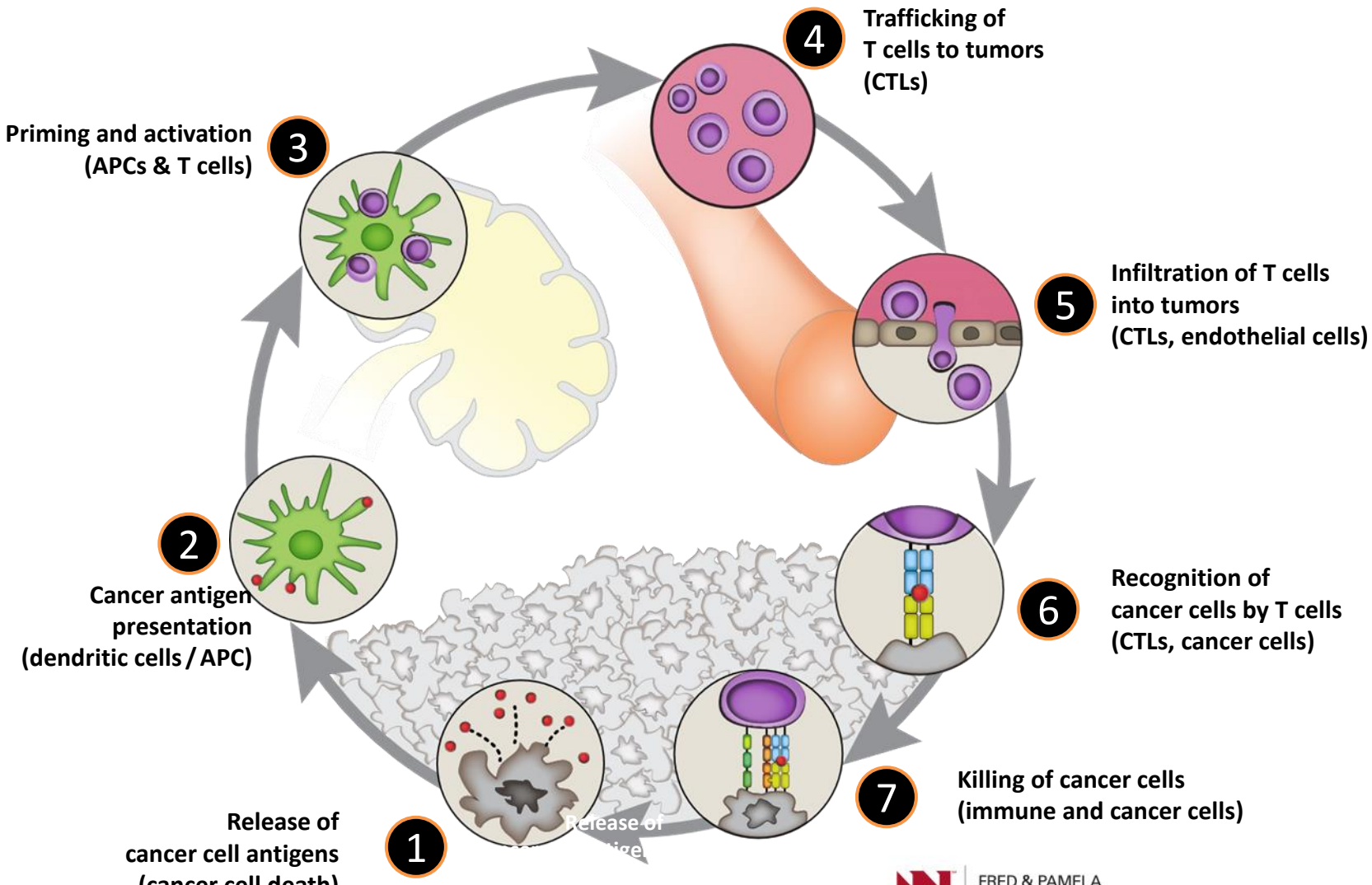
Courtesy of Susan Blumel

Normal T-cell role



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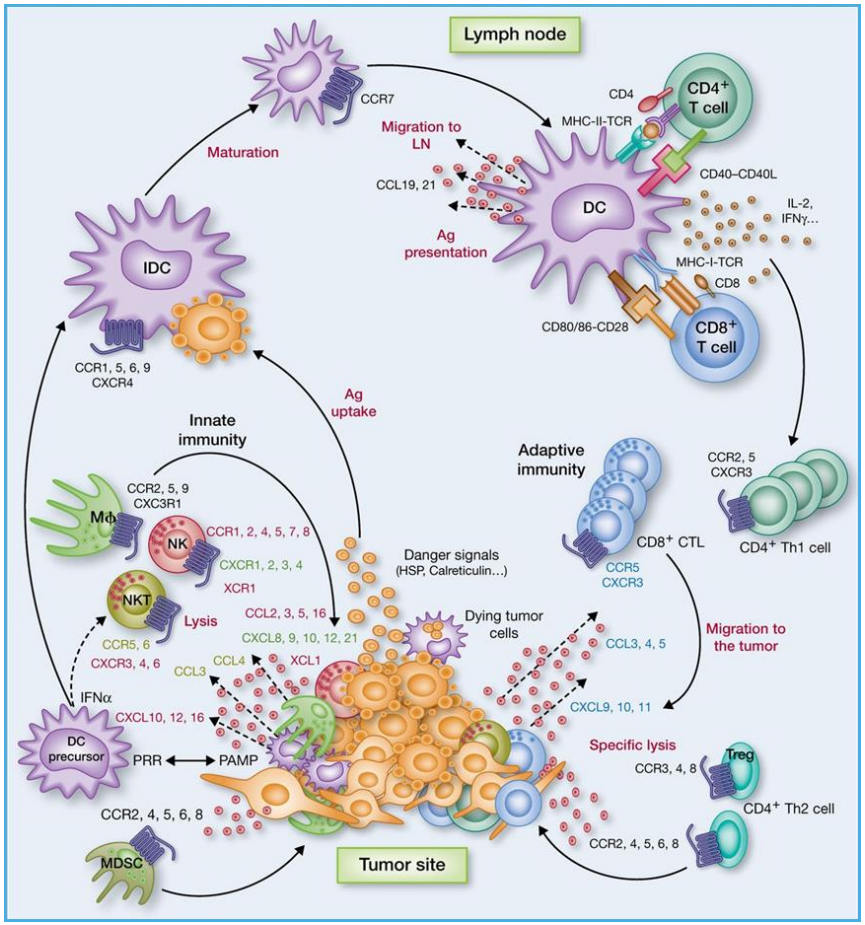
Chen DS, Mellman I. *Immunity.* 2013;39:1-10

T-cells Secrete Cytokines



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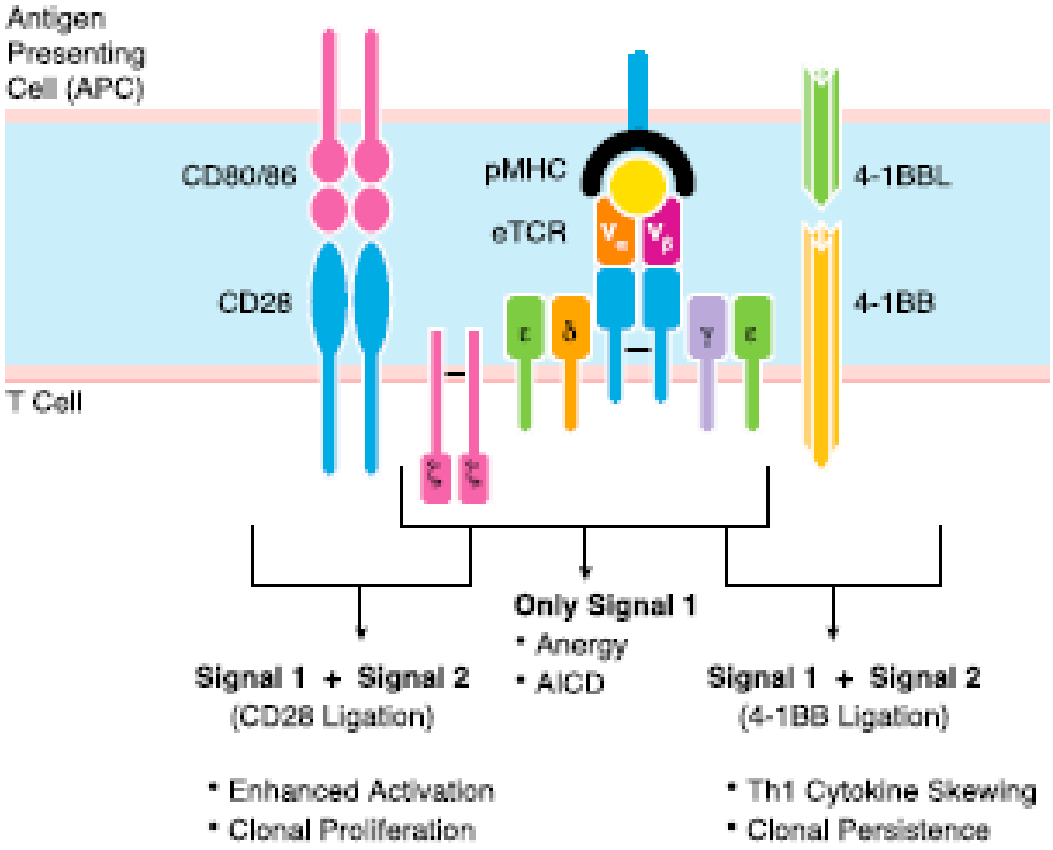
Franciszkiewicz K, et al. *Cancer Res.* 2012;72:6325-6332

T-cell Immunology

CD4+→MHC class 2
CD8+→MHC class 1



AICD= Activation induced cell death

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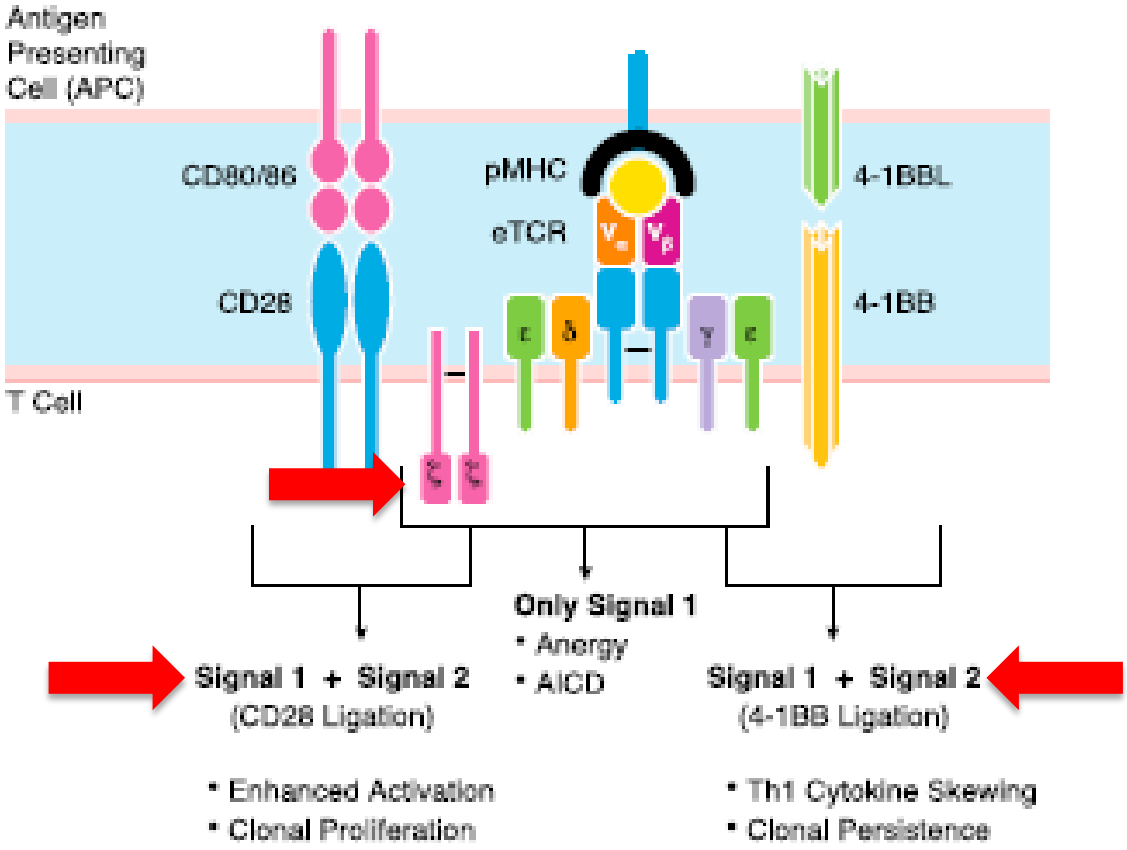
Daniyan et al. Journal of Leukocyte Biology 2016

Building Blocks to CAR-T

CD4+→MHC class 2
CD8+→MHC class 1



AICD= Activation induced cell death

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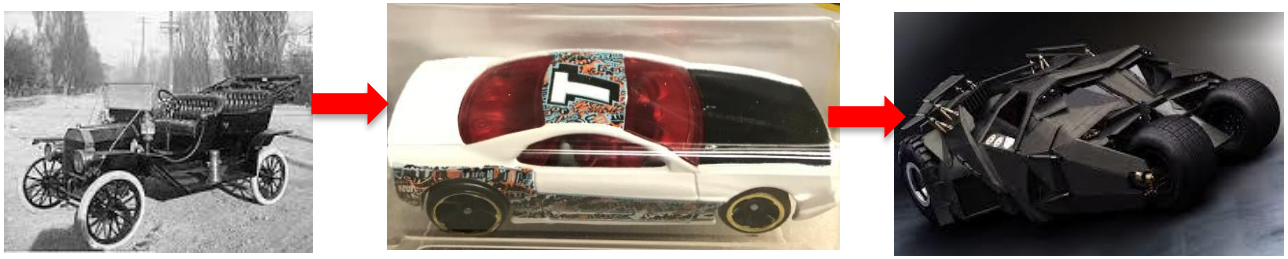
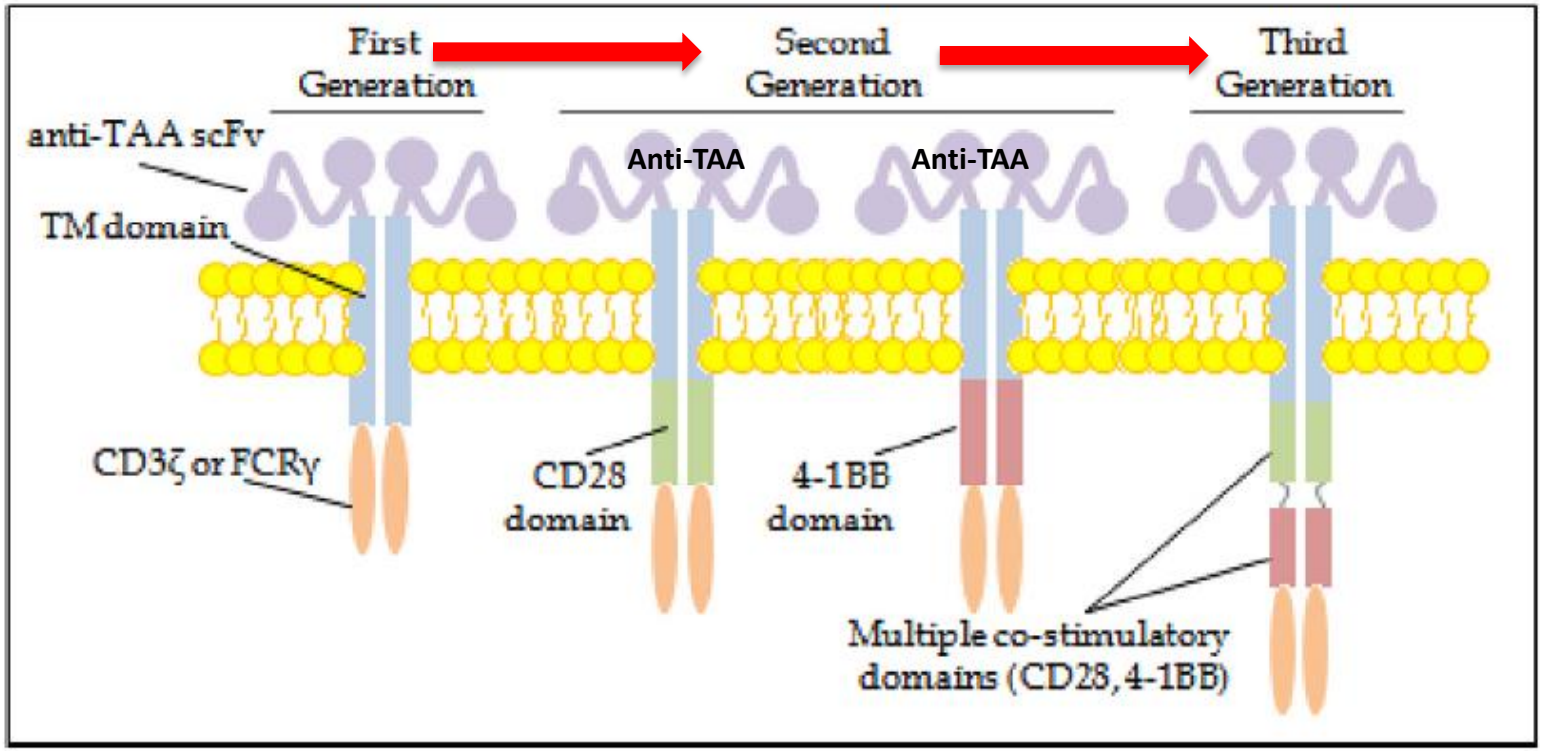
Daniyan et al. Journal of Leukocyte Biology 2016

Evolution of CAR-T





TAA= Tumor associated antigen

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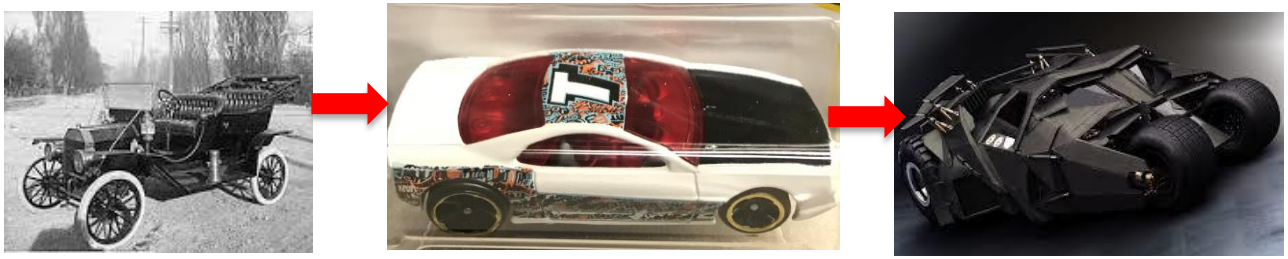
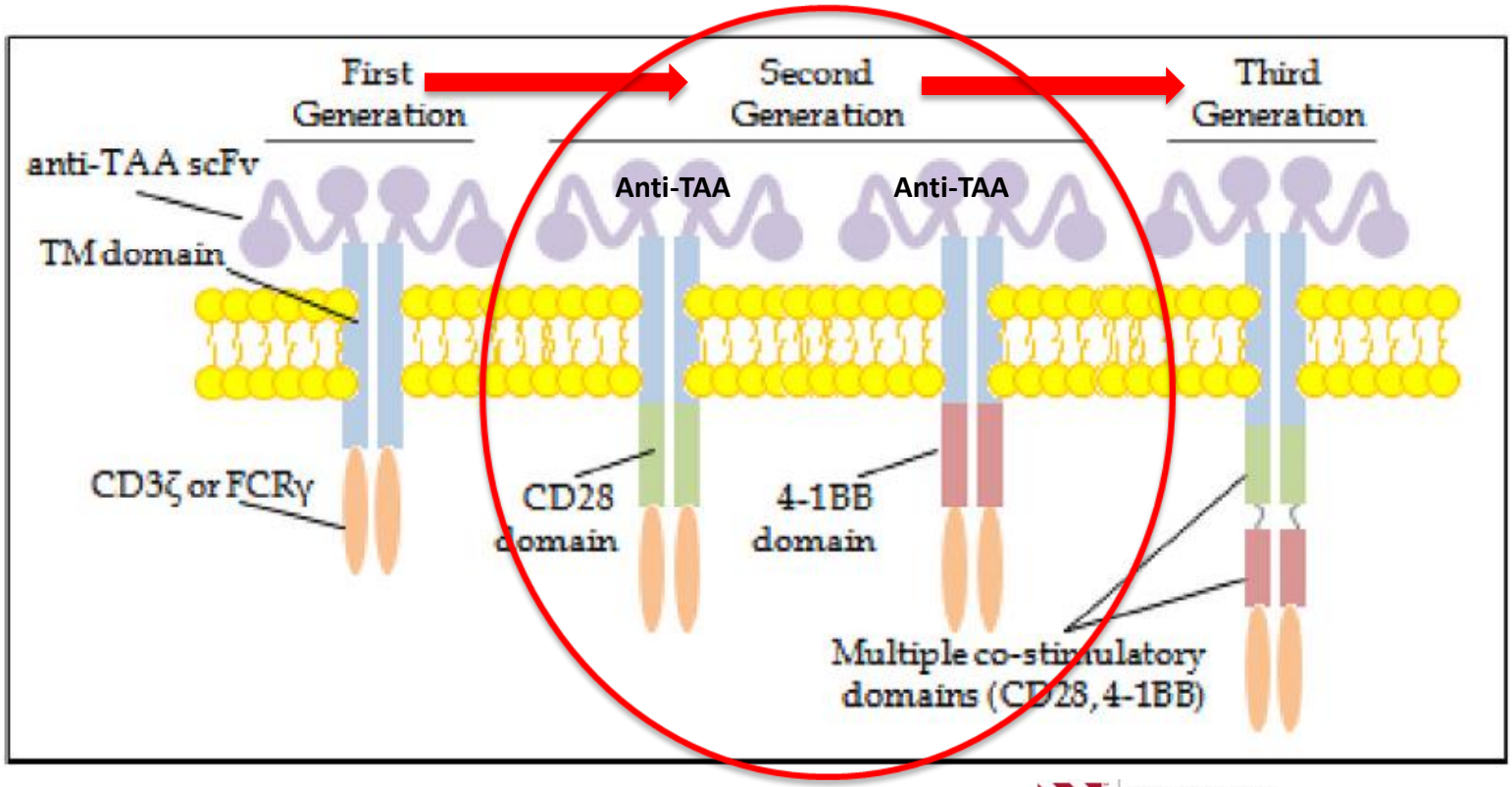
Geyer et al. Cytotherapy 2016

Evolution of CAR-T





TAA= Tumor associated antigen

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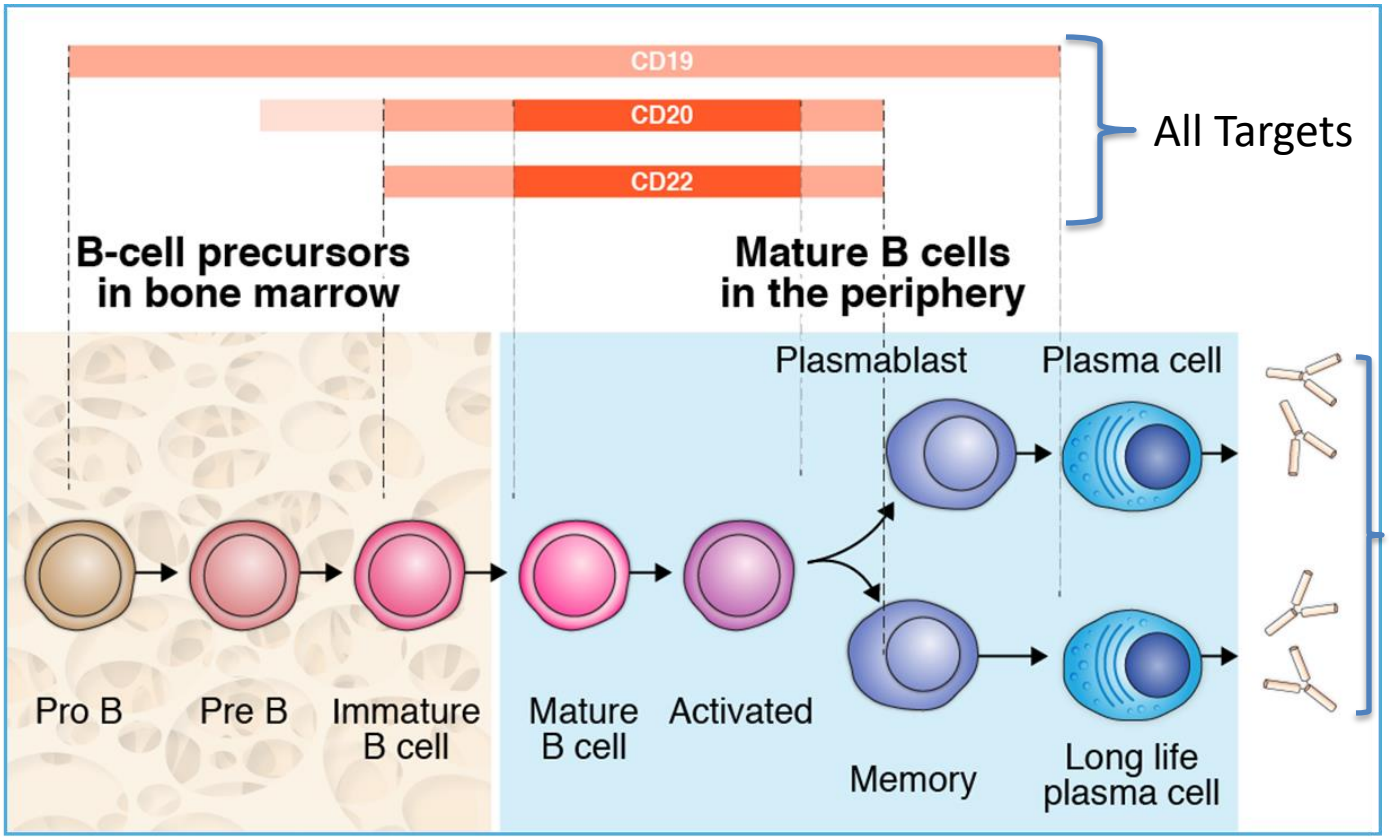
Geyer et al. Cytotherapy 2016

The Target and Why



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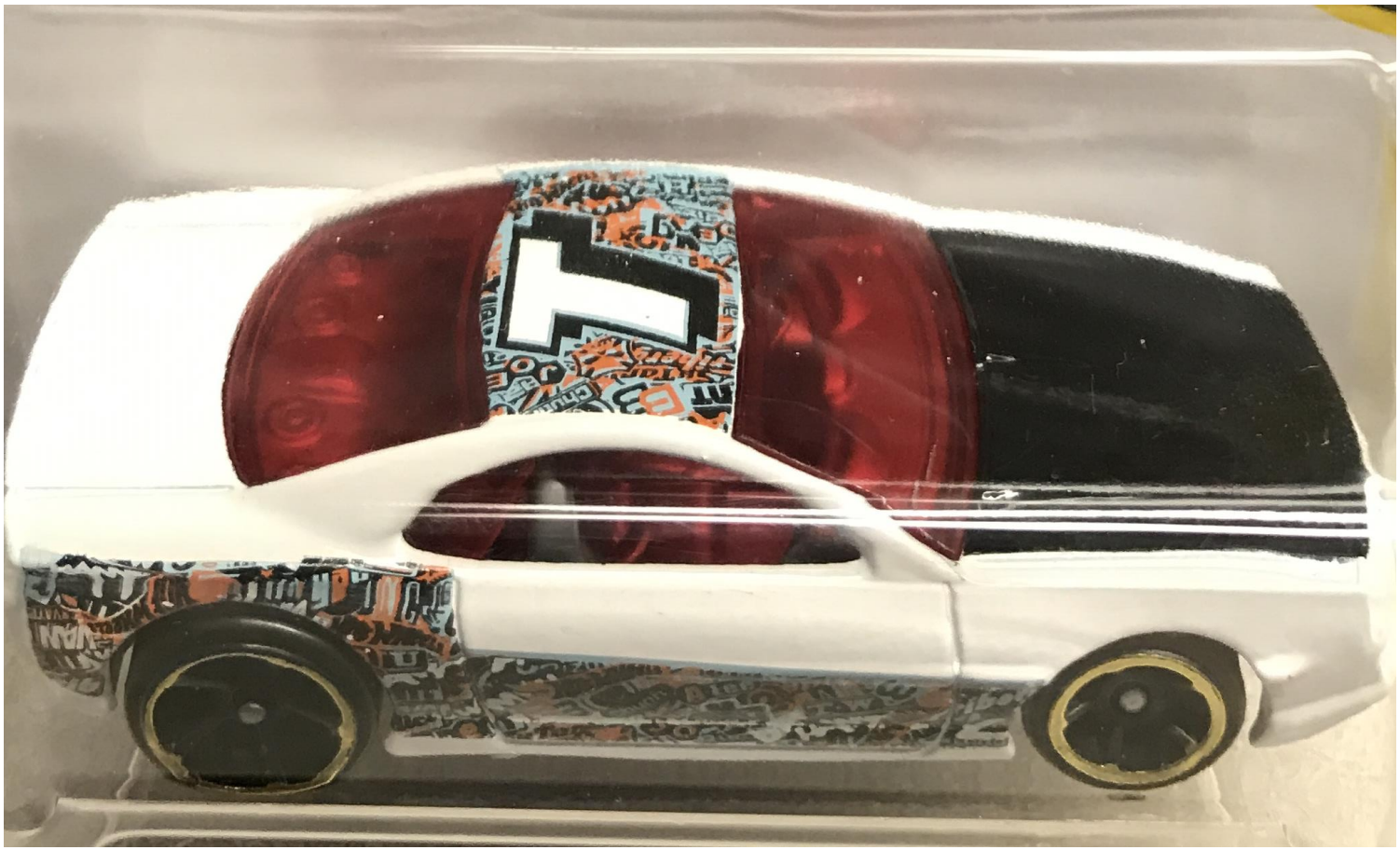
Giraldo WAS. *Rheumatol Clin.* 2012;8(4):201-207.

Manufacturing CAR T-cells



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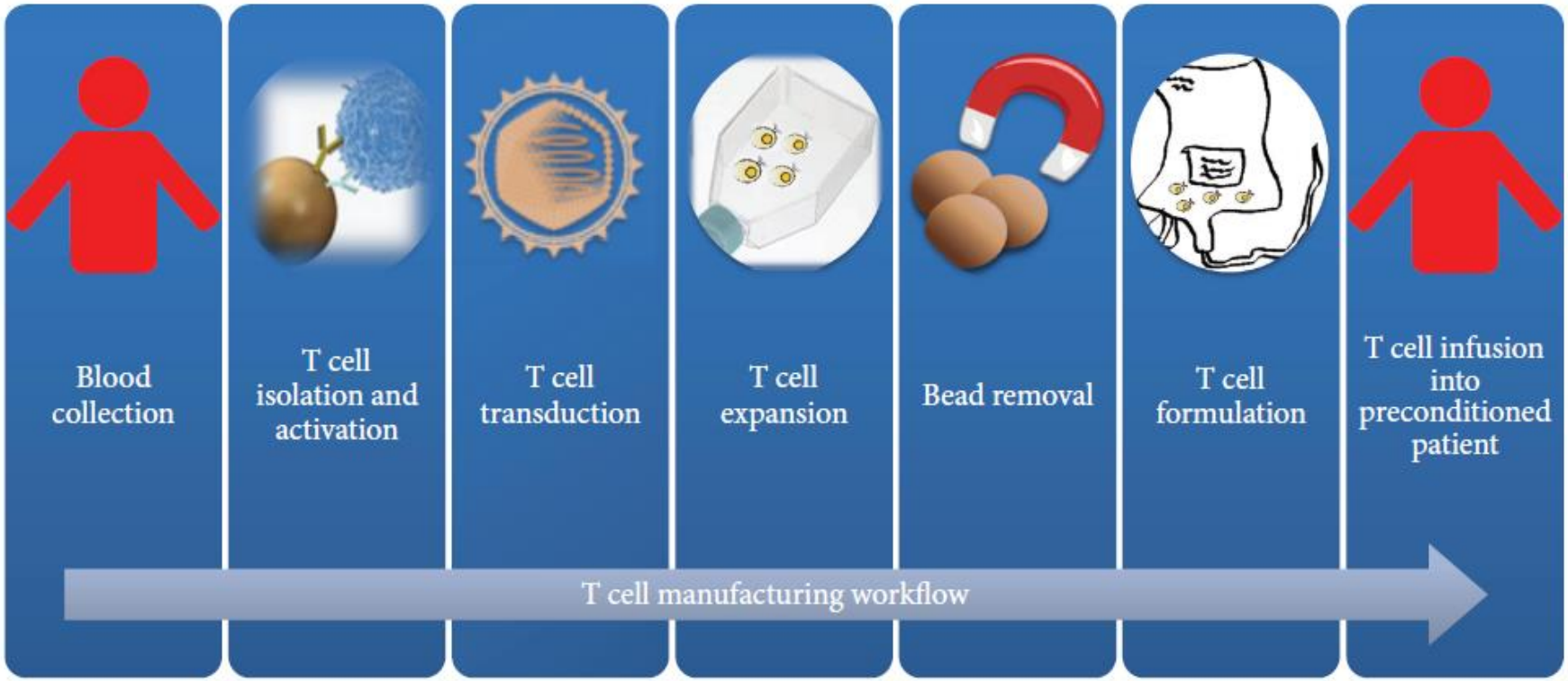
Many Hands



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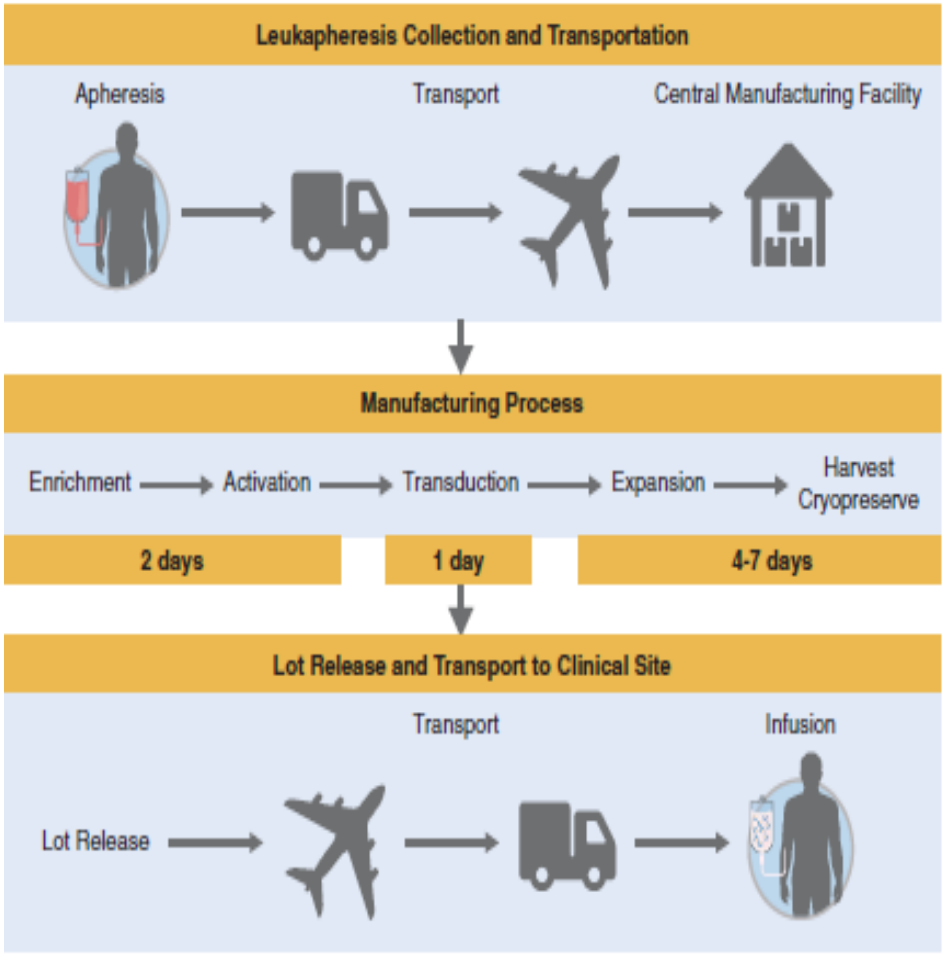
Almasbak el a. J. Immunology Research 2016

Many Days



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Roberts et al. Leukemia & Lymphoma 2017

Patient level Popcorn

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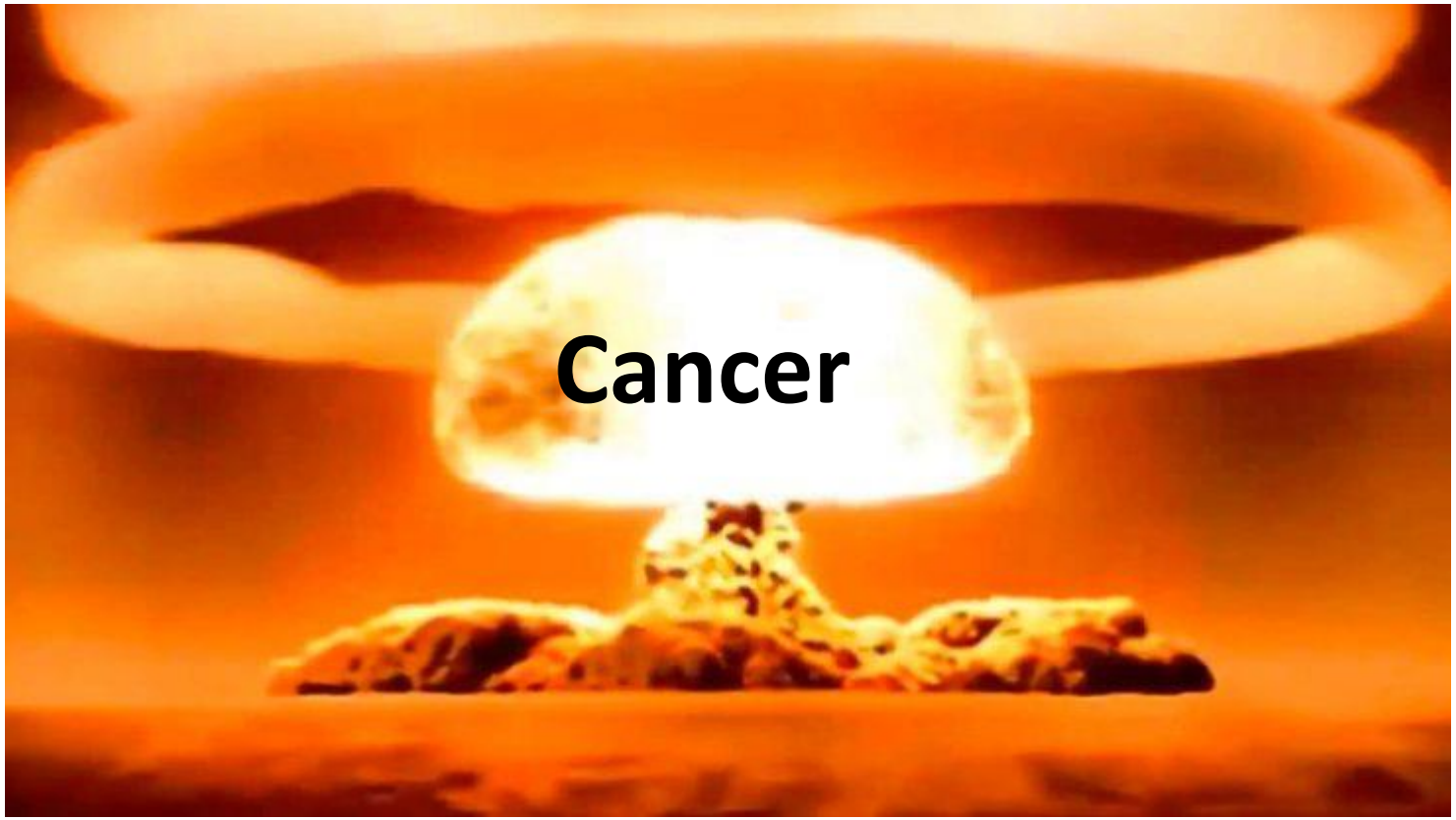
Provider level WMD



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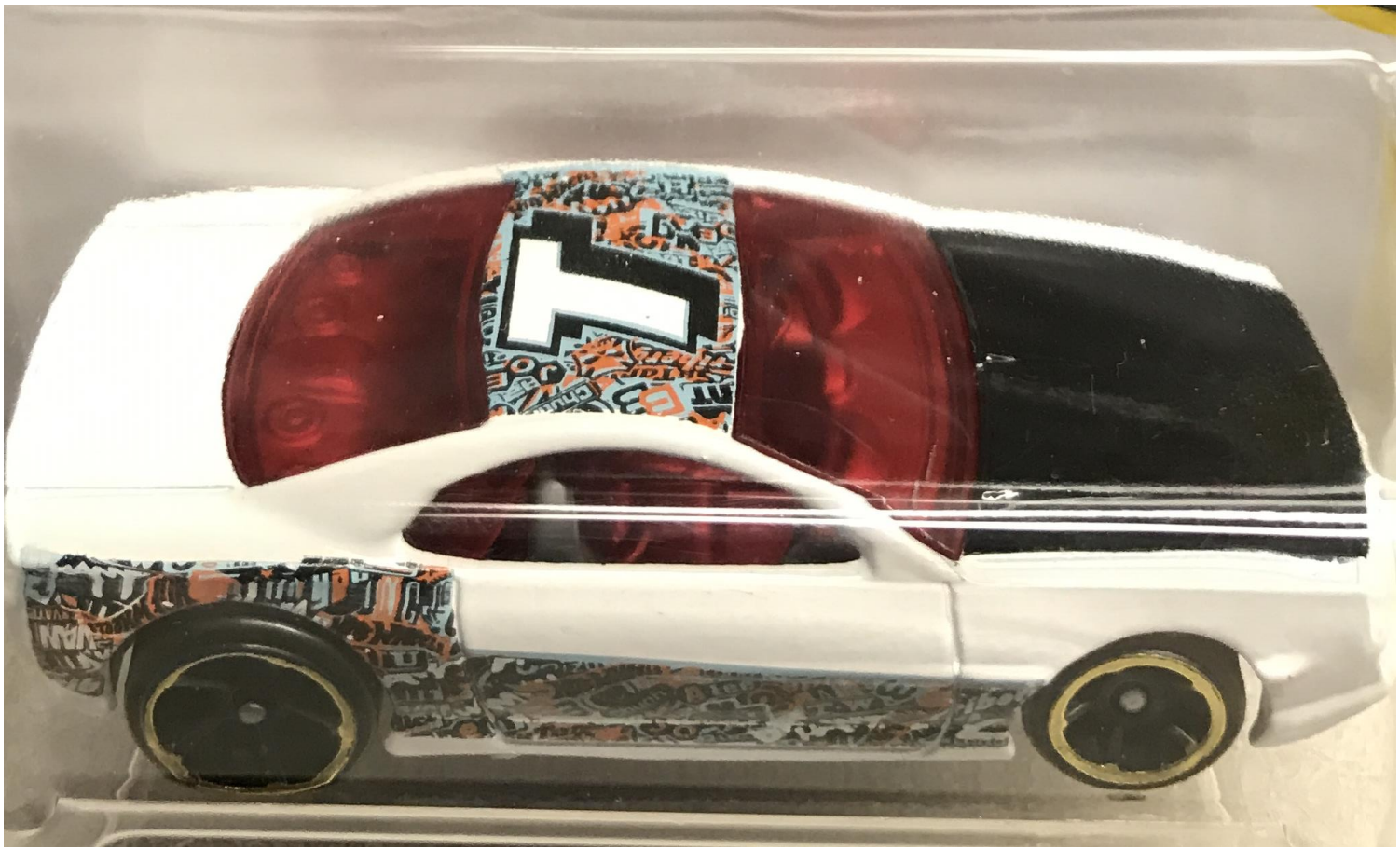
Current Role of CAR-T in Cancer



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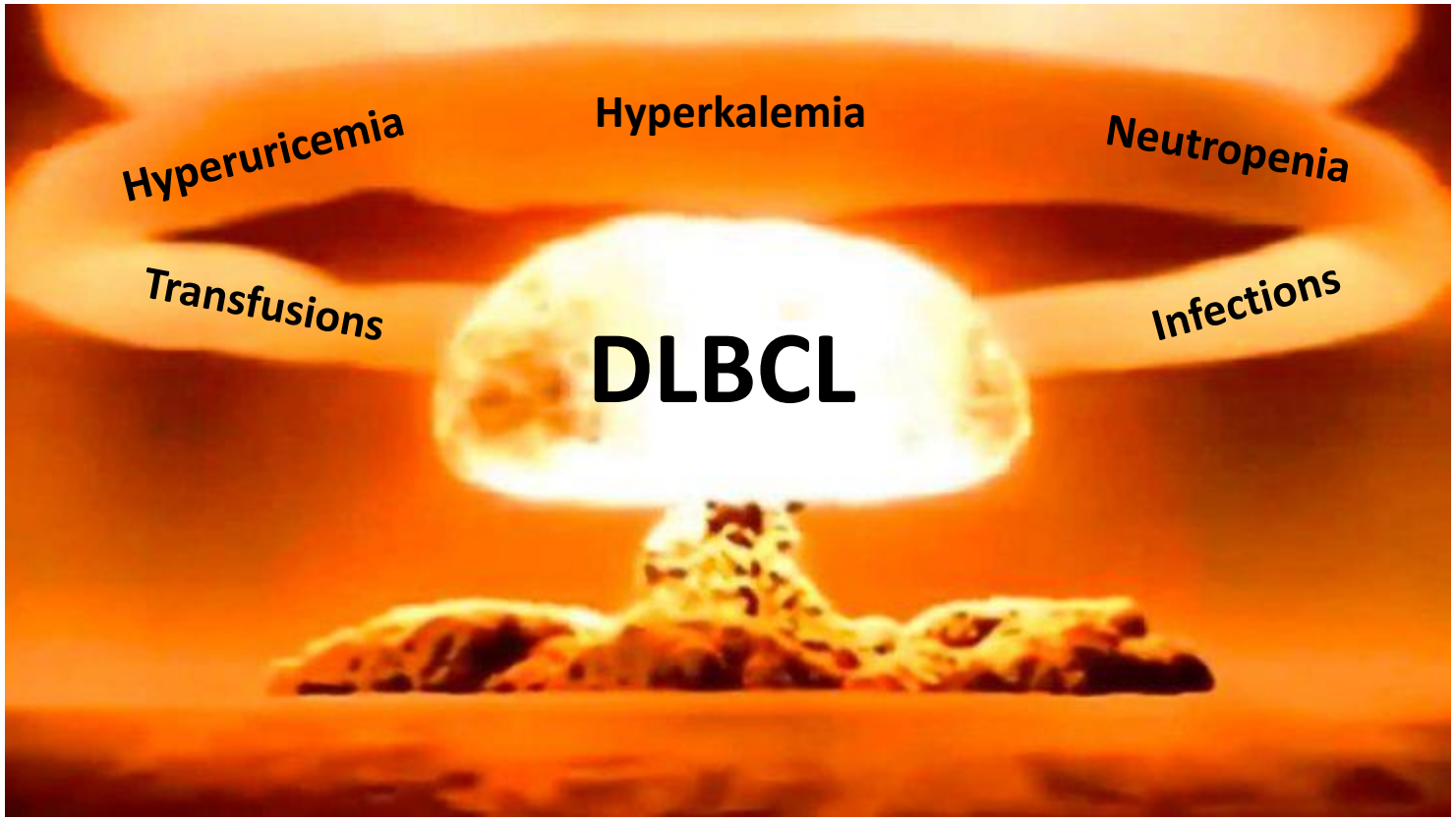
A Short List

Academic Group	Company (Drug)	Co-Stimulatory Domain	Vector Delivery	Indications
UPenn	Novartis (Tisagenlecleucel) (CTL019)	4-1BB	Lentiviral	ALL CLL, DLBCL, FL
Fred Hutchinson	Juno (JCAR017)	4-1BB	Lentiviral	ALL, CLL, various B-cell malignancies
NCI (NIH)	Kite, A Gilead Company (Axicabtagene Ciloleucel) (KTE-C19)	CD28	Retroviral	DLBCL ALL, MCL
MDACC	Ziopharm/Intrexon	CD28 → 4-1BB	Transposon/transposase	B-cell malignancies
Institute Pasteur	Cellectis/Pfizer (UCART19)	4-1BB	Lentiviral	ALL, CLL, AML, MM
Baylor	Bellicum (BPX-401)	MyDBB + CD40	Retroviral	Various
Dartmouth	Cardio3	DAP-10	Retroviral	AML, MDS, MM

WMD

WMD



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CAR T-cell in Rel/Ref DLBCL

CAR-T Product	Viral Vector	Costimulatory
Axi-Cel (KiTE/Gilead)	Gamma-retrovirus	CD28
Tisagenlecleucel (Novartis)	Lentivirus	41BB
Liso-Cel (JUNO/Celgene)	Lentivirus	41BB

Efficacy of Axi-Cel ZUMA-1

	N=101	
Median Follow Up (Months)	27.1	
	ORR	**CR**
Best Overall Response Rate(ORR; %)	**83%**	**58%**
Refractory > /+ 2 lines		**53%**
Relapse within 12 months post Auto txp		**72%**
Double expressers (MYC, BCL2, and BCL6)		**68%**
Duration of response (DOR; Months)	11.8 (4.2 to NE)	
Median Progression Free Survival (PFS; Months)	5.9 (95% CI 3.3 to 15)	

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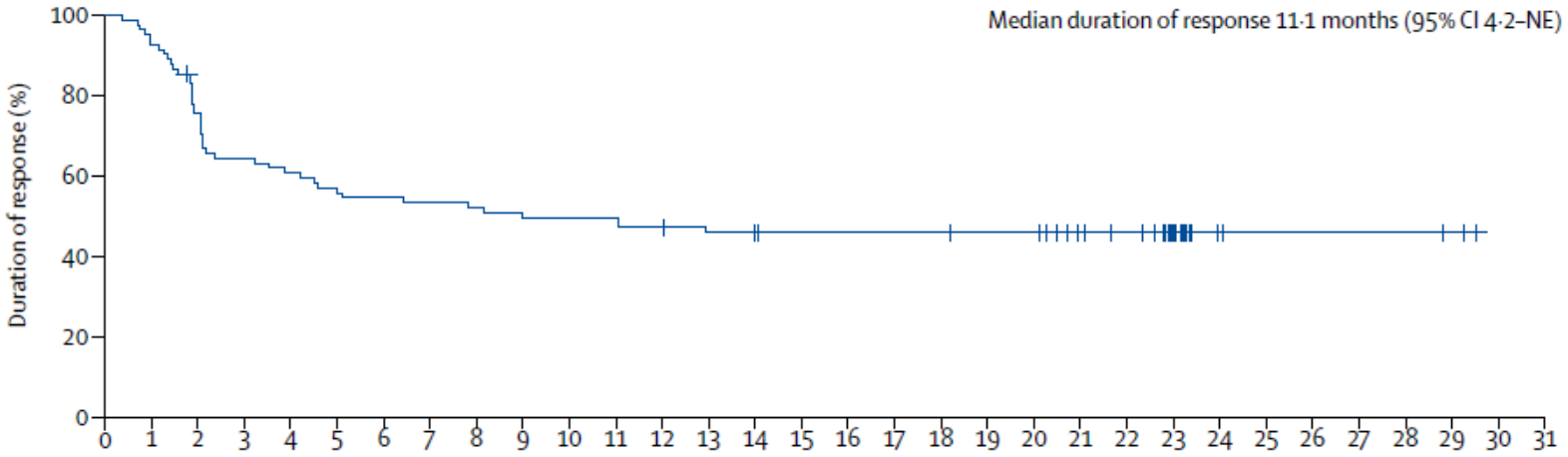
Neelapu S et al. Lancet Oncol 2019

Duration of Response post Axi-cel (ZUMA-1)



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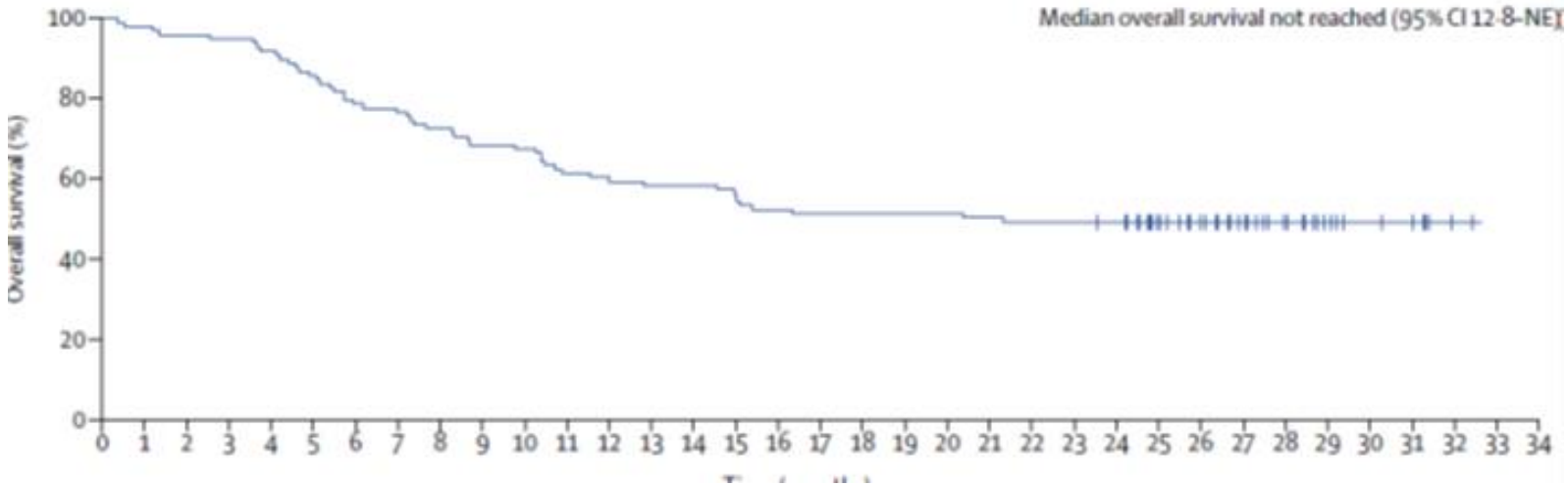
Neelapu S et al. Lancet Oncol 2019

Overall Survival of Axi-Cel (ZUMA-1)



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Neelapu S et al. Lancet Oncol 2019

Efficacy Of Tisagenlecleucel (JULIET)

	N=93	
Median Follow Up (Months)	14.0	
	ORR	**CR**
Best ORR (%)	**52%**	**40%**
12 months post response (%)		
Relapse free survival Relapse free in CR	**65%** **79%**	

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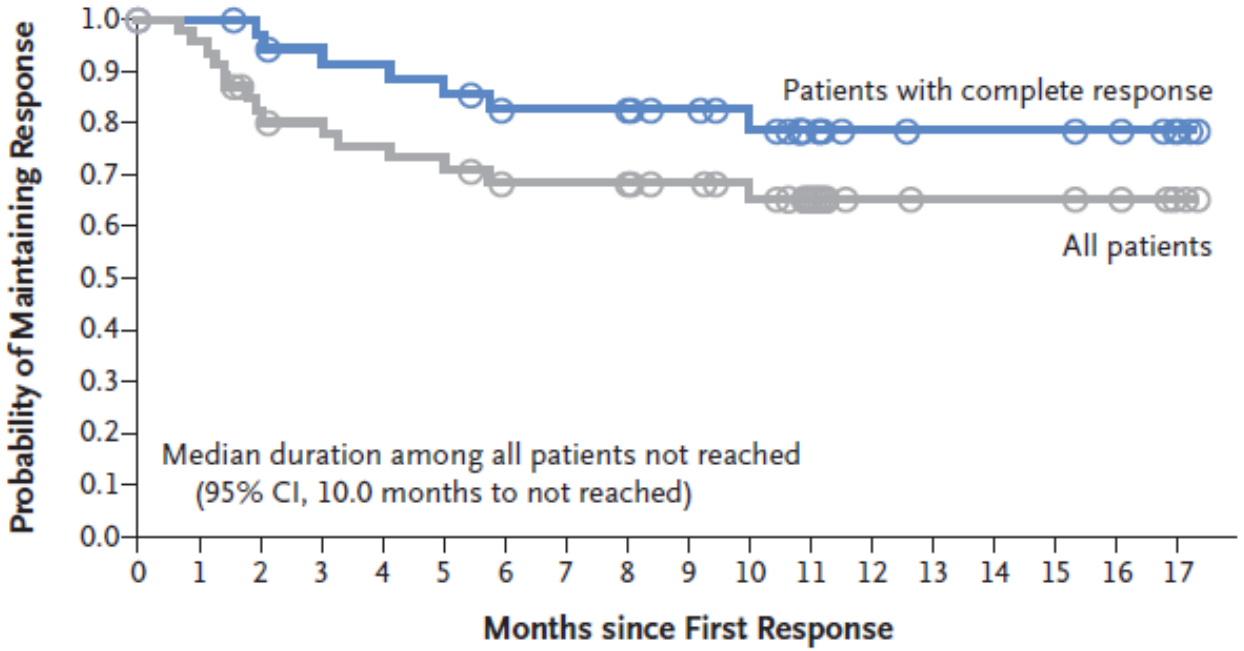
Shuster S et al. NEJM 2019

Duration of Remission Of Tisagenlecleucel (JULIET)



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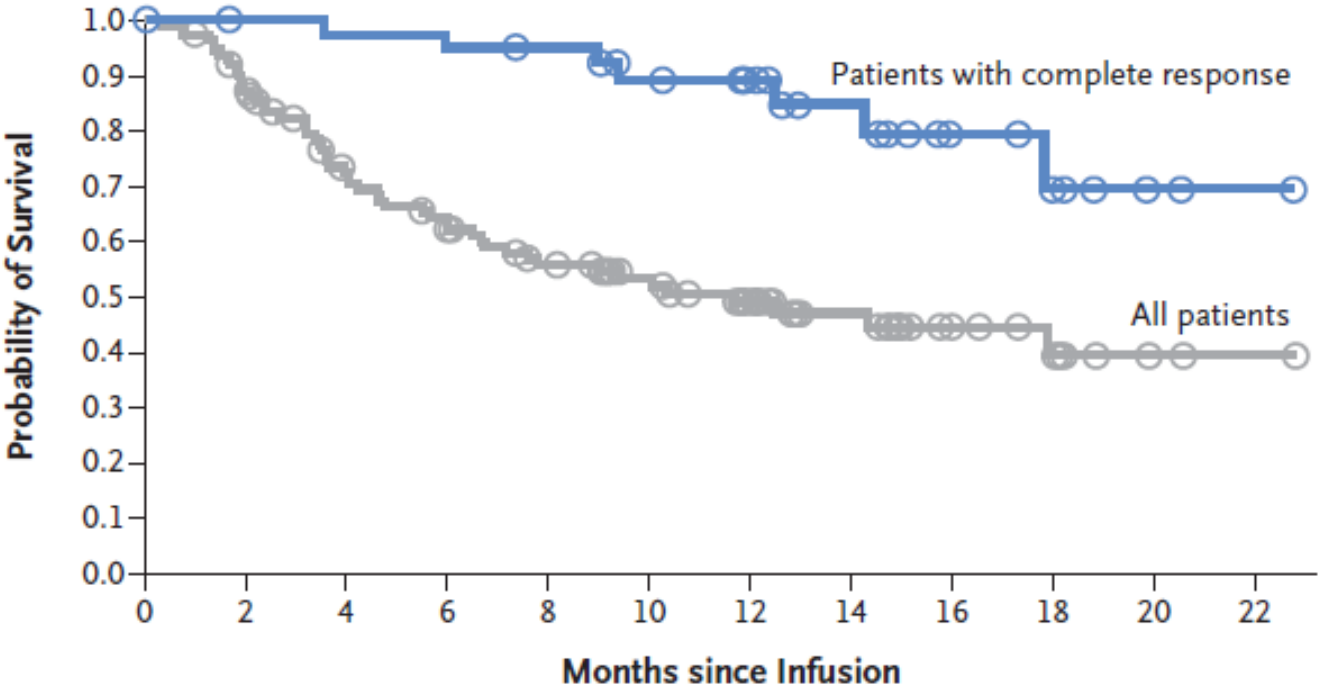
Shuster S et al. NEJM 2019

Overall Survival of Tisagenlecleucel (JULIET)



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Shuster S et al. NEJM 2019

Liso-cel (Not FDA approved)

- Late stage clinical trial (TRANSCEND)
- How is Liso-cel different?
  - Individually formulated CD4 and CD8 suspensions through lentiviral transduction
  - Low ALC requirement
  - Flat dosing
    - 1:1 ratio of CD4:CD8
  - 41BB costimulatory

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Abramson J et al. EHA 2018

TRANSCEND: CORE

- DLBCL-NOS
- Transformed FL
- High grade B-cell lymphoma (DH/TH)

- ECOG 0-1
- No ALC minimum

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Abramson J et al. EHA 2018

TRANSCEND Cohort/Dose

Core group

- DLBCL-NOS
- Transformed FL
- High grade B-cell lymphoma (DH/TH)
- ECOG 0-1
- No ALC minimum

Dosing Levels

5 X 10^7 cells single dose (DL1S)

5 X 10^7 cells double dose (DL1D)

1 X 10^8 cells single dose (DL2S)

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Abramson J et al. EHA 2018

TRANSCEND
Pivotal Cohort

FOCUS ON:

Core + DL2S
Outcomes, unknown results of accrued
PIVOTAL cohort

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Abramson J et al. EHA 2018

Liso-Cel Efficacy (Transcend)

Core & DLS2	N=37
Best ORR	80%
Best CR	55%
ORR @ 6 months	50%
CR @ 6 months	50%

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Abramson J et al. EHA 2018

Axi-cel Post Approval Gloves On Vs Gloves Off

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Excluded From ZUMA-1

	N~242
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)

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Nastoupil L et al. ASH 2018

Let's Box

		 N (%)	 N (%)
Median follow up, months		3.9	15.4
Day 30 ORR, N (%)	238	191 (80)	N/A
Day 30 CR, N (%)		113 (47)	N/A
Best ORR at Day 90, N (%)	248[a]	201 (81)	89 (82)
Best CR at Day 90, N (%)		142 (57)	63 (58)

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Nastoupil L et al. ASH 2018

Too Sick To Fight?

Variables	CR @ 3 month N (%)	p value
Age <60 vs. ≥60	37 (51) vs. 52 (64)	0.11
DLBCL vs. PMBCL vs. TFL	59 (58) vs. 4 (40) vs. 26 (63)	0.41
COO GCB vs. ABC	50 (62) vs. 30 (53)	0.29
DHL/THL vs. Not	19 (59) vs. 65 (57)	0.77
IPI 0-2 vs. 3-5	45 (58) vs. 43 (58)	0.96
Bridging therapy Yes vs. No	40 (53) vs. 49 (64)	0.17
Tocilizumab Yes vs. No	51 (58) vs. 38 (59)	0.86
Steroids Yes vs. No	49 (58) vs. 40 (61)	0.71
ICU Admission Yes vs. No	26 (52) vs. 63 (61)	0.28

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Nastoupil L et al. ASH 2018

Fittest Fighters?

Variables	CR @ 3 month N (%)	p value
Female vs. male	39 (72) vs. 50 (51)	0.009
ECOG 0-1 vs. ≥ 2	82 (62) vs. 7 (35)	0.024
Relapsed vs. primary refractory/refractory	27 (79) vs. 24 (47)/38 (56)	0.011
Non-bulky vs. bulky (≥ 10cm)	76 (62) vs. 13 (42)	0.040
Met eligibility for ZUMA-1 vs. not	62 (65) vs. 27 (47)	0.037

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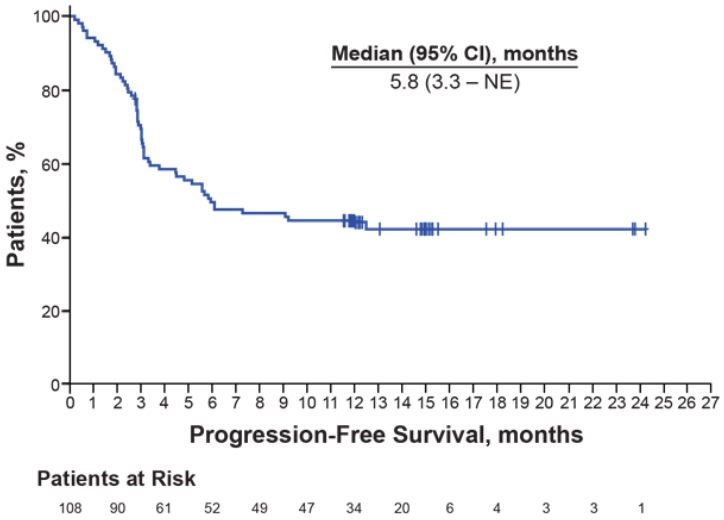
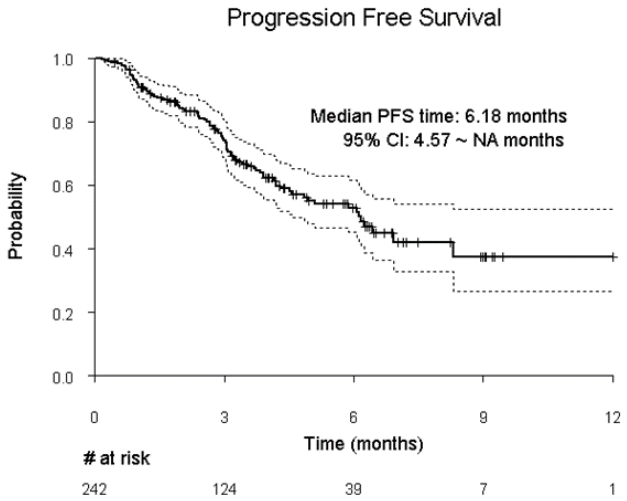
Nastoupil L et al. ASH 2018

Should We Keep Fighting?





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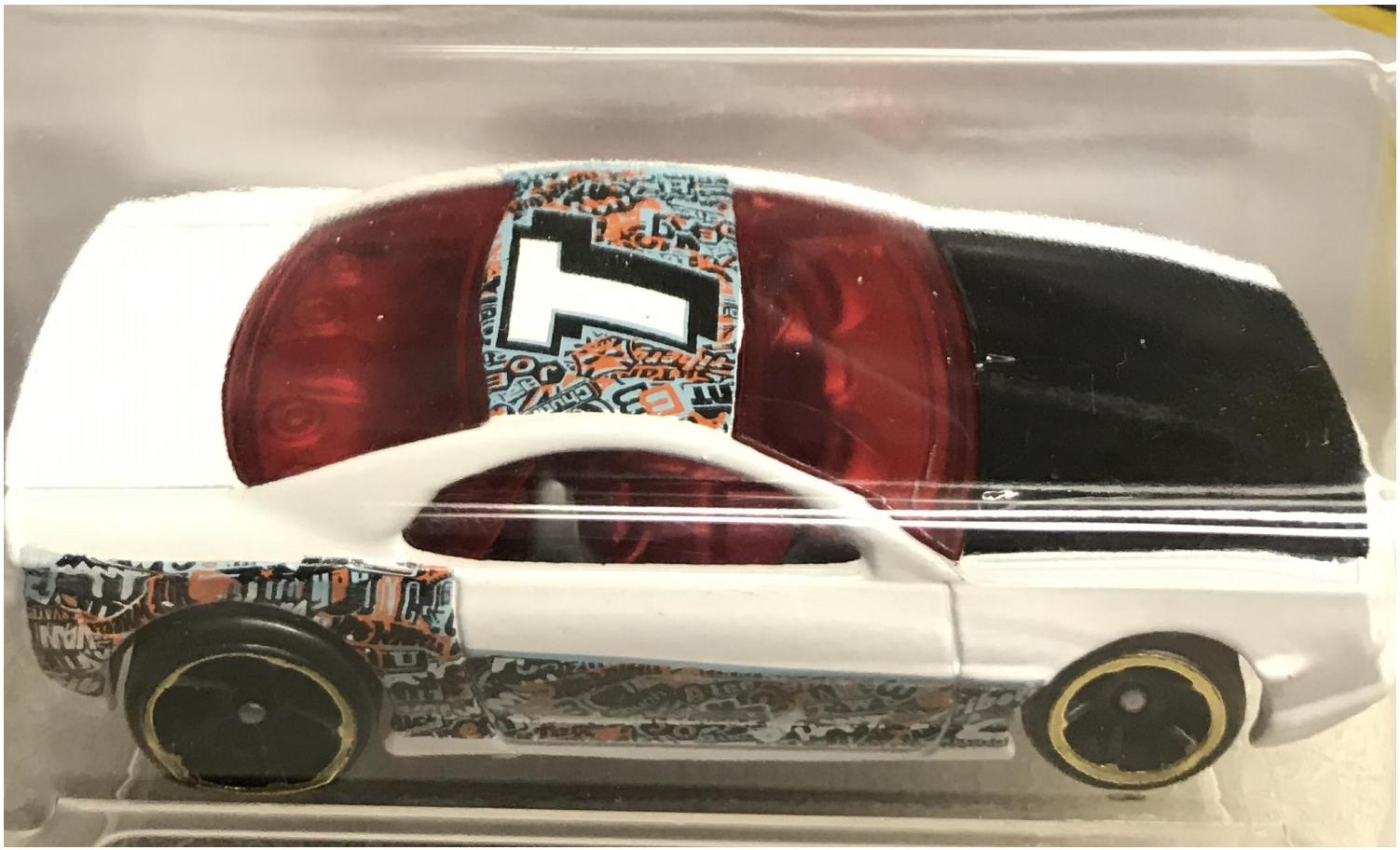
Nastoupil L et al ASH 2018; Neelapu et a. Lancet Oncol 2019

Who Should Get CAR-T?



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The Right Disease And Right Situation

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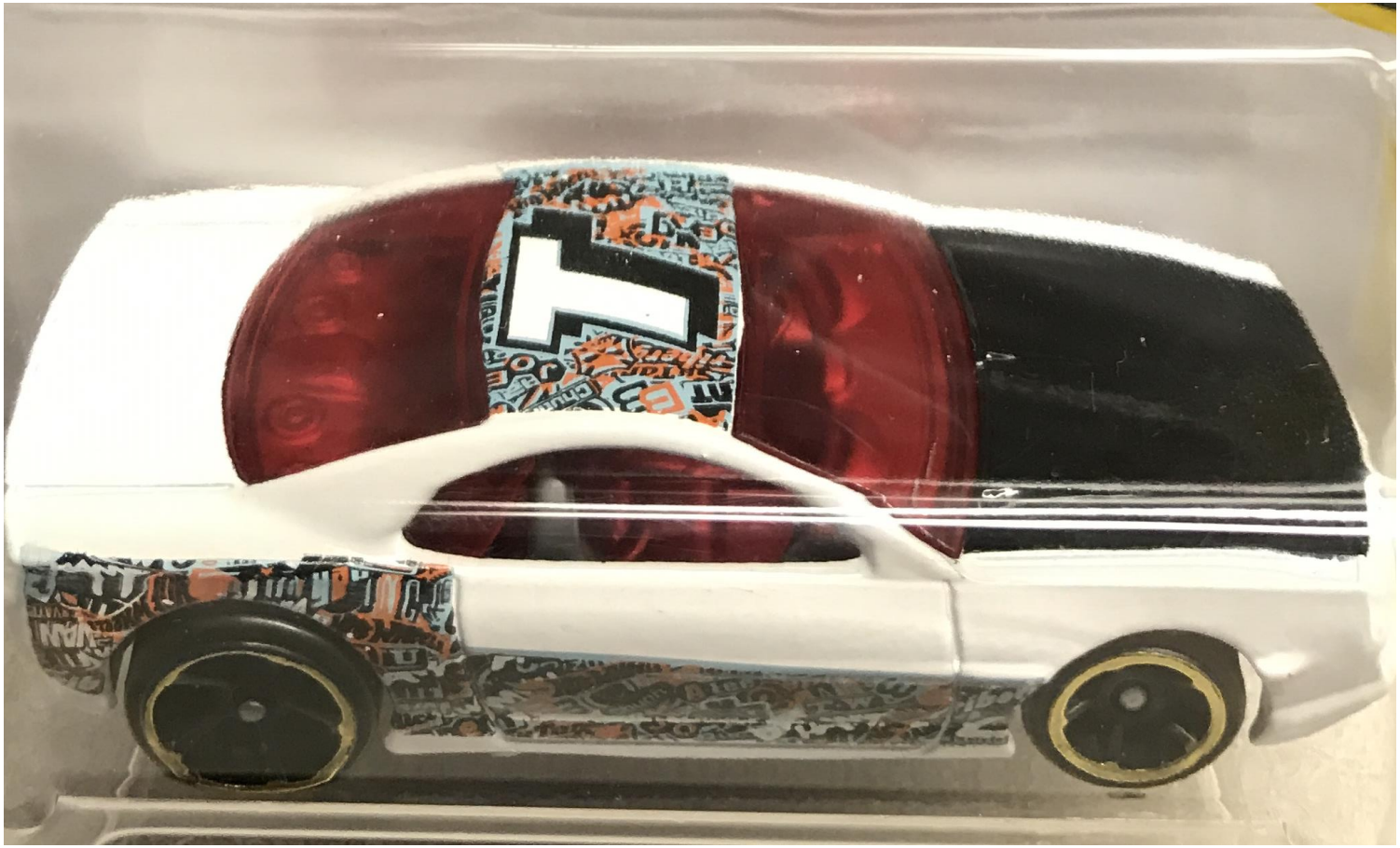
Who Can Weather the Fall Out?

Baseline Tests

1. Transthoracic echocardiogram
2. Pulse oximetry
3. CBC, CMP, and DIC panel
4. Lactate dehydrogenase (LDH)
5. Pre-CART disease burden assessment

Selection of a Specific CAR-T



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Courtesy of Susan Blumel

Finding a CAR T Site ASBMT→ASTCT

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Within Our CAR T Site

Case Manager Process and Checklist:

- Binder specific to each product and diagnosis
- Overall Checklist
- Details of each stage of process with screen shots:
  - Eligibility/Consult
  - Evaluation
  - Insurance
  - Collection
  - Enrollment, Ordering, & PO process
  - Chemotherapy
  - Infusion
  - Discharge
  - Long-Term Follow-up

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Courtesy of Kim Schmit-Pokorny

Before the CAR T

- Risk Evaluation and Mitigation Strategy (REMS) training
- CAR T education…education….education
- Tocilizumab supply process and documentation
- Policies for each product (includes Foundation for the Accreditation of Cellular Therapy (FACT) requirements)
  - Includes Wallet Card process and tocilizumab process
- Patient Consents for each product
- Treatment Plans for each product and diagnosis
- Pharmacy iVents
  - Patient specific notes used by pharmacists to communicate information
    - Dose and location of rescue agents
    - Other pertinent patient and product information
  - Crosses inpatient and outpatient care areas
  - Visible to all pharmacists viewing the EMR
- Formal Patient/Caregiver Education
  - Handouts, web-based, 1:1
  - Documentation via Template with teaching points
- On-Call/Triage
  - CAR T trained staff
  - Who to call and when to call
- IT

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Courtesy of Kim Schmit-Pokorny

Our Patient Tracker

Date of First Contact	Place on Waitlist	Patient Name	Referred By	Patient City of Residence	Short Disease History	MR Number	Investigator	Case Manager or Research Coordinator	Date of Consult
1/4/2018	1	Test Patient	John Doe	Anywhere, USA	DLBC	123456	Bierman	Tawny	1/4/2018

IRB 736-15 JCAR017 Juno Transcend	IRB 611-17 JCAR017 Celgene Platform	xxx-18 JCAR017 Celgene Transfor	IRB 400-17 Axi-Cel Kite Zuma-9	Study Insurance Notes
			Only if commercial product does not meet spec	

Commercial Kite Yescarta	Commercial Novartis Kymri	Date of Referral (HSCT form)	Payor Source	Date Pre Determination Received	Date Pre Auth - Approved	Date Single Case Agreement Approved	Insurance Comments
Yes		1/22/2018	BCBS	N/A	3/7/2018	3/1/2018	Pre-Certification denied: not med neces, peer to peer by Dr. Bierman

Date Enrolled Yescarta & Kite ID#	PO & Invoice	Apheresis Date	Chemo Start Date	Admission Date	Infusion Date	Comments	Toxicities
		3/22/2018	4/13/2018	4/17/2018	4/18/2018		

Blue = Demographic Information
Green = Study Information
Yellow = Insurance Information
Gold = Treatment Plan Dates

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After Selection of a CAR-T construct

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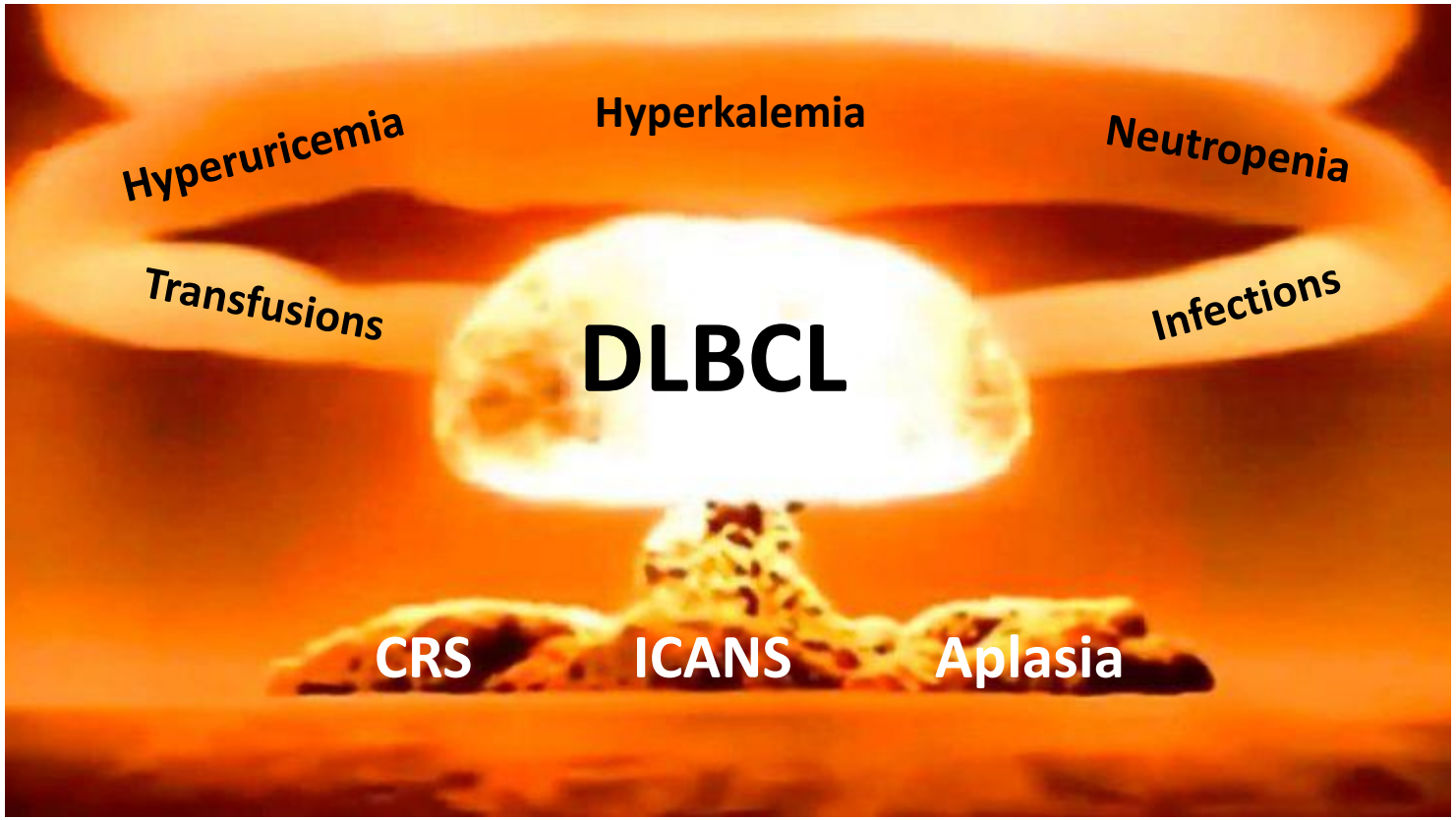
Bridging Therapy

- Insurance
- Need to bridge?
  - Yes or No
- If Yes
  - Prior treatments (R-CHOP; ICE)
- Cell of origin (Hans)
  - GCB—Bendamustine or Gemcitabine
  - Non-GCB—Ibrutinib or Lenalidomide
- Late bridging
  - Steroids
  - Low dose oral Cytoxan, etoposide, prednisone
  - BOOM-BOOM (XRT)

Lymphodepletion

- Cy/Flu vs Benda vs None
  - Known the dose
  - Know when not to use (Tisagenlecleucel)
- Renal
  - Know the CrCl and how you will handle the fludarabine dosing
- Timing
  - Know the current EGOC & volume of disease
  - Know the product is ready
  - Know you have beds

WMD



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CRS = Cytokine Release Syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome

"Old" CRS Grading

6

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 4.03 [11]	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate)	Life-threatening consequences; pressor or ventilatory support indicated
CTCAE version 5.0 [13]	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention needed
Lee criteria [14]	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO_2 OR • Hypotension responsive to i.v. fluids or low dose of one vasopressor OR • Grade 2 organ toxicity*	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥40% FiO_2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity* or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity* (excluding transaminitis)
Penn criteria [17]	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for i.v. therapies (not including fluid resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
MSKCC criteria [16]	Mild symptoms requiring observation or supportive care only (eg, antipyretics, antiemetics, pain medication)	Hypotension requiring any vasopressors <24 h Hypoxia or dyspnea requiring supplemental oxygen <40%	Hypotension requiring any vasopressors ≥24 h Hypoxia or dyspnea requiring supplemental oxygen ≥40%	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation
CARTOX criteria [12]	Temperature ≥38°C Grade 1 organ toxicity†	Hypotension responds to IV fluids or low-dose vasopressor Hypoxia requiring FiO_2 <40% Grade 2 organ toxicity†	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥40% Grade 3 organ toxicity† or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity† except grade 4 transaminitis

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Lee D et al. BBMT 2018

"Old Neurotoxicity Grading

Grading System	Adverse Event Term/	Neurotoxicity Domain	Grade 1	Grade 2	Grade 3
Grade 4 CTCAE v5.0 [13],* Life-threatening consequences; urgent intervention indicated		Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL
	Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New-onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences
	Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly	
	Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	
	Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	
	Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Life-threatening consequences; coma; urgent intervention indicated	Depressed level of	consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse
	Cerebral edema			New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated
CARTOX criteria [12]	Neurologic Assessment Score (CARTOX-10)	7-9 (mild impairment)	3-6 (moderate impairment)	0-2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
	Elevated ICP	N/A	N/A	Stage 1-2 papilledema† or CSF opening pressure <20 mmHg	Stage 3-5 papilledema†, or CSF opening pressure ≥20 mmHg, or cerebral edema
	Seizures or motor weakness	N/A	N/A	Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness

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Lee D et al. BBMT 2018

Reported Toxicity of Axi-Cel (ZUMA-1)

	CRS	NT
All Grades	93%	64%
Grade ≥ 3	11%	32%
Median Time to onset (range) in days	2 (1-12)	5 (1-17)
Median Time to Resolution	8 days	17 days
Tocilizumab Usage	43%	
Dexamethasone Usage	27%	

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Neelapu S et al. NEJM 2018; Neelapu S et al. Lancet Oncol 2019; NT=CTAE 4.03

Reported Toxicity of Tisagenlecleucel (JULIET)

	CRS*	NT
All Grades	58%	21%
Grade ≥ 3	22%	12%
Median Time to onset (range) in days	3	6
Median Time to Resolution	7	14
Tocilizumab Usage	14%	
Dexamethasone Usage	10%	

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Shuster S et al. NEJM 2019 *CRS =UPENN criteria; NT=CTAE 4.03

Reported Toxicity of Liso-Cel (TRANSCEND)

Core & DL2S or Full	CRS	NT
All Grades	30%	24%
Grade ≥ 3	0%	8%
Median Time to onset (range) in days	5	10
Median Time to Resolution	NR	NR
Tocilizumab Usage (FULL)	17%	
Dexamethasone Usage	21%	

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Abramson J et al. EHA 2018; CRS per Lee D et al; NT=CTAE 4.03; NR=Not reported

" New" CRS Grading:

Starts with Fever

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

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Lee D et al. BBMT 2018

ICANS Grading: Starts with ICE

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS = Immune effector cell-associated neurotoxicity syndrome

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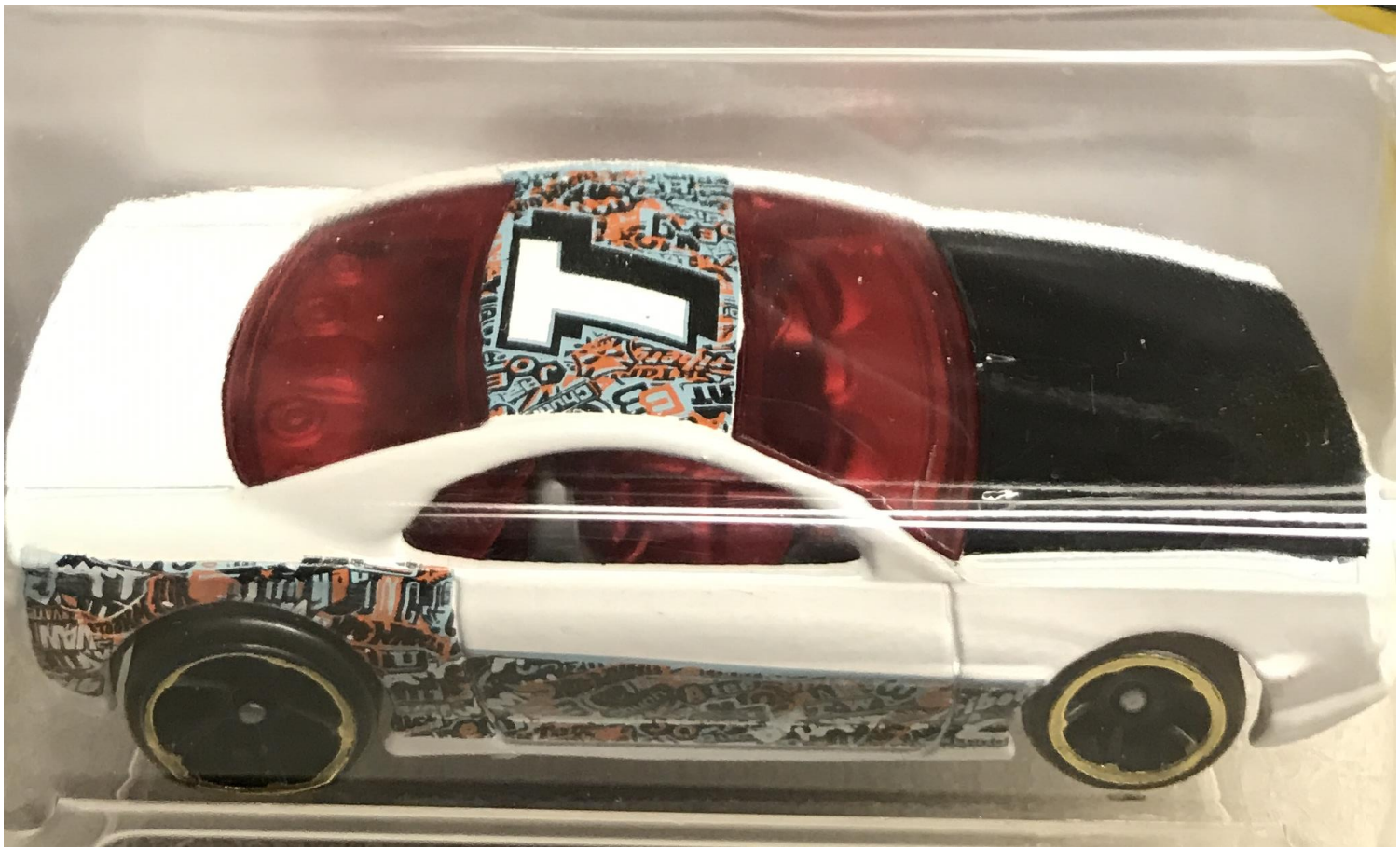
Lee D et al. BBMT 2018

Post CAR-T Infusion



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Courtesy of Susan Blumel

Post CAR-T

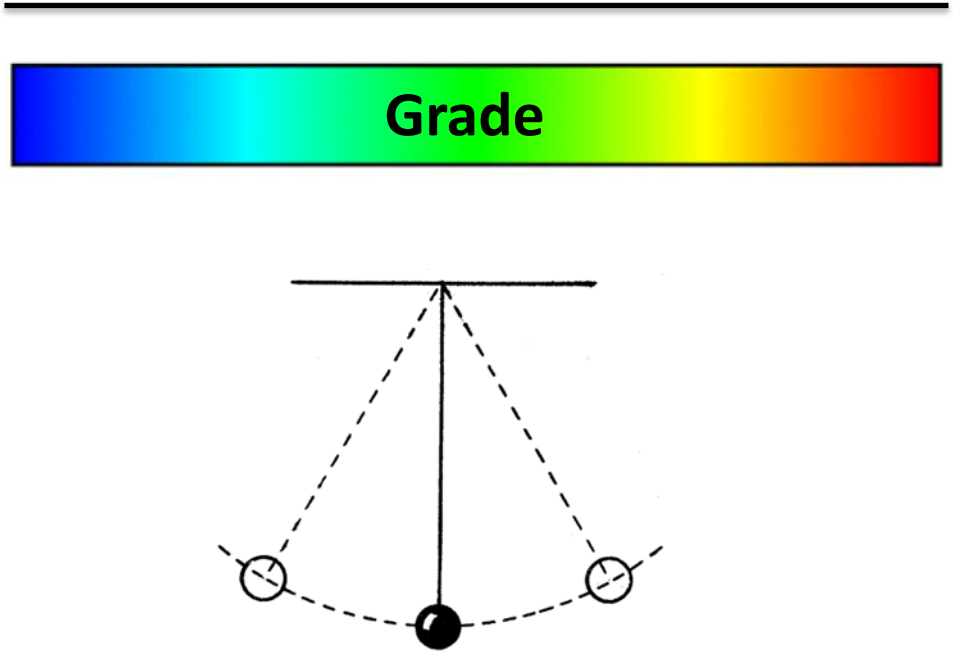
Early Post CAR-T

- Mini Mental Status Exam (30) or ICE (10)
- CBC/CMP
- DIC panel
- Ferritin
- CRP

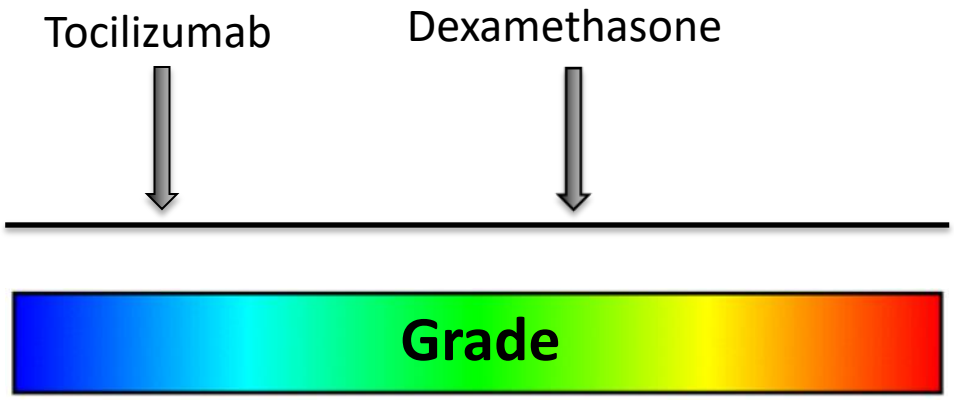
Long-term Post CAR-T

- Prophylaxis (Acyclovir, Levofloxacin, Fluconazole)
- Caregiver (24 hours)
- Vaccinations
- No driving for 2 months (research opportunity)

Management of Toxicity: Experience Matters



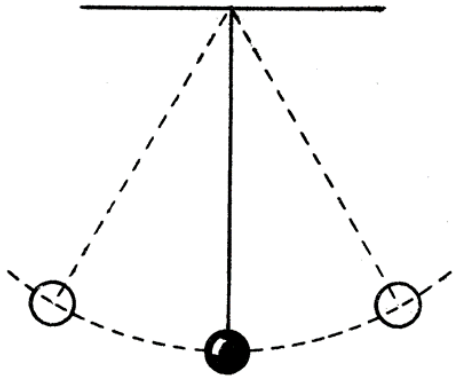
Management of CRS



Fever
Fatigue
Nausea/Vomit
Myalgias
Hypotension

Hypotension
Resp dysfunction
Renal dysfunction
Liver dysfunction

Tocilizumab—IL-6 receptor mAB



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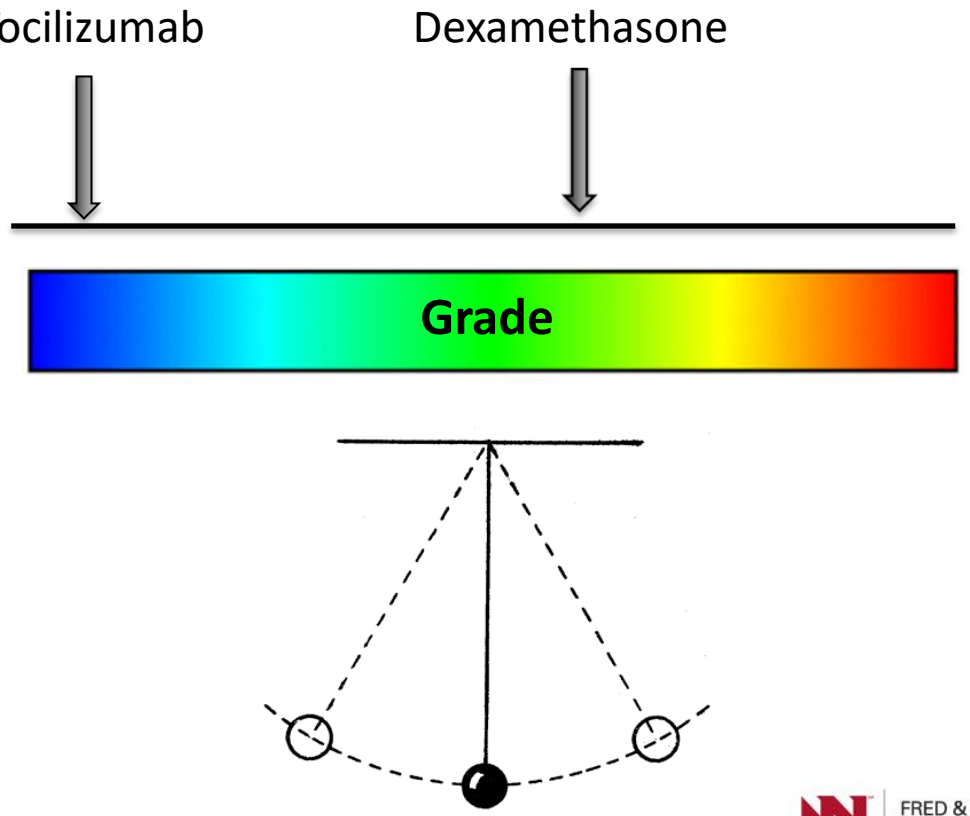
Abramson ASH 2017; Neelapu ASH 2017; Schuster ASH 2017

Management of CRS



Fever
Fatigue
Nausea/Vomit
Myalgias
Hypotension

Hypotension
Resp dysfunction
Renal dysfunction
Liver dysfunction

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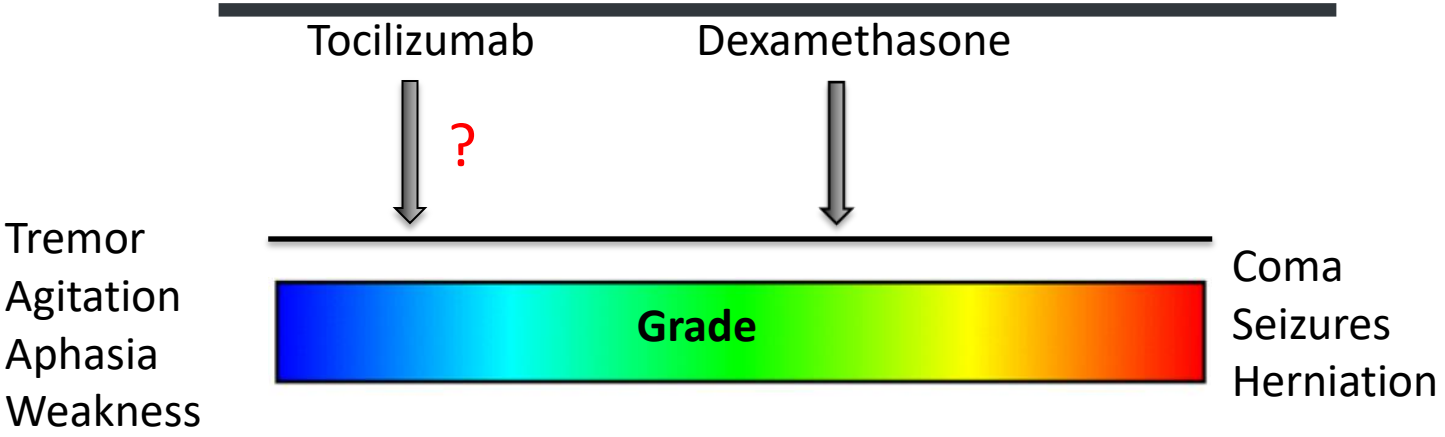
Abramson J et al. ASH 2017; Neelapu S et al. ASH 2017; Schuster S et al. ASH 2017

Management of ICANS

Shake of the Hand



ICANS = Immune effector cell-associated neurotoxicity syndrome

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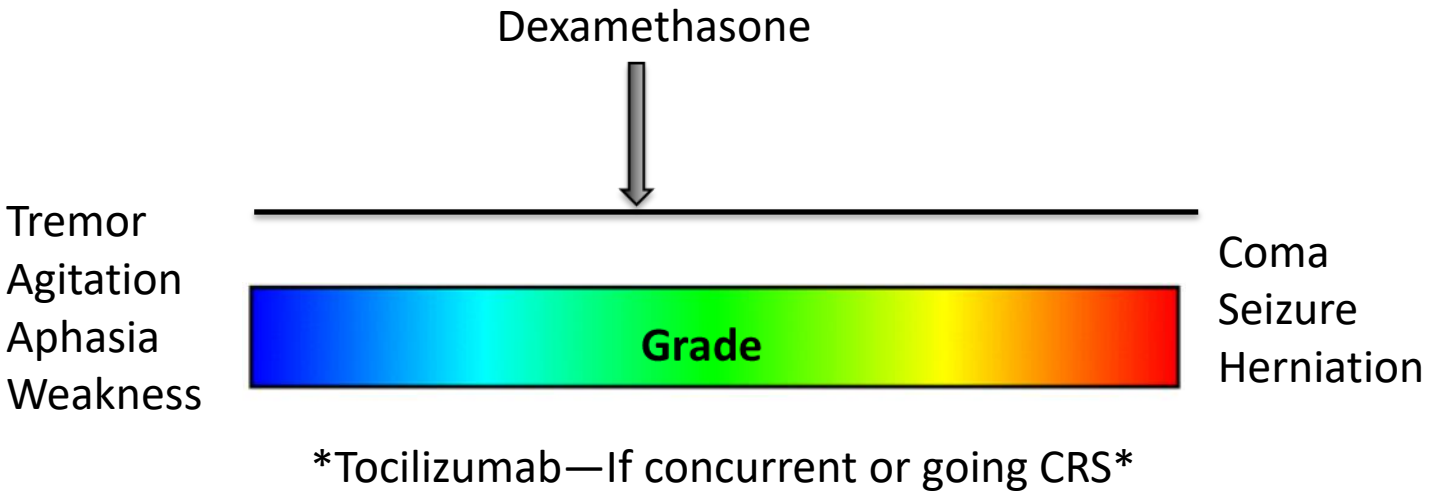
Abramson J et al. ASH 2017; Neelapu S et al. ASH 2017; Schuster S et al. ASH 2017

Management of ICANS



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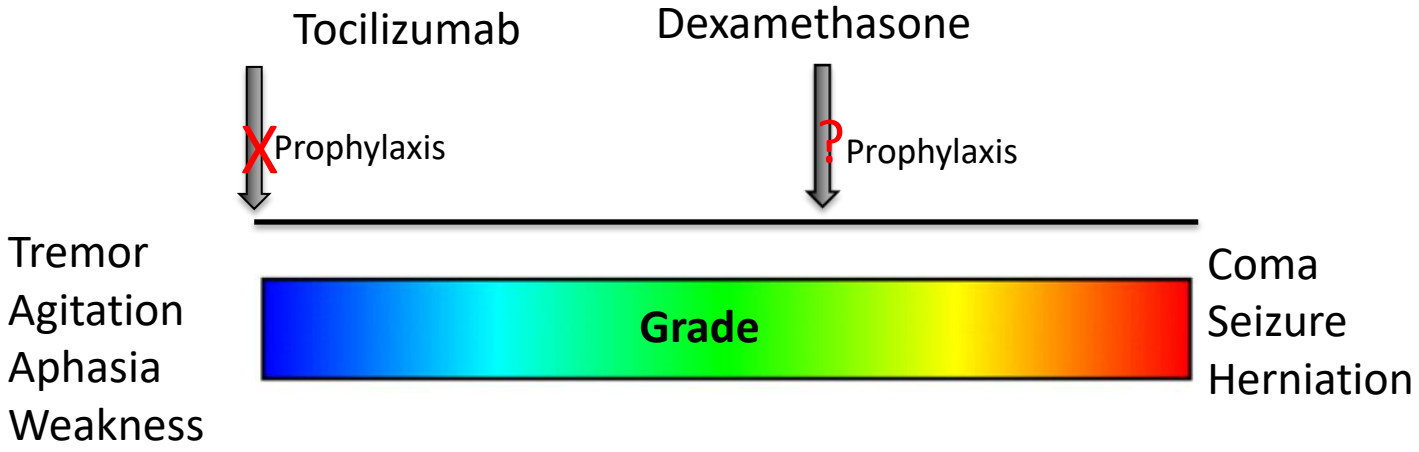
Abramson ASH 2017; Neelapu ASH 2017; Schuster ASH 2017

Management of ICANS

Prophylaxis



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Abramson ASH 2017; Neelapu ASH 2017; Schuster ASH 2017

Late Infectious Toxicities

Patient	SAE Start Time Post Axi-cel Infusion (months)	Grade	SAE
1	8.7	3	Lung infection
2	16.7	3	Recurrent viral upper respiratory infection
	18.6	3	Rotavirus infection
3[b]	12.5	3	Pneumonia
4	7.2	4	Sepsis
	7.2	3	Left lower lobe pneumonia
	7.2	3	Atrial fibrillation with rapid ventricular response
5	9.1	3	Lung infection
	9.2	3	Febrile neutropenia
6	7.1	3	Influenza B infection
7	7.9	3	Infection other - pneumonia
8	6.7	1	Muscle weakness right side
	6.7	2	Slurred speech
9[c]	9.3	3	Heart failure
10	14.4	3	Community acquired pneumonia

B-cell aplasia with hypogammaglobulinemia: Use of IVIG

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Neelapu S et al. ASH 2017

The Hematologic Double Dip

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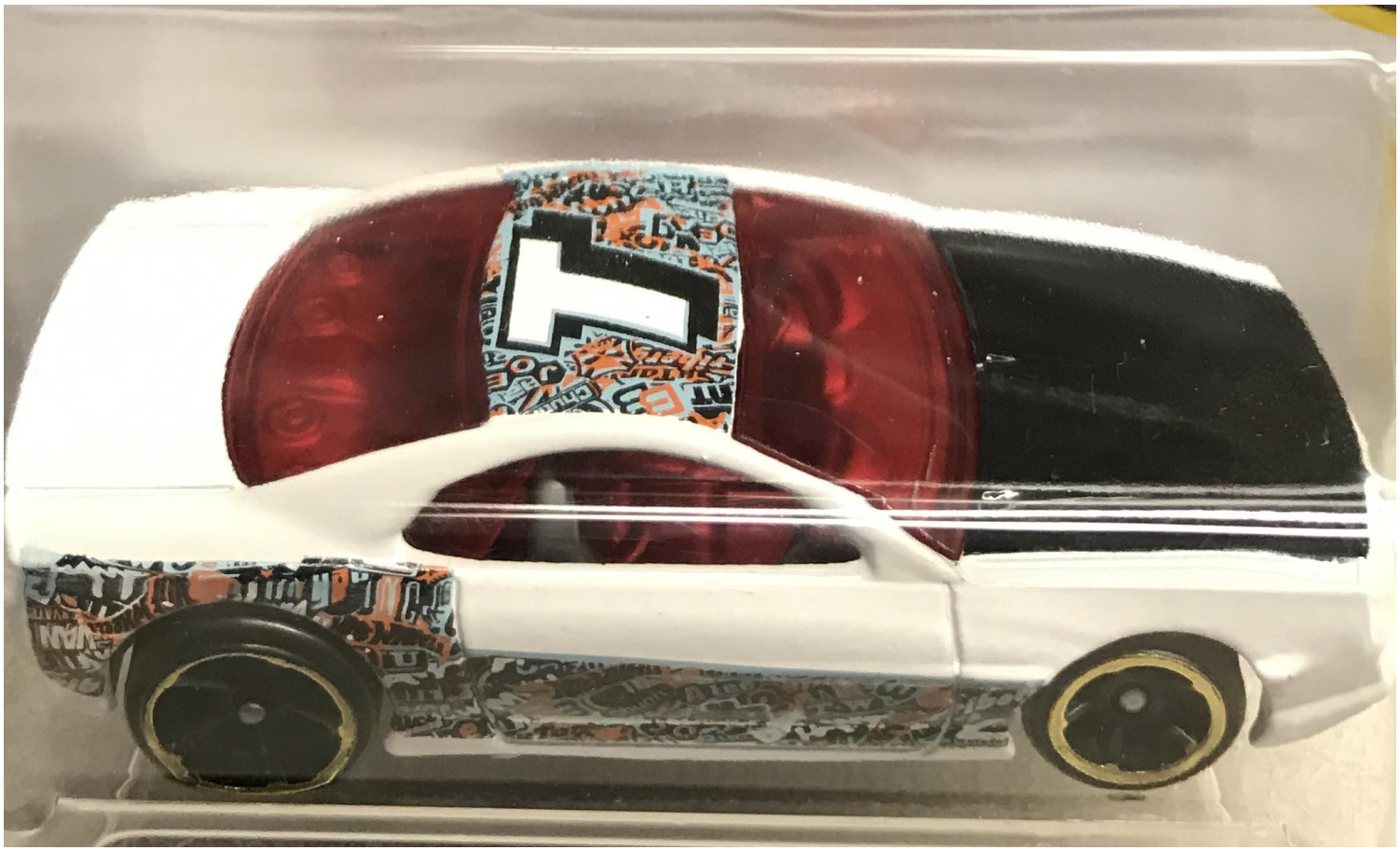
Future Strategies for CAR-T



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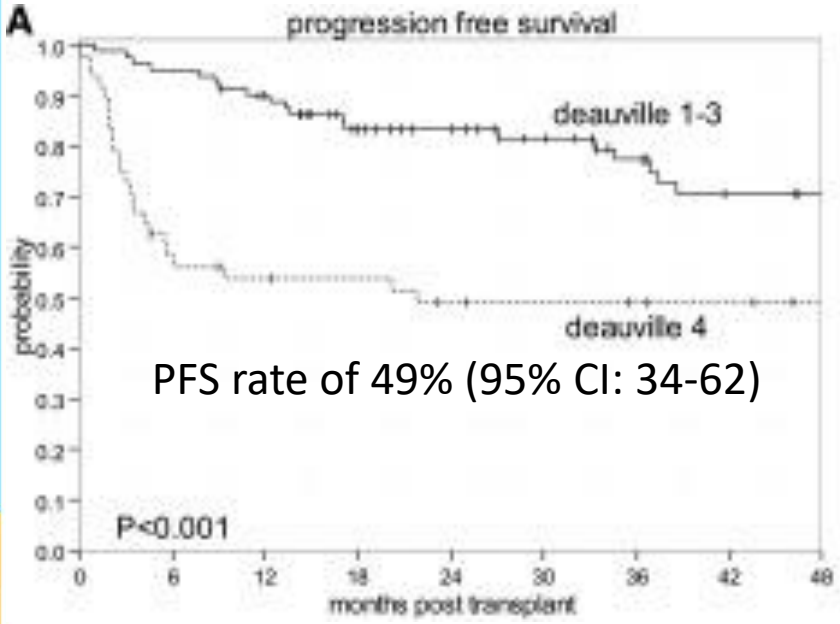
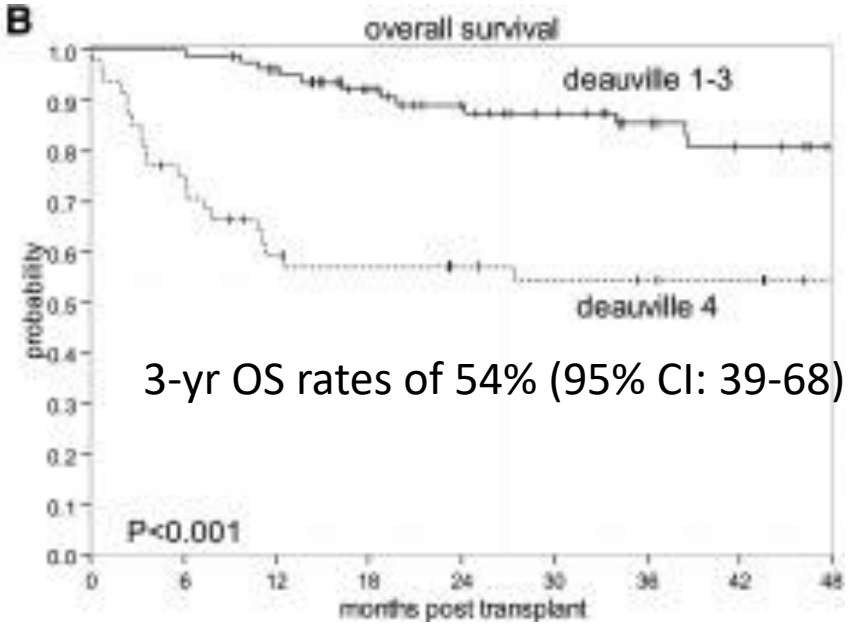
CAR-T in 1st Relapse of DLBCL



PFS rate of 49% (95% CI: 34-62)



3-yr OS rates of 54% (95% CI: 39-68)

No significant differences in PFS and OS were observed according to

- sAA-IPI
- Relapse <12 months
- Primary refractory disease vs relapse ≥12 months
- Type of salvage therapy

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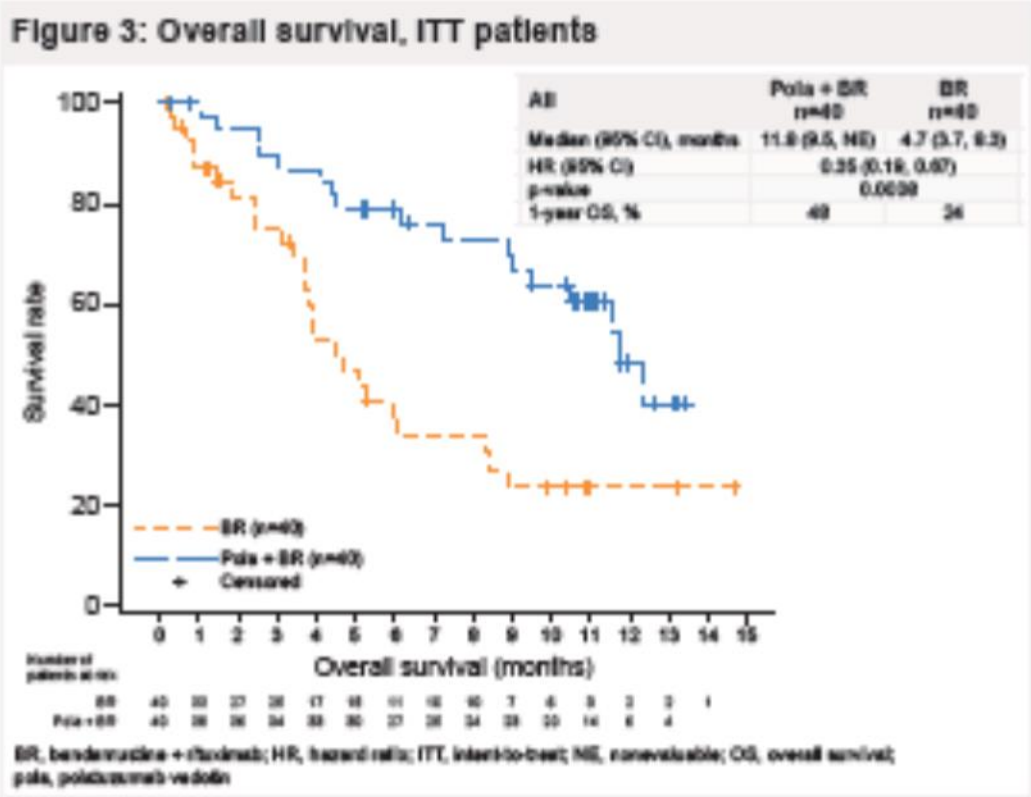
Sauter S et al. Blood 2016

PBR Me ASAP?

Polatuzumab* + Bendamustine Rituximab (PBR)



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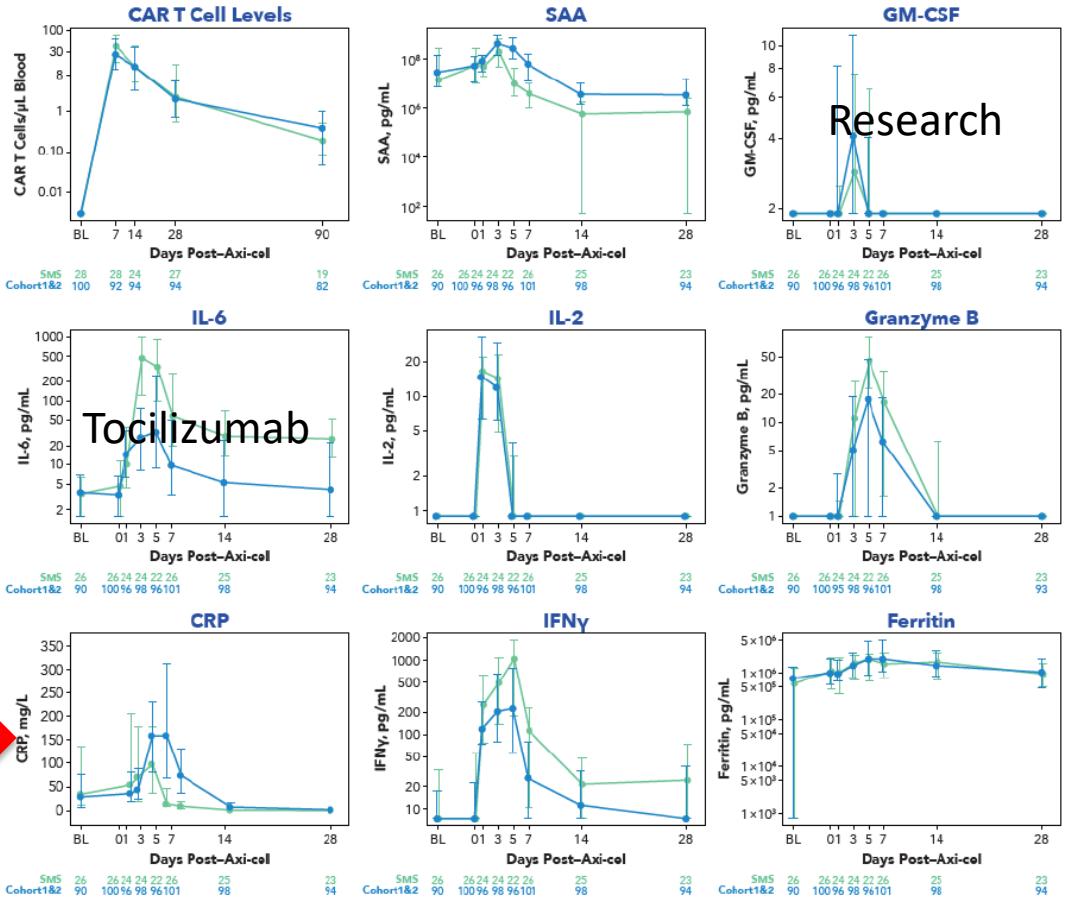
Sehn L et al. ASH 2017

*CD79b ADC

Prediction of Toxicities*



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Locke F et al. ASH 2017; *Product Axi-cel

Access, Referrals and other drugs

DLBCL

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Omaha, Nebraska

Questions 1

1. **Current clinical trials involving chimeric antigen therapy (CAR) T-cell therapy various hematologic malignancies target the following antigens except:**

   A. CD19
   B. CD20
   C. CD22
   D. CD28

Question 2

2. Prior to the delivery of cyclophosphamide and fludarabine based lymphodepleting chemotherapy a change in this may necessitate a dose reduction:

   A. Creatinine clearance
   B. ECOG performance status
   C. Absolute neutrophil count (ANC)
   D. Hemoglobin

Question 3

3. In monitoring for cytokine release syndrome (CRS) these factors are taken into consideration except:

   A. Temperature
   B. Oxygen saturation
   C. Blood pressure
   D. Pain score

Question 4

4. **In the treatment of neurotoxicity related to CAR-T therapy when may it appropriate to consider the use of tocilizumab?**

   A. At onset of fever
   B. When there established concurrent CRS
   C. At the onset of grade 1 neurotoxicity
   D. At the resolution of grade 1 neurotoxicity

Question 5

Axi-cel is commonly delivered in the outpatient setting?

A. True
B. False