CART therapy for Diffuse Large B cell Lymphoma

Edmund K. Waller, MD, PhD, FACP
Winship Cancer Institute Emory University

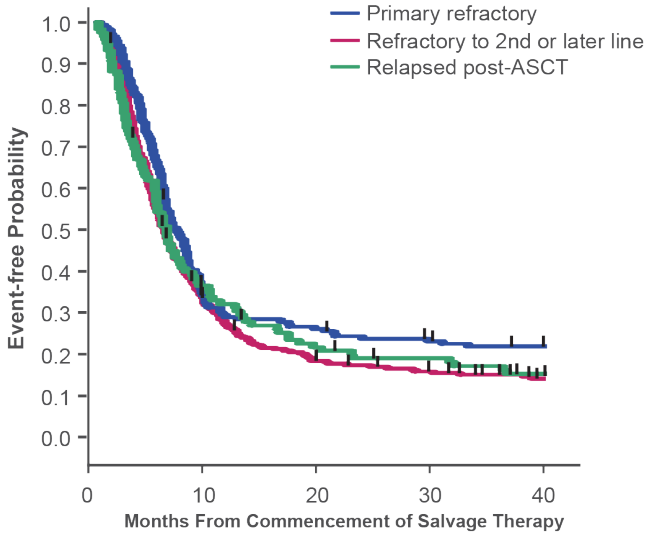
Disclosures

- Consulting fees from Novartis
- Clinical Research supported by Novartis and Celgene
- Co-founder and equity holder of Cambium Medical Technologies & Cambium Oncology
- I will be discussing non-FDA approved indications during my presentation.

The Clinical Problem: poor survival in patients with relapsed/refractory DLBCL

SCHOLAR-1 Patient Response Rate to Chemotherapy	
Measurement (n/N)	**Integrated Response Rate (n=636)**
Number of patients evaluated for response	529
Response rate, % (95% CI)	26% (22,31)
- Complete Response Rate	**8% (4,15)**
- Partial Response Rate	**18% (13,23)**

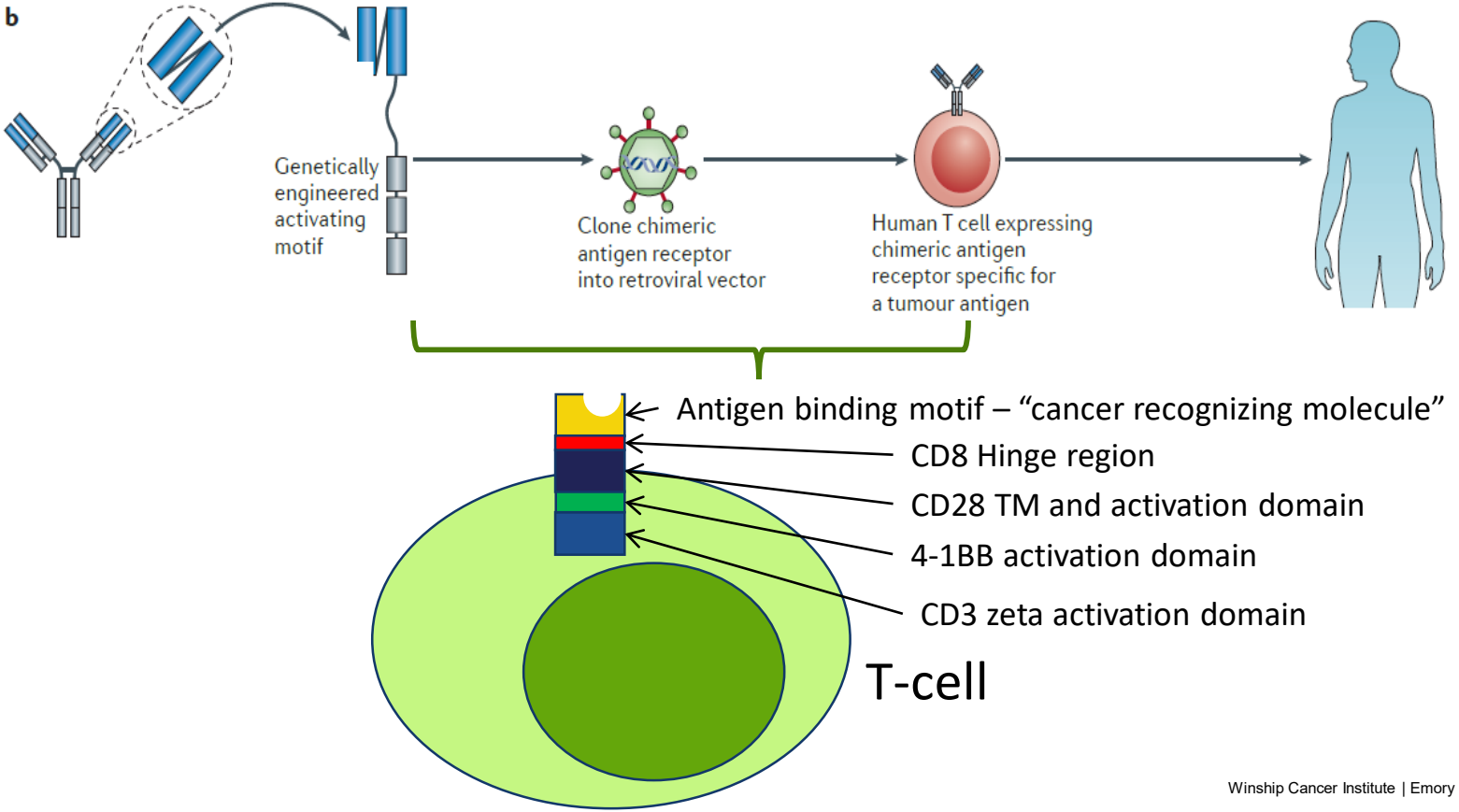
Adapted with permission from the American Society of Hematology.



Median overall survival was 6.6 months in the SCHOLAR-1 meta-analysis of patients with r/r DLBCL who were primary refractory, chemorefractory, or who relapsed <= 1 year post ASCT

Crump M et al. *Blood*. 2017

Chimeric Antigen Receptor (CAR) Technology

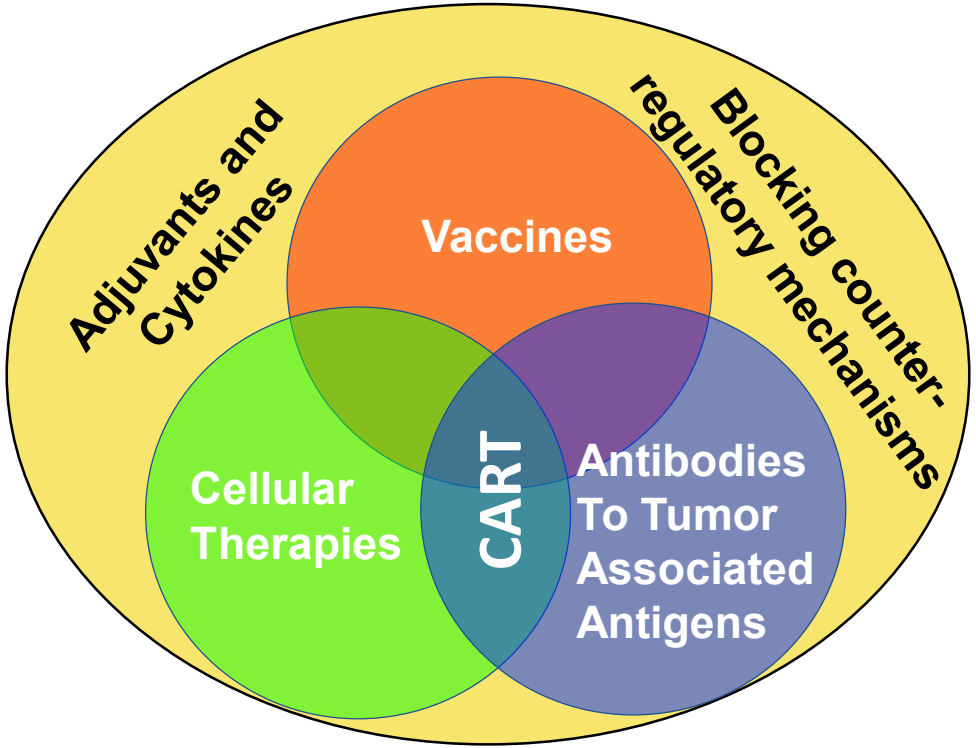


FDA-approved CAR T cell therapies for hematologic malignancies

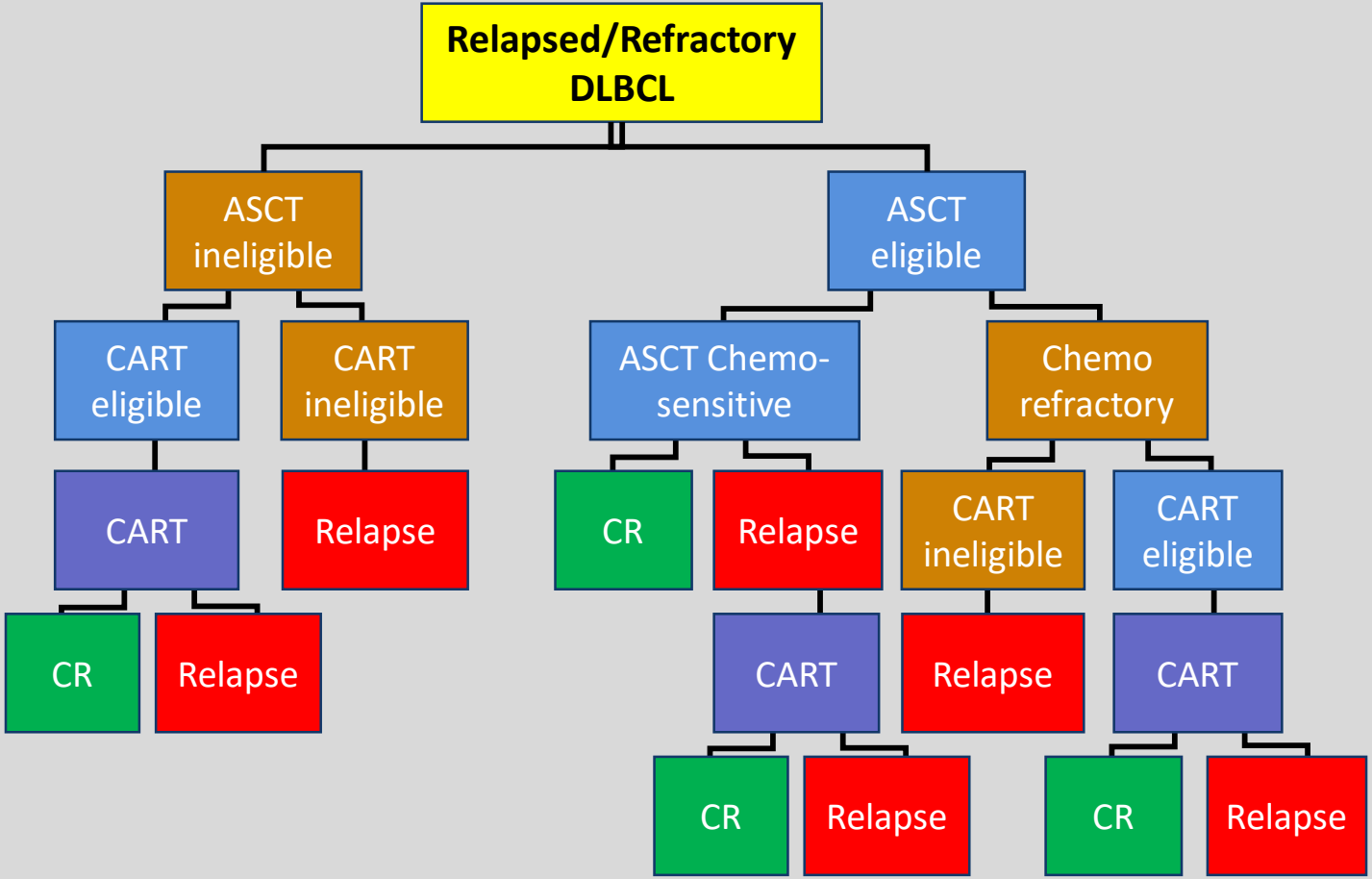
- Kymriah (tisagenlecleucel)
  - Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
  - Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
  - Accelerated approval – B-ALL: August 30th, 2017, DLBCL: May 1st, 2018.

- Yescarta (axicabtagene ciloleucel)
  - ZUMA-1: 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, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
  - Accelerated approval – B-ALL: October 18th, 2017

CART are part of broader immunological armamentarium to treat cancer

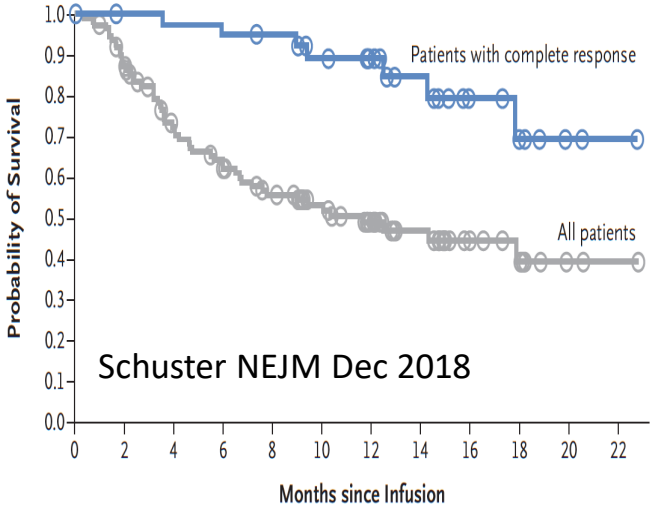


Treatment algorithm for relapsed/refractory DLBCL



Long-term efficacy of CD19 CART in adult patients with large B-cell lymphoma: 30-40% durable CR

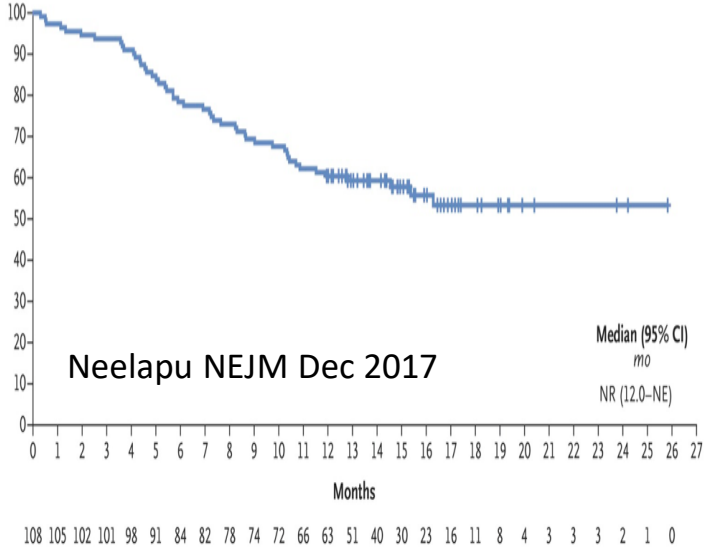
Tisagenleceucel



Schuster NEJM Dec 2018

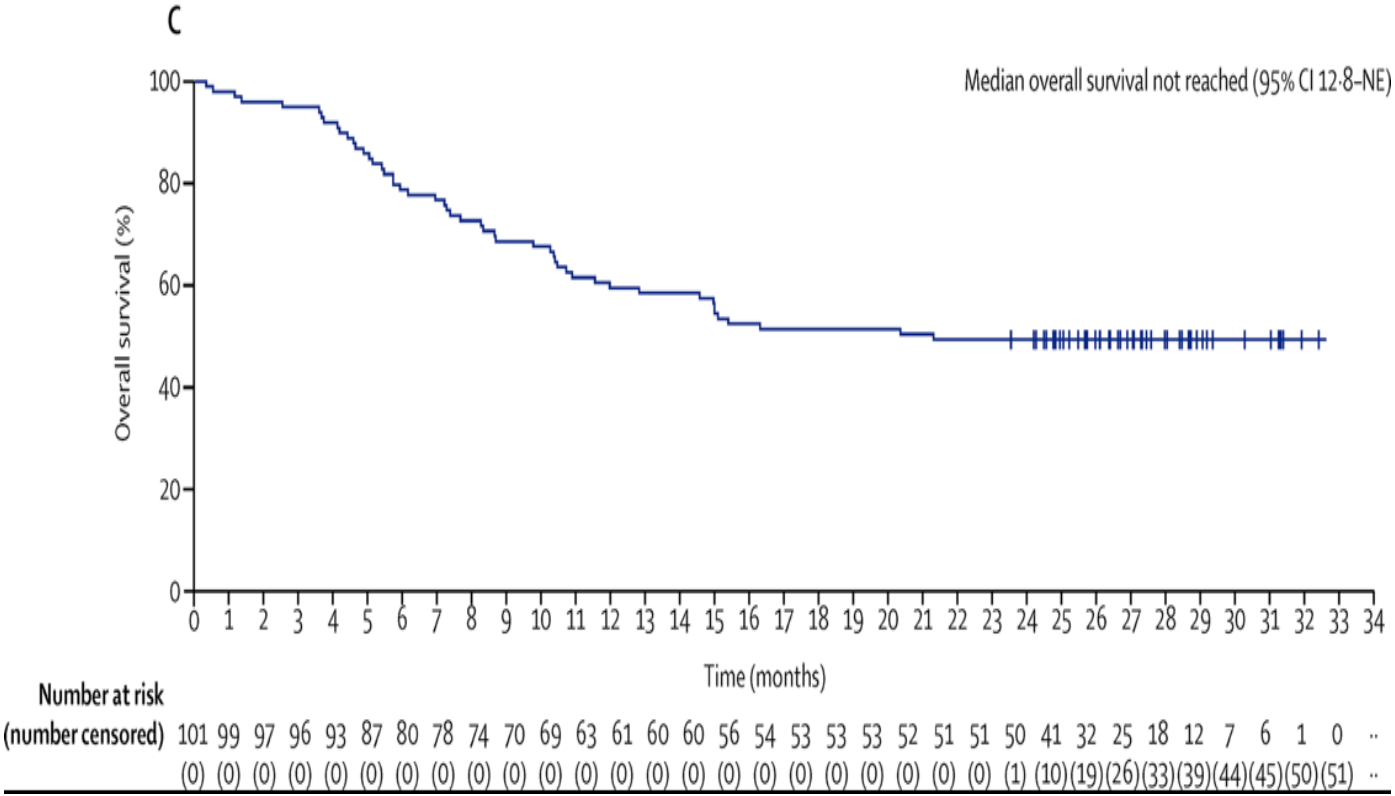
No. at Risk																					
Patients with complete response	40	40	40	40	39	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111		94		71		60		50		40		28		19		11		8		2		1

Axicabtagene Ciloleucel



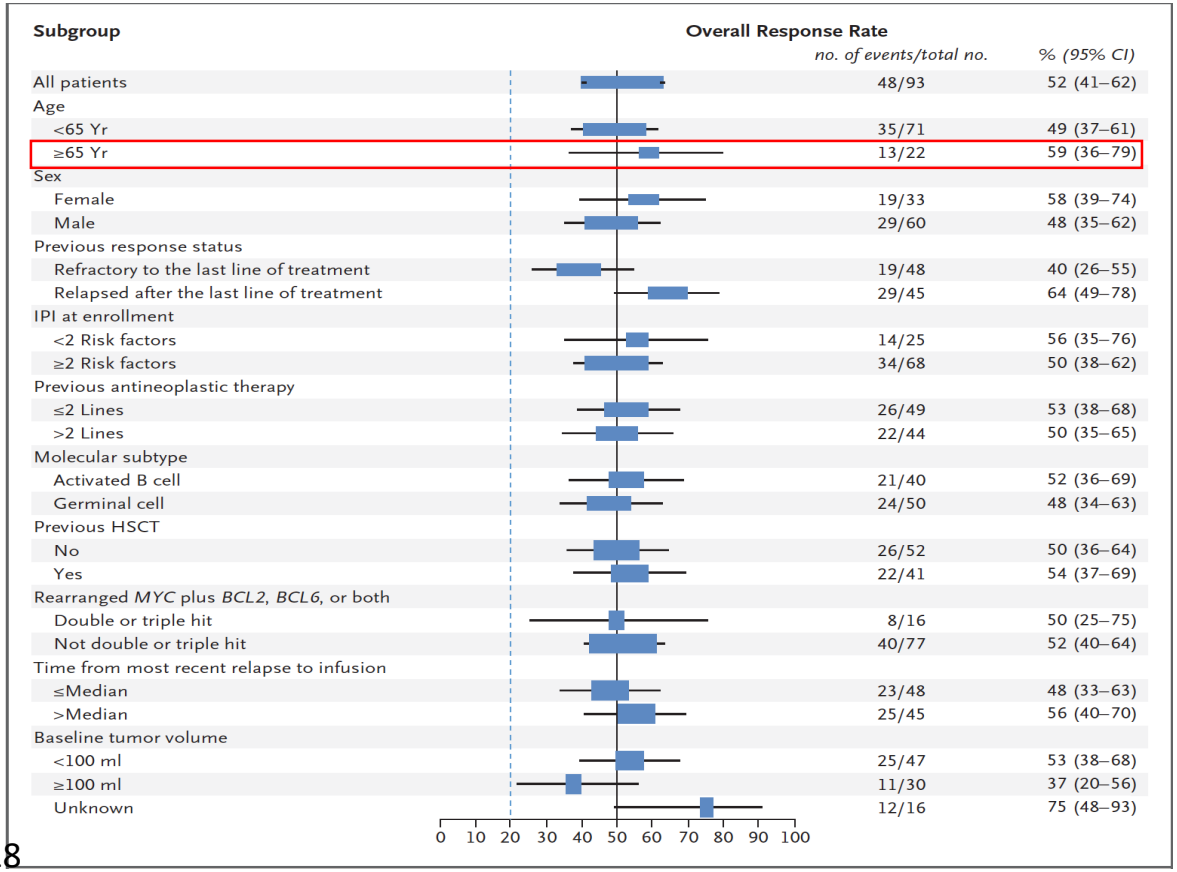
Neelapu NEJM Dec 2017

CR is stable among DLBCL patients enrolled on ZUMA-1



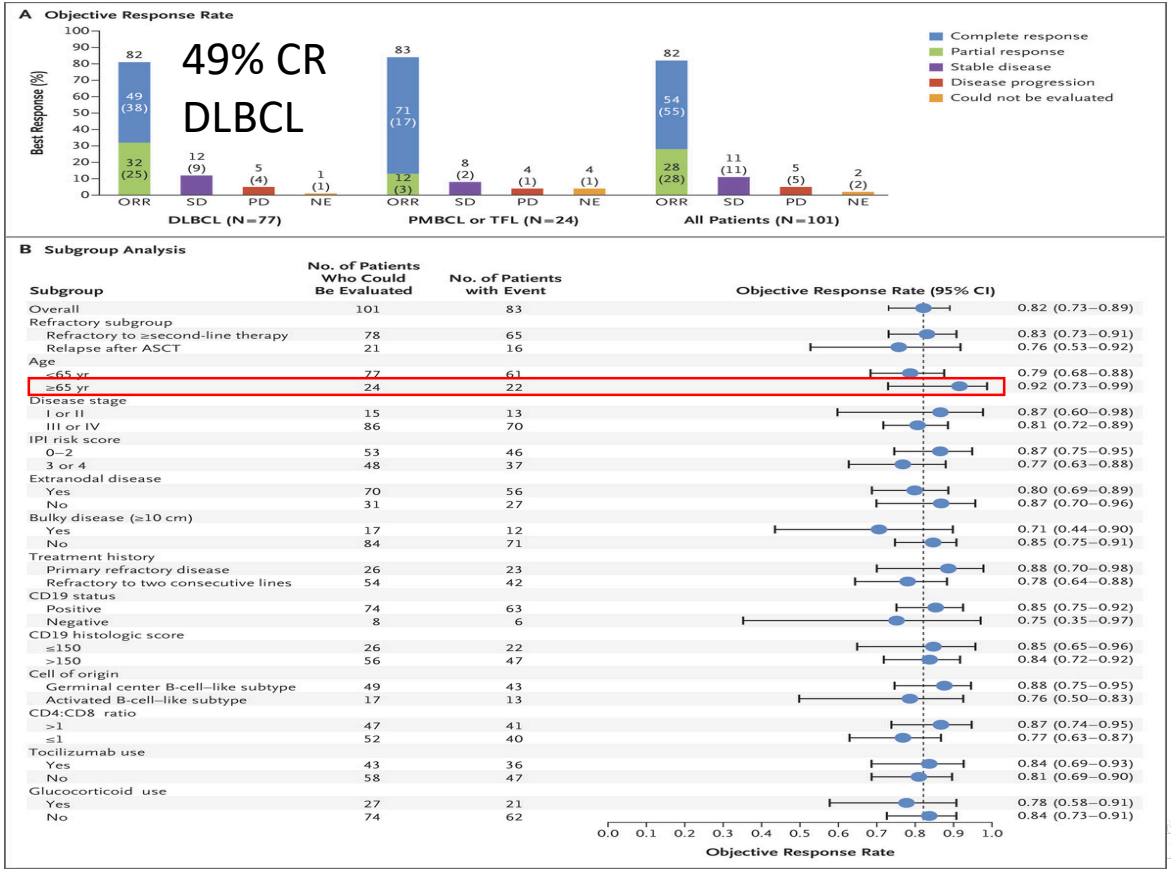
Locke 2019 The Lancet Oncology

Overall response rate consistent across DLBCL subgroups treated with Tisagenlecleucel



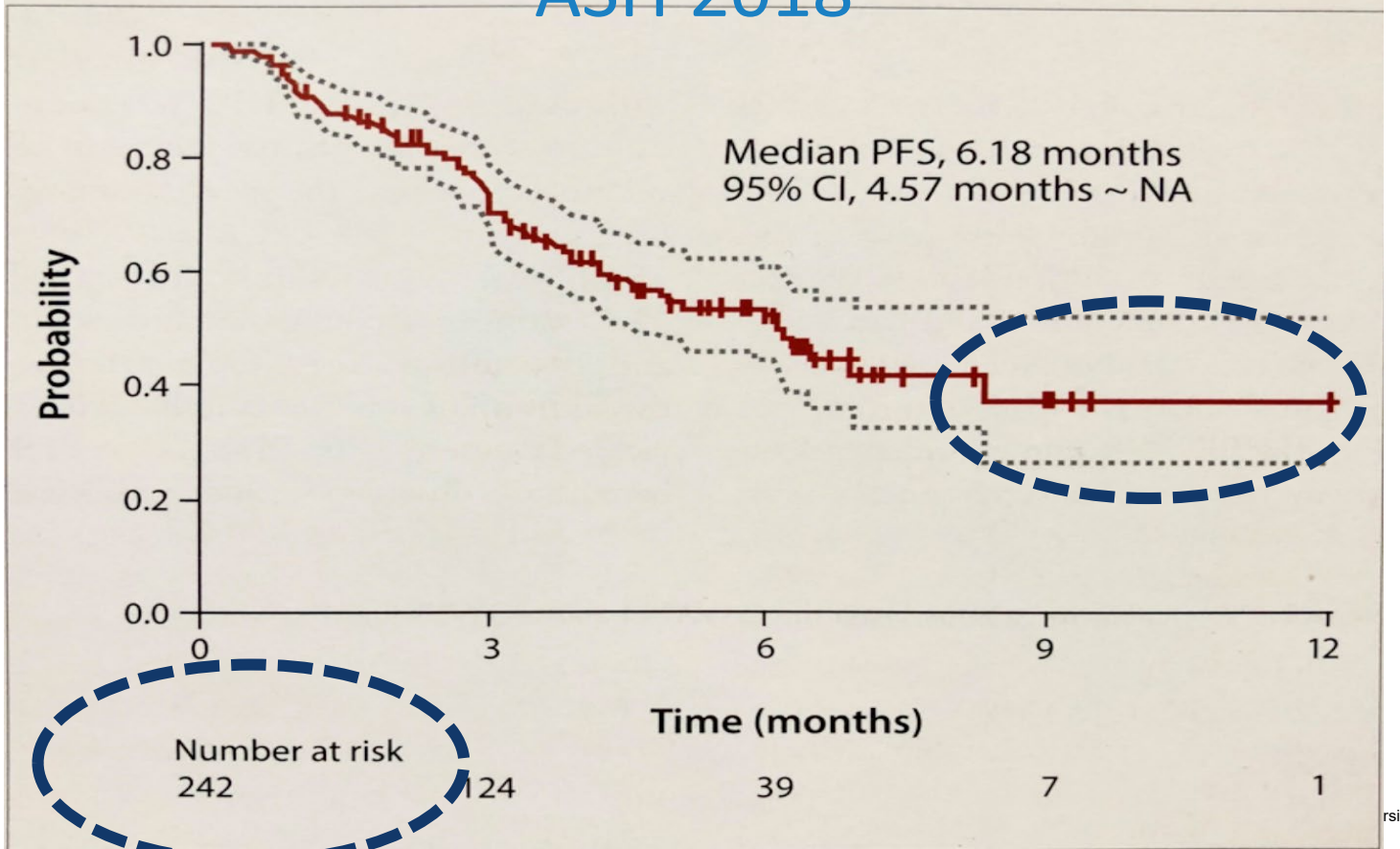
Schuster NEJM Dec 2018

Objective responses seen across subgroups among Axicabtagene Ciloleucel treated patients.

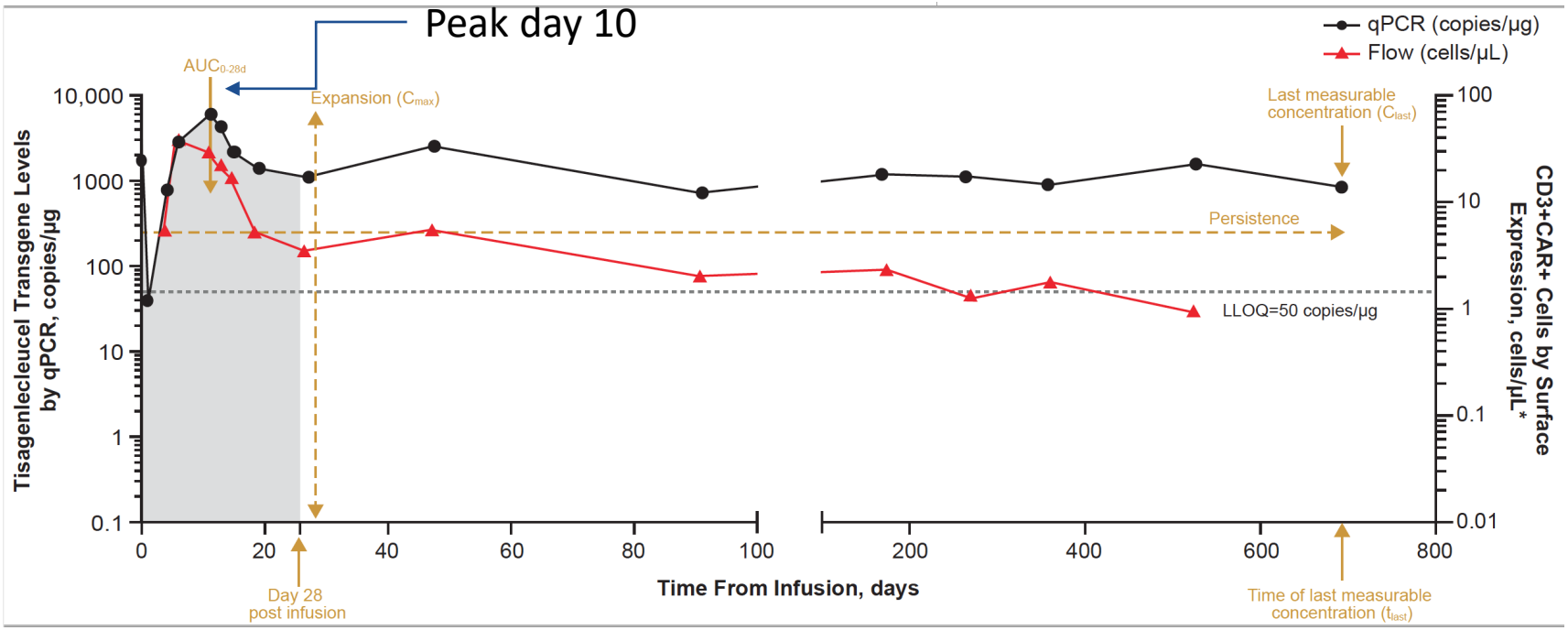


Neelapu NEJM 2017

Yescarta "Real-world" Experience: ASH 2018

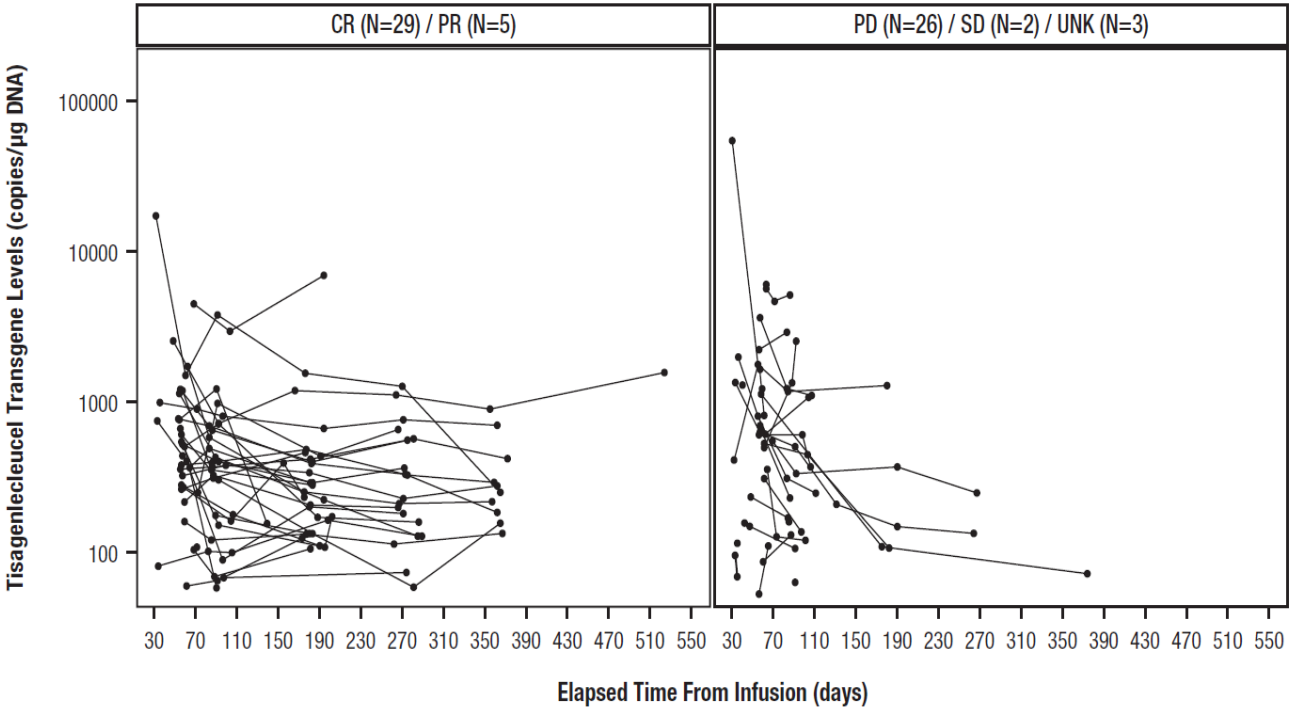


Cellular kinetics of axi-cel and tisagenlecleucel expansion and persistence



Neelapu NEJM 2017; Awasthi submitted

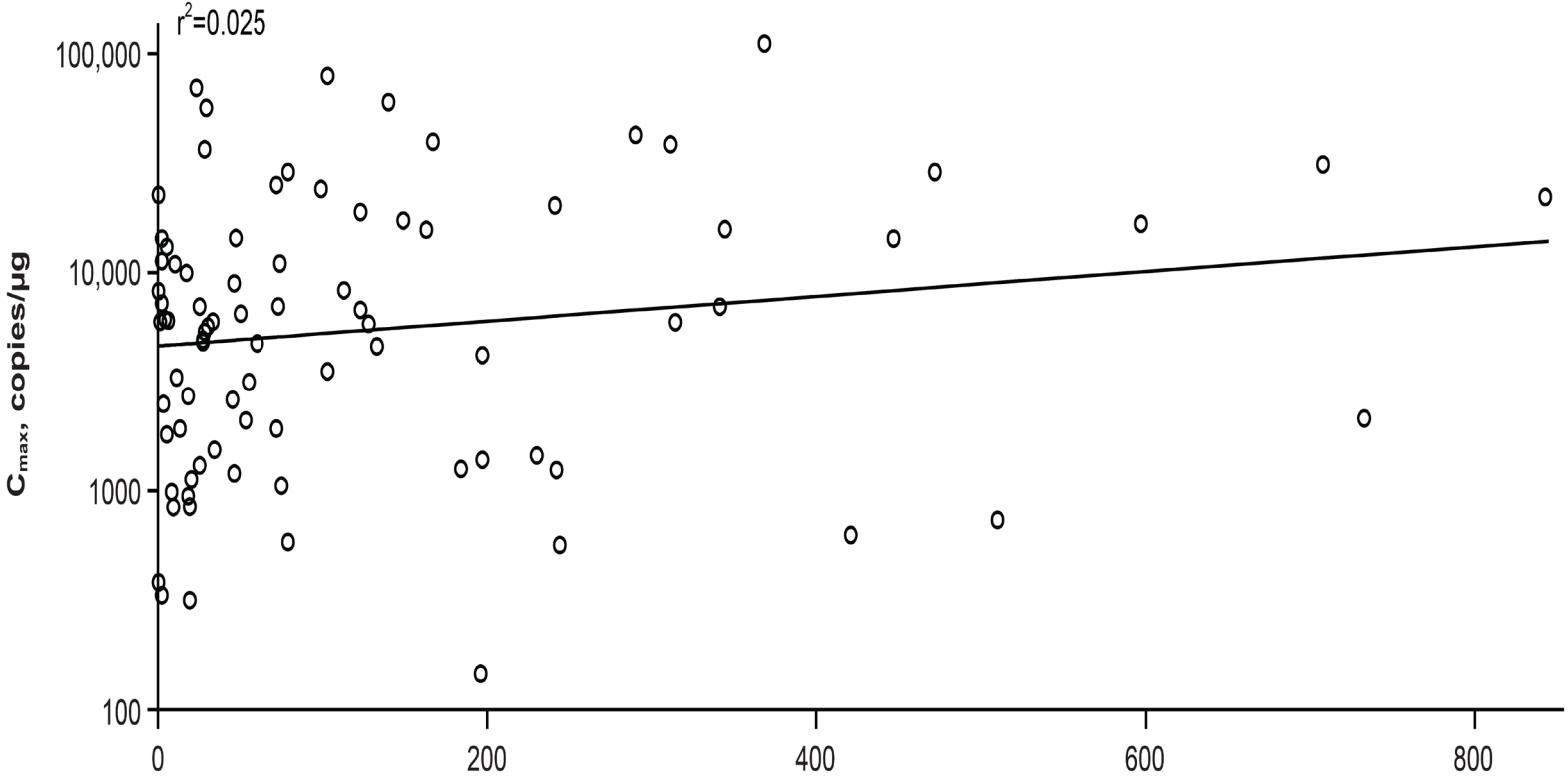
Long-term persistence of Tisagenlecleucel observed in both responding and non-responding patients



- **The mean exposure in responding and non-responding patients were similar**
- **CTL019 persisted beyond 400 days in CR patients**

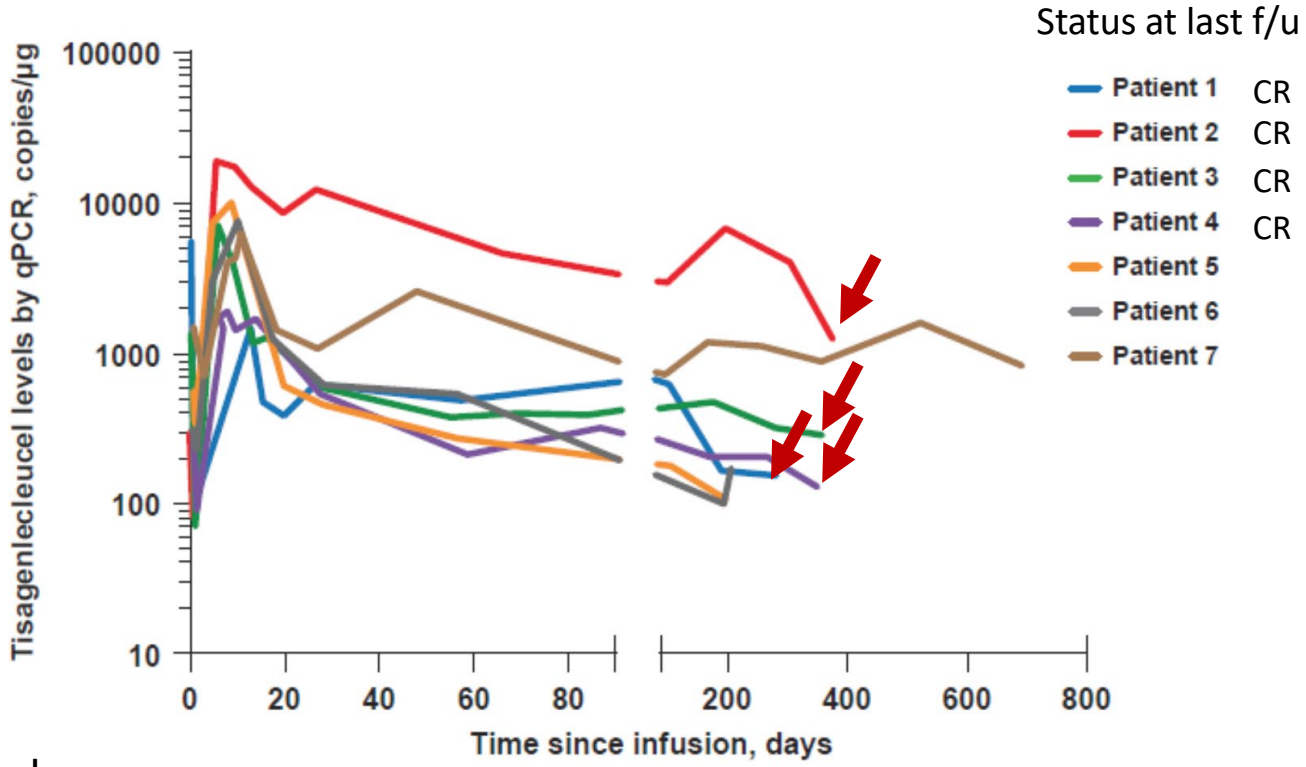
Schuster NEJM Dec 2018

Tumor burden did not change CTL109 CART expansion



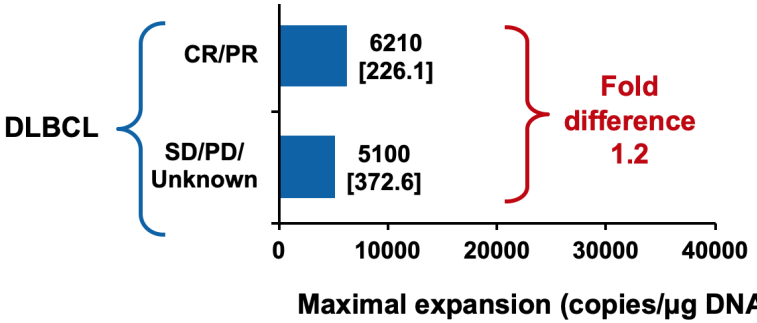
Awasthi submitted

Patients who received CART in CR after bridging therapy had similar expansion kinetics and response as other CART patients

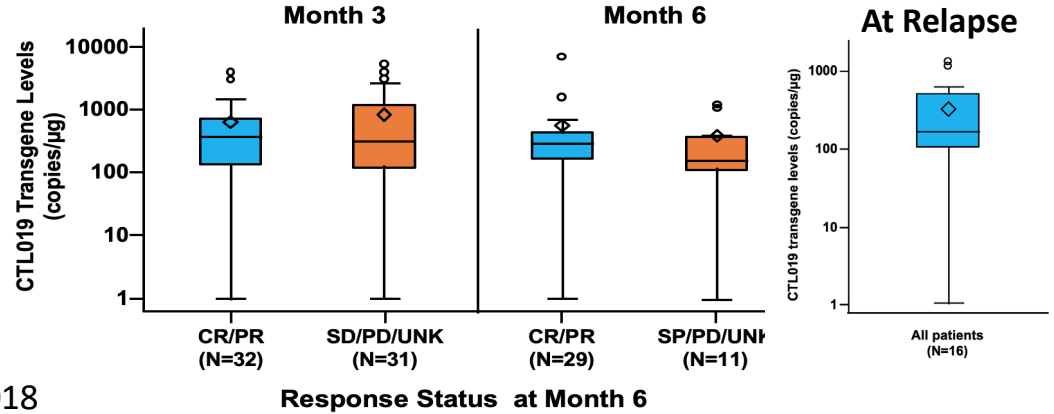


Bishop submitted

Peak & long-term tisagenlecleucel CART levels in DLBCL were not associated with response



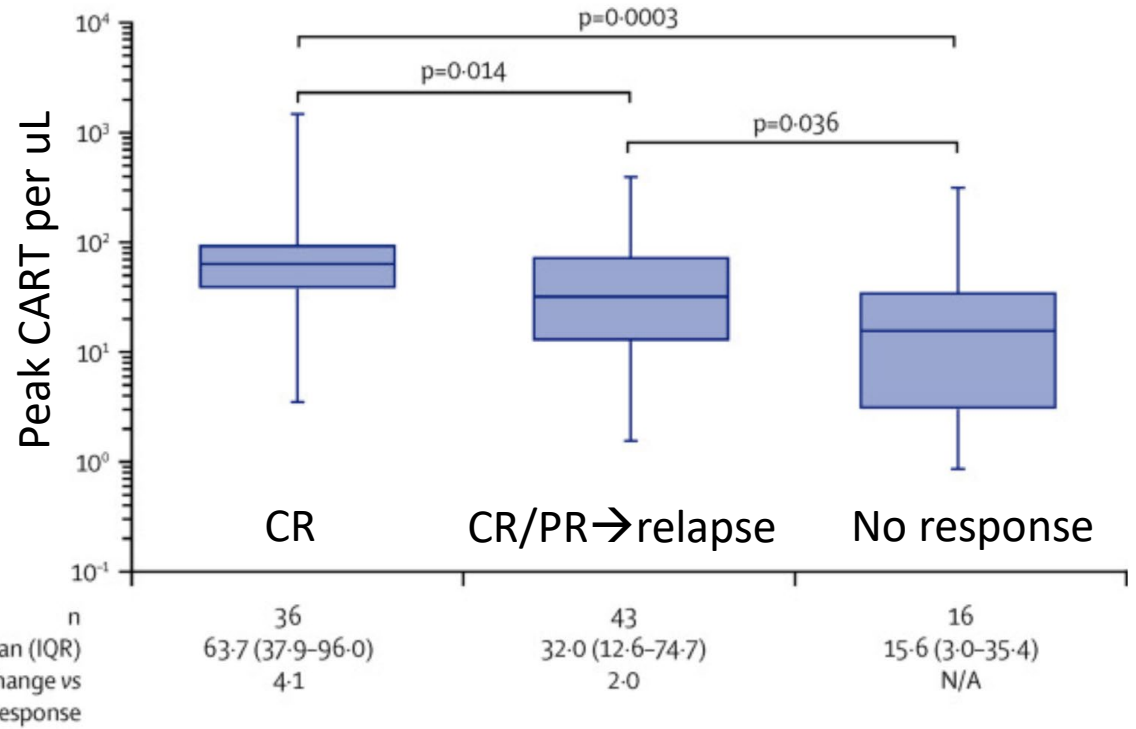
Peak: 5000 copies/ug= 200 CART/uL



3 months 500 copies/ug= 10 CART/uL

Awasthi Blood 2018

Higher peak levels of Axicabtagene Ciloleucel were associated with CR



Locke 2019 The Lancet Oncology

What about CART Toxicities?

Safety results for anti-CD19 CAR T-cell therapies in relapsed or refractory aggressive B-cell lymphoma

Study/ Sponsor	N	CRS All grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Tocilizumab usage	Corticosteroid usage
ZUMA-1/ Kite	108	93%	13%	65%	31%	45%	29%
JULIET/ Novartis	111	58%	**17%**	21%	12%	15%	11%
TRANSCEND/ Juno	102	37%	1%	23%	13%	17%	21%

Nair Best Practice & Research Clinical Haematology 2018; Maziarz EBMT 2019

CRS – Cytokine release syndrome;
NT – Neurological toxicity.

ASBMT consensus Cytokine Release Syndrome (CRS) Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hy		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)

Tocilizumab

D.W. Lee et al. / Biol Blood Marrow Transplant (2019)

ASBMT consensus on Immune effector cell-associated neurotoxicity syndrome (ICANS) Grading

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

D.W. Lee et al. / Biol Blood Marrow Transplant (2019)

CARTOX 10 questions

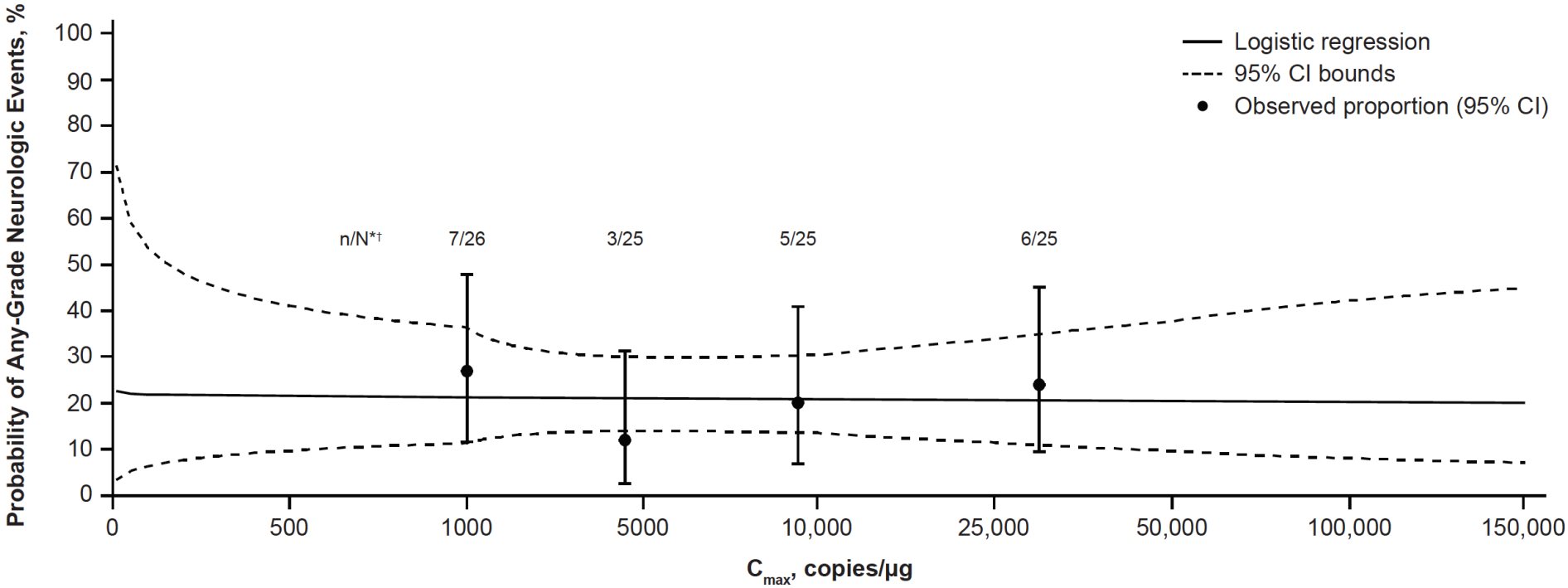
ICE 10 questions

- orientation to year
- orientation to month
- orientation to city
- orientation to hospital

4 points

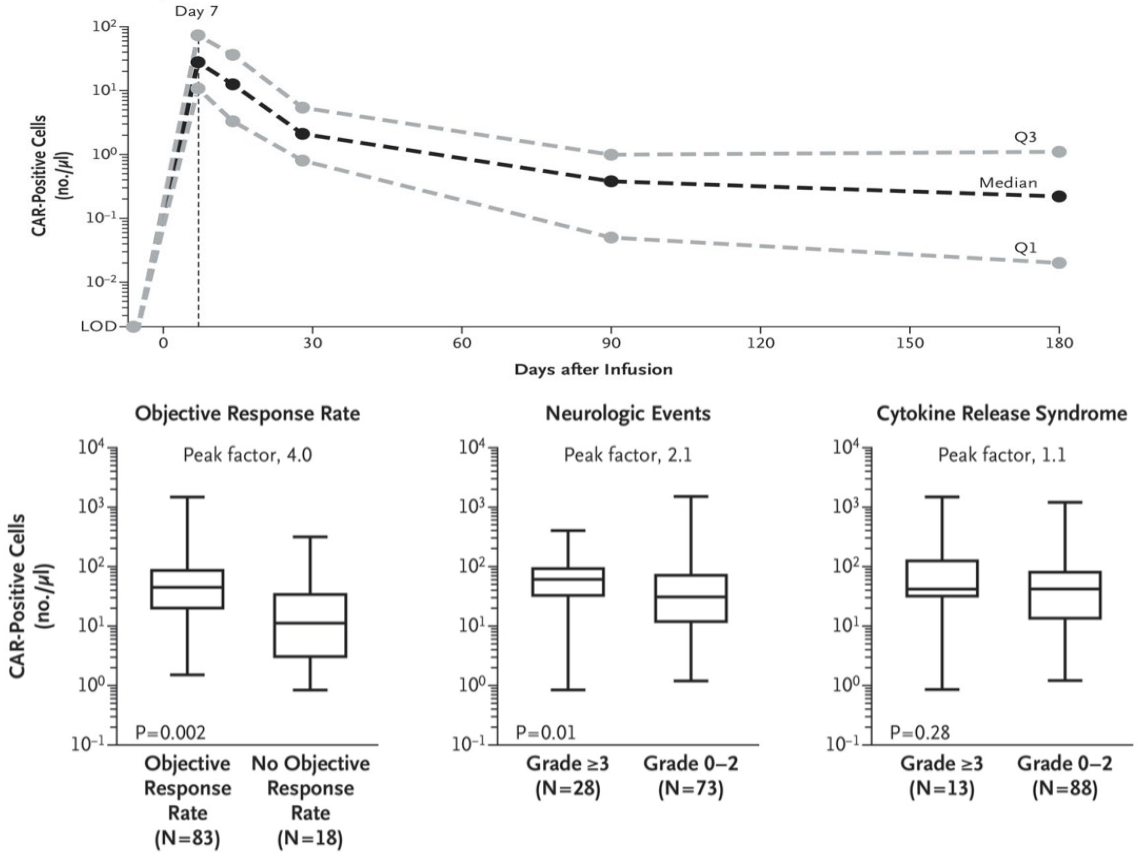
- Follow a command “touch your nose with … “ (1 point)
- name three objects (maximum of 3 points)
- write a standard sentence (1 point)
- count backwards from 100 in tens (1 point)

Higher numbers of infused Tisagenlecleucel and cMax were associated with more severe CRS but not neurotoxiicty



Awasthi, submitted

Higher peak level of Axicabtagene Ciloleucel during expansion associated both with response and neurotoxicity



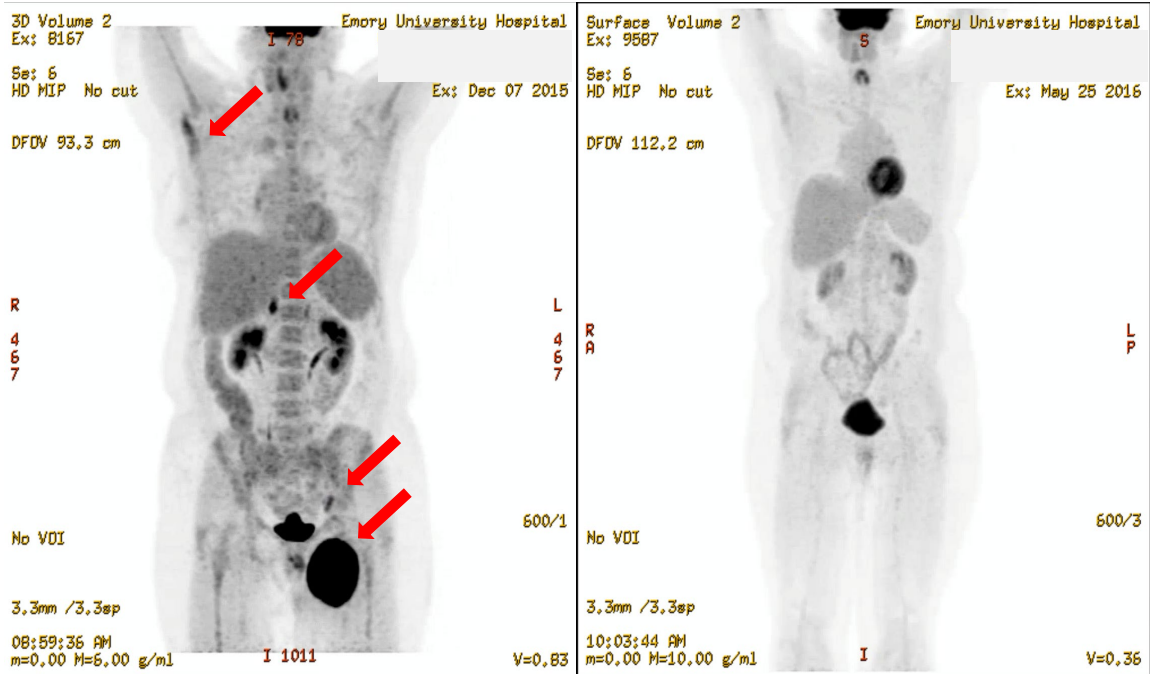
Neelapu NEJM 2017

Summary of CART PK & PD

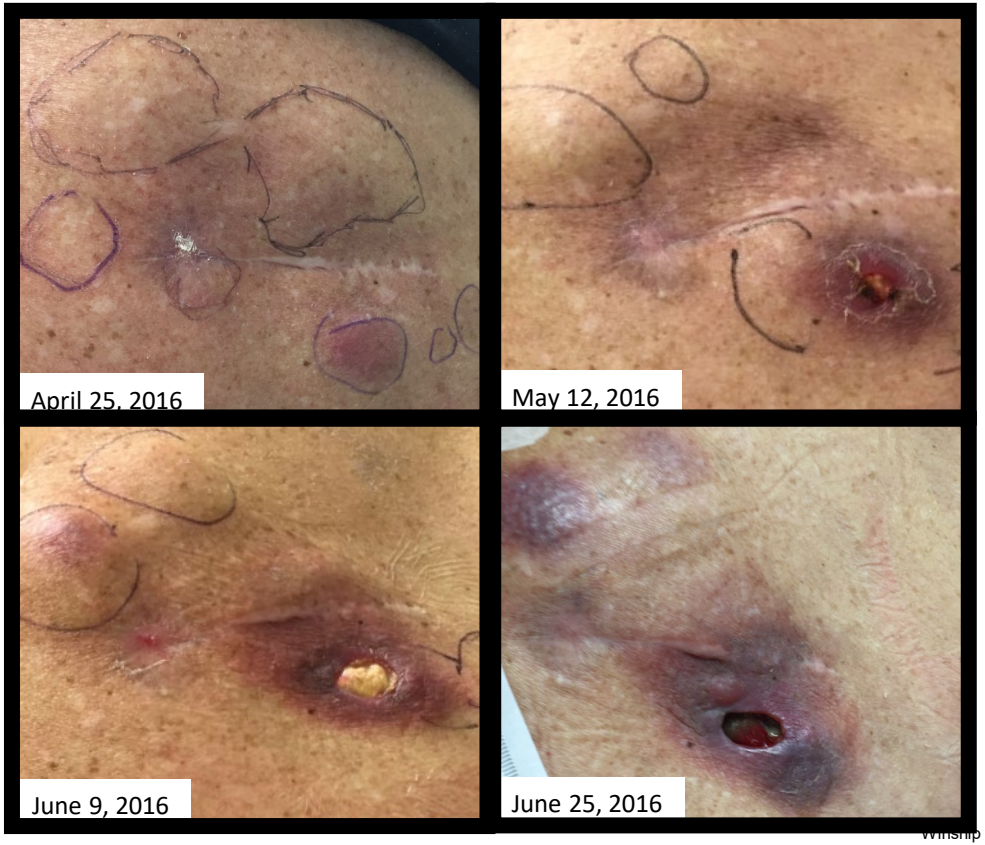
- Tisagenlecleucel transgene persistence observed for up to 400 days in responding patients
- Increased probability of severe CRS with increased Tsiagenlecleucel infused dose and expansion.
- More neurotoxicity with Axi-cel and severity of neurotoxicity related to peak expansion
- No clear impact of humoral and cellular immunogenicity on exposure or clinical outcome with Tisagenlecleucel

What do responses look like for CART patients?

Scintographic complete regression of DLBCL 3 months following CART therapy

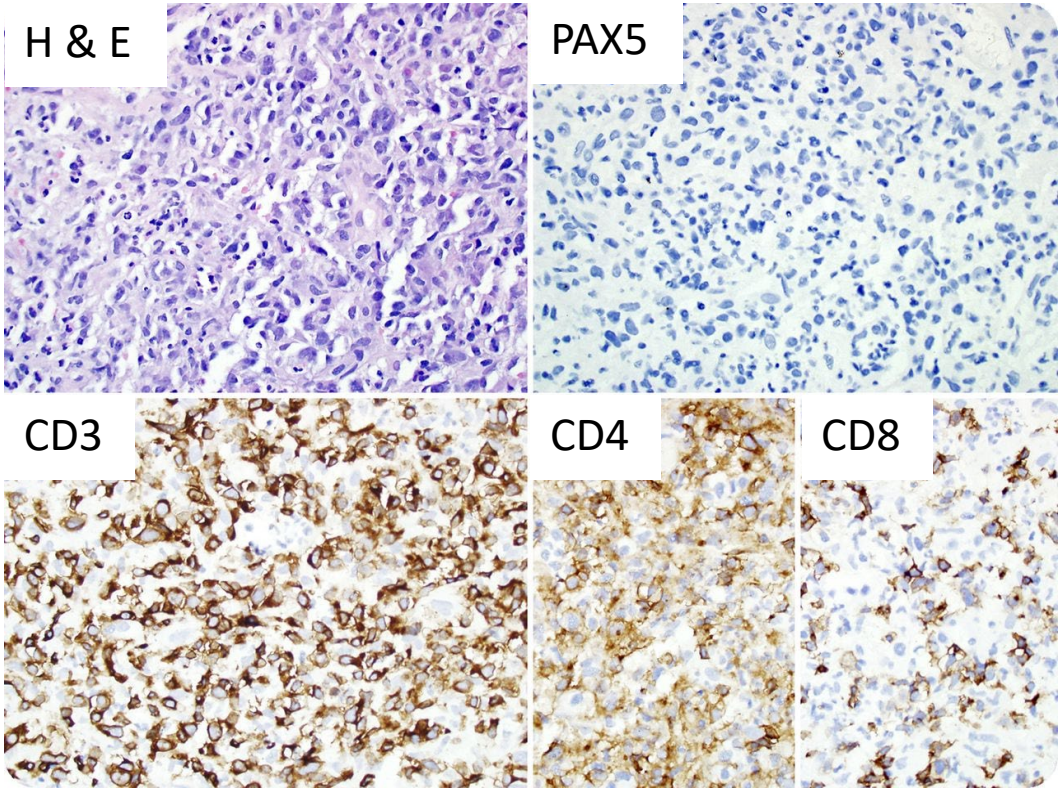


Clinical response of sub-cutaneous lymphoma to CART



Funk 2018 Int J Mol Sci.

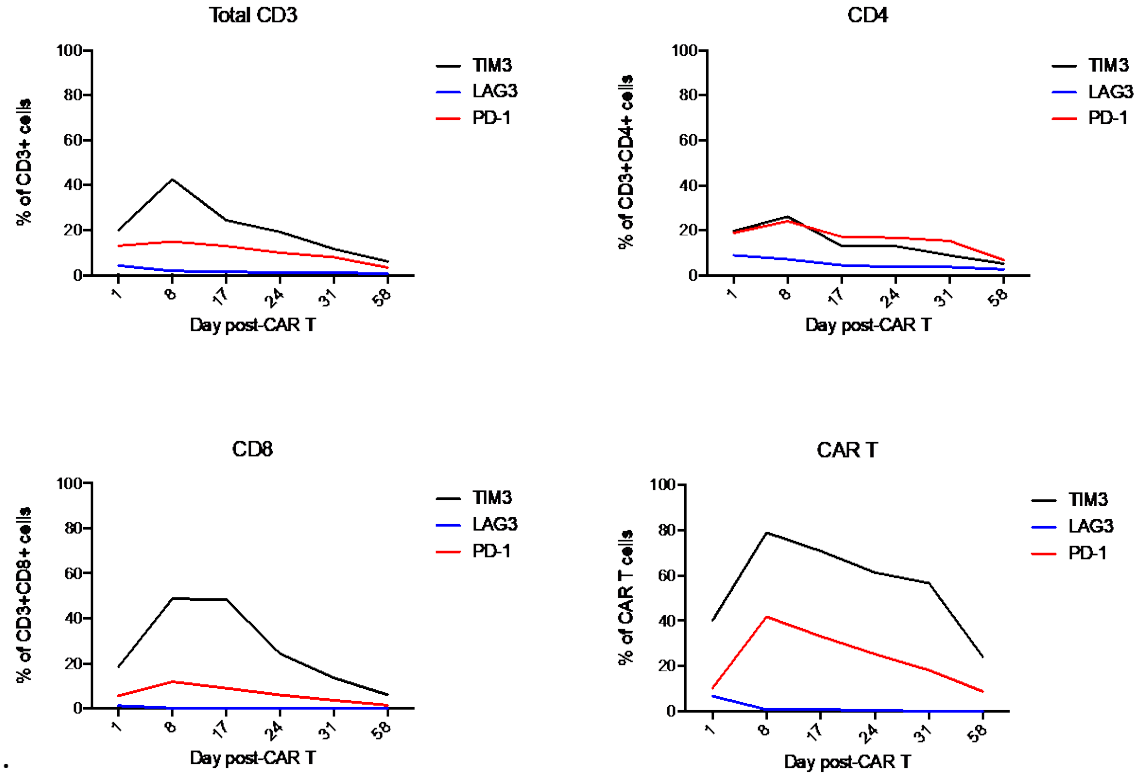
CD19-CAR T cells in the skin at a site of prior lymphoma in the skin 1 week after CART infusion



Song and Herrera Blood 2019

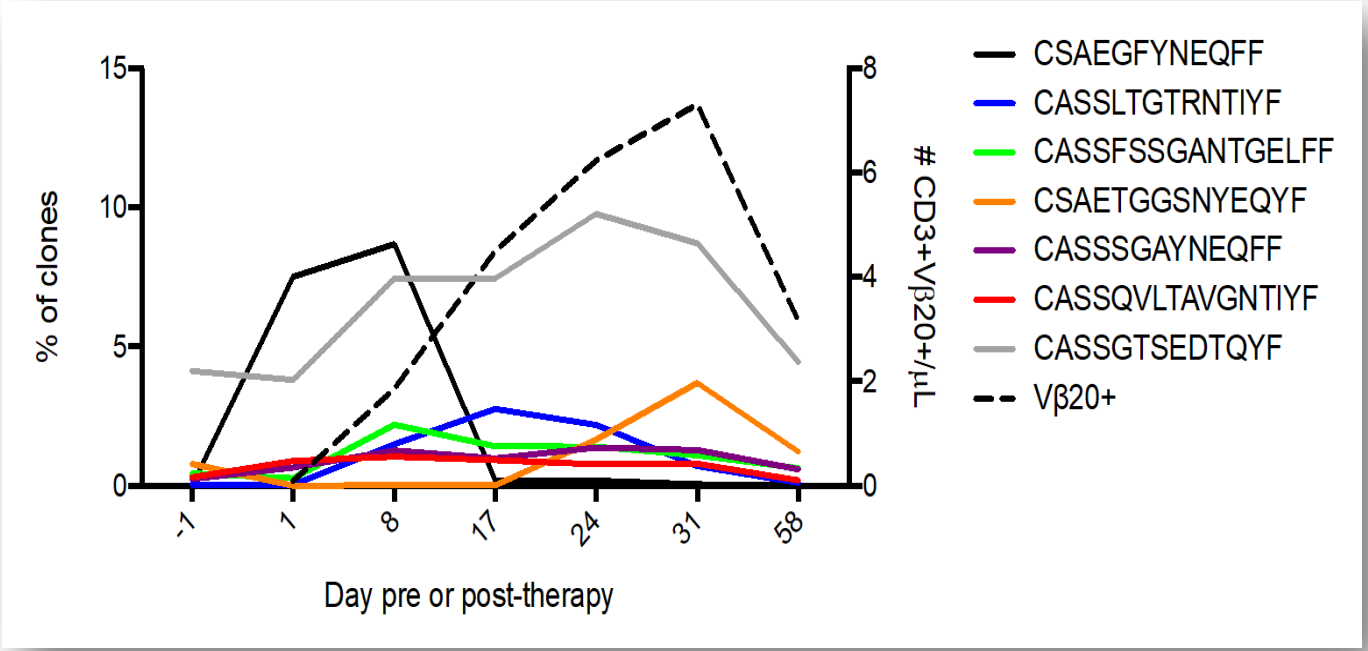
Markers for CART during *in vivo* expansion

Over-expression of negative-regulatory receptor TIM3 and PD1 on CART during expansion



Funk 2018 Int J Mol Sci.

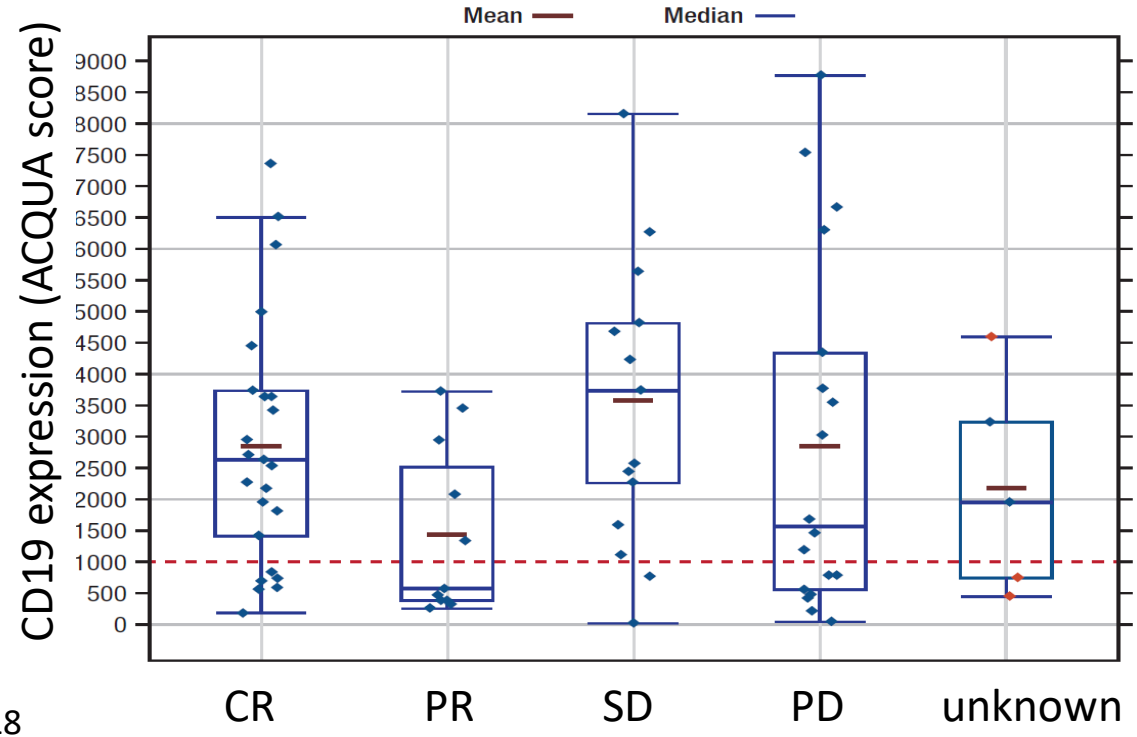
Oligoclonal T Cell Expansion During Tisagenlecleucel CAR T Therapy



Funk 2018 Int J Mol Sci.

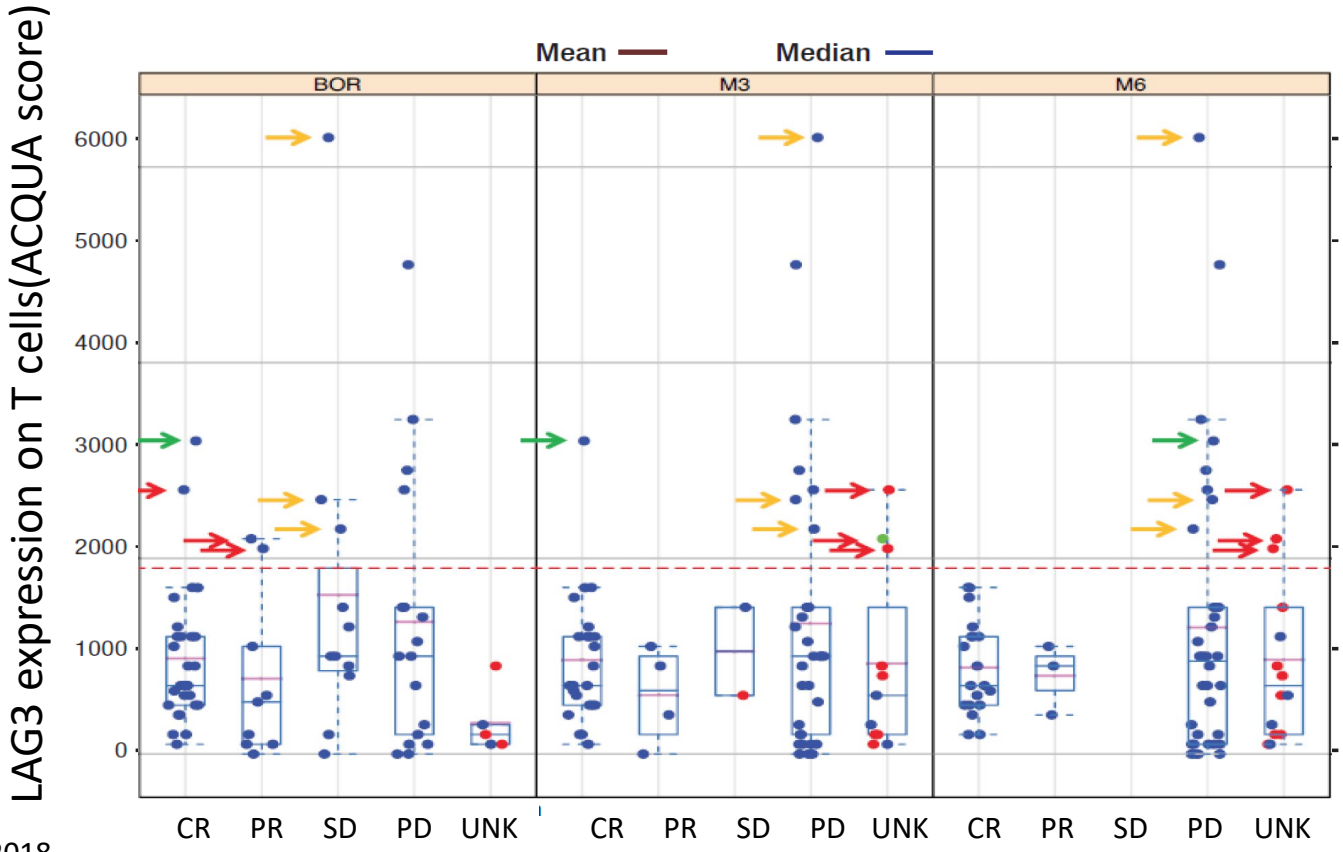
What factors predict response to CART?

CD19 expression at baseline was not necessary for Tisagenlecleucel response



Schuster NEJM 2018

High PD1:PDL1 interaction and LAG-3 expression in pre-Rx tumor-infiltrating T cells was seen in non-responding patients



Schuster NEJM 2018

High Pre-CART LDH and cytokines predict poor outcomes

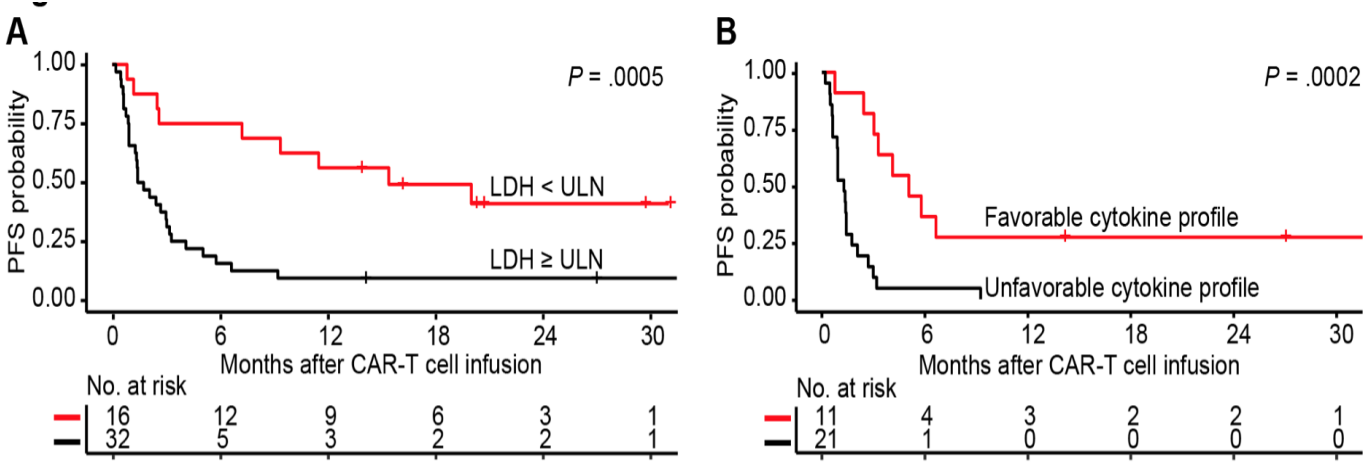


Table S4. Multivariable model for factors impacting PFS in aggressive NHL adjusting for new treatment after CAR-T cell infusion as a time-dependent covariate*

Variable	Hazard Ratio	95% CI	*P* value
LDH, pre-lymphodepletion†	1.37	1.14-1.63	.0007
MCP-1, day 0 (pre-CAR-T cell infusion)‡	0.29	0.09-0.90	.03
IL-7, peak§	0.89	0.77-1.04	.14
New treatment (Y)‖	1.12	0.45-2.78	.80

Hirayama Blood 2019 (presented at 2018 ASH meeting)

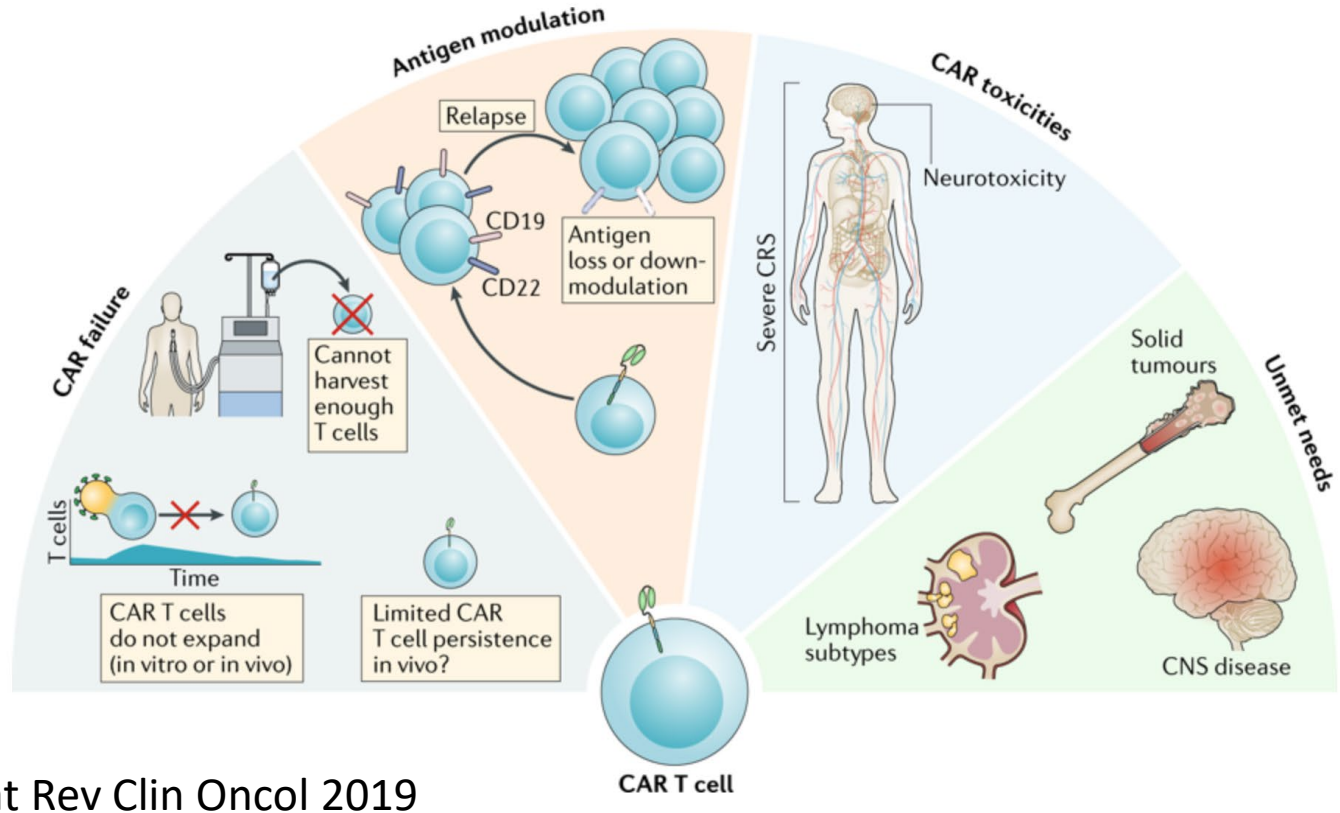
Do anti-CART immune responses affect CTL019 CART efficacy?

- No apparent impact of anti-CART humoral and cellular immunogenicity on exposure and response was observed
- Treatment-induced anti-mCAR antibodies were observed in 5% of the patients
- Pre-existing humoral immunity did not appear to impact duration of response
- T cell responses were consistent over time, and no impact on transgene expansion or patient outcome was observed.

How to follow disease after CART therapy

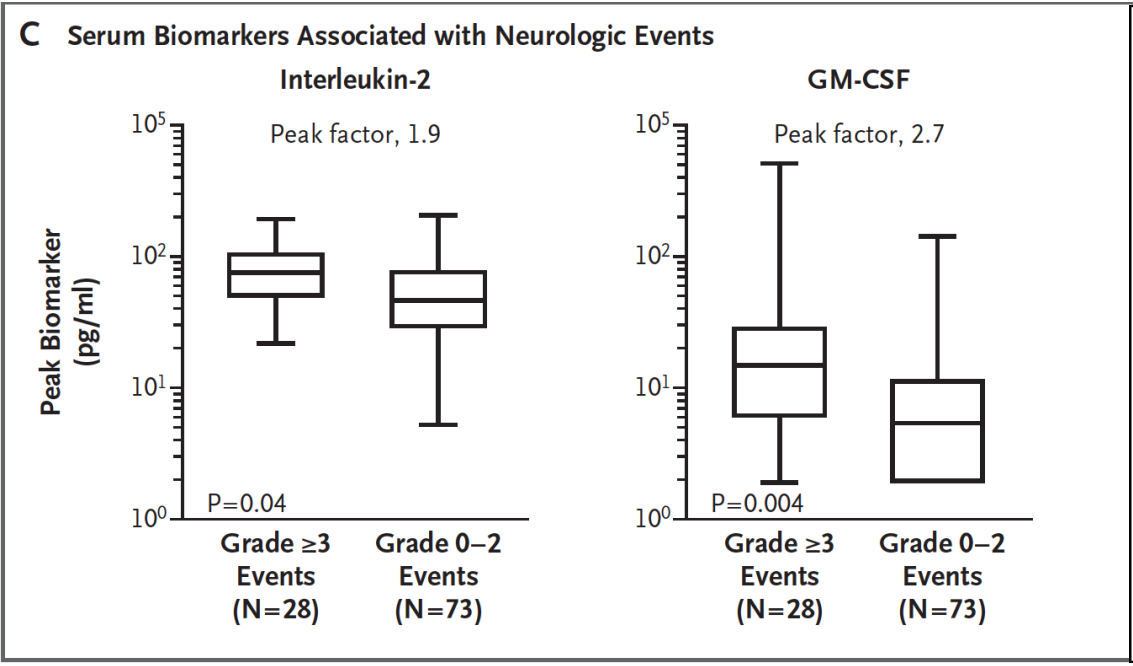
- Repeat staging (PET/CT) at 3 months
- If positive but patient not progressing, repeat again in 1-2 months
- Confirmed CR at 3 months and 6 months- follow lymphoma surveillance guidelines
- Biopsy PET+ residual disease, asses CD19 expression
- Consider involved filed XRT for localized relapse

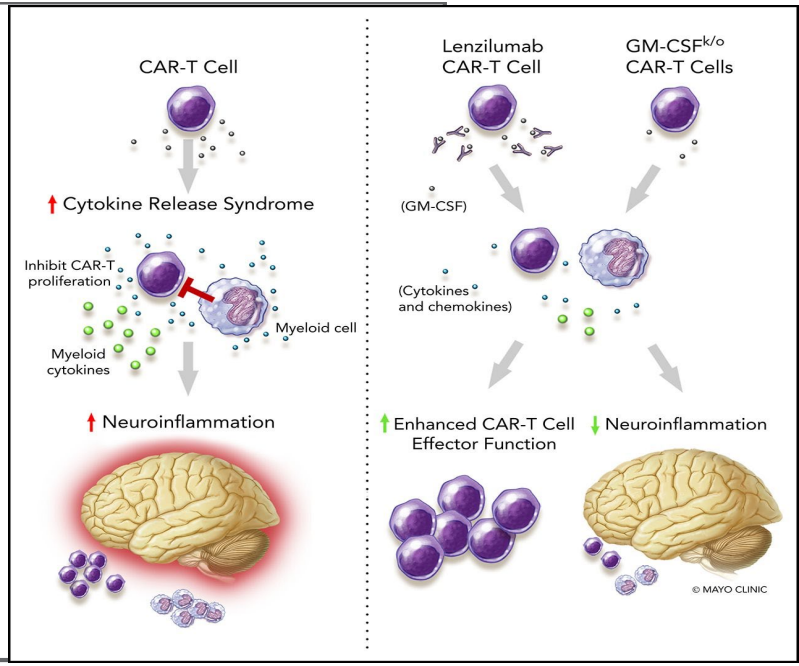
Limitations of CART therapy



Shah and Fry Nat Rev Clin Oncol 2019

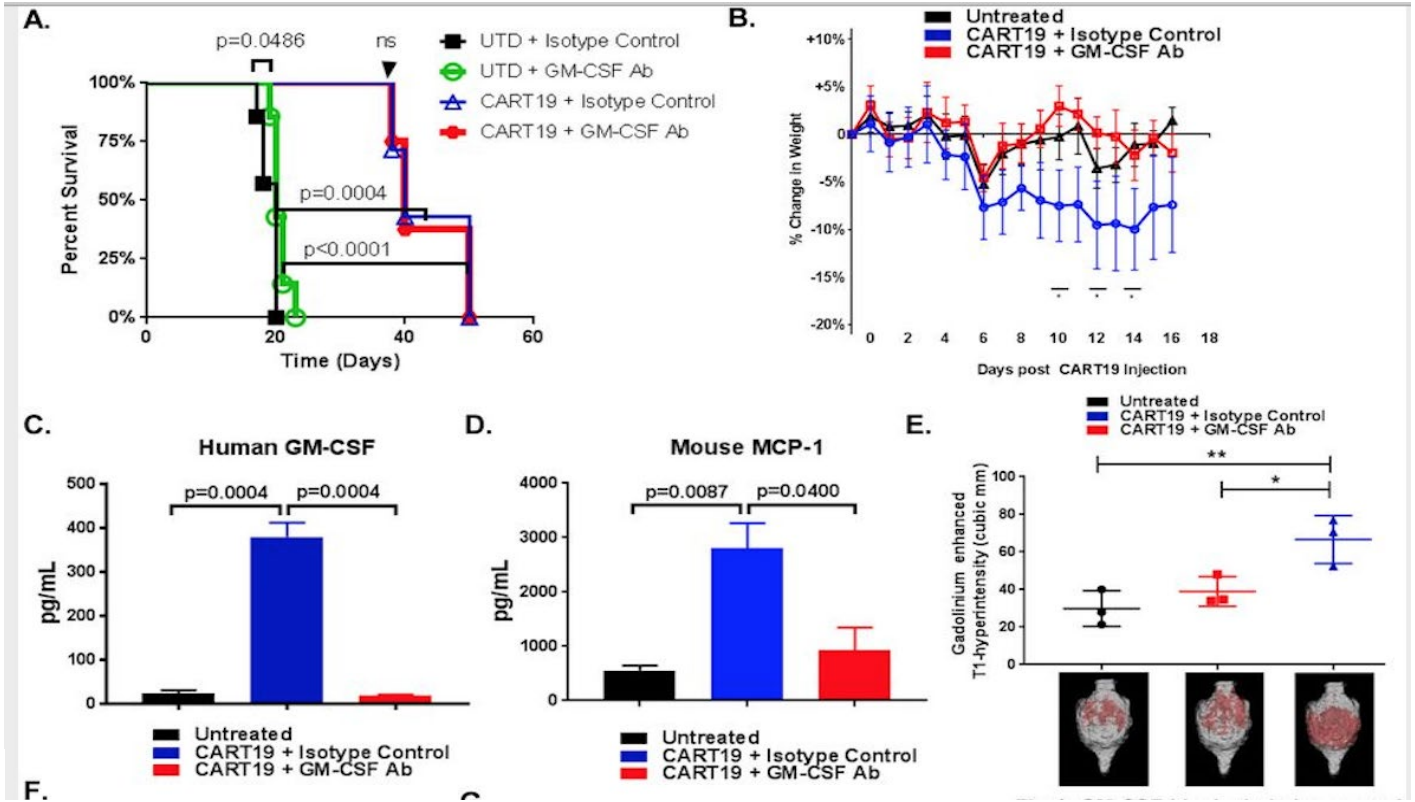
Blocking GM-CSF signaling may enhance CART activity while decreasing CRS





Neelapu NEJM 2017; Sterner ASH 2018

Anti-GM-CSF antibodies decease toxicity of CART without compromising efficacy

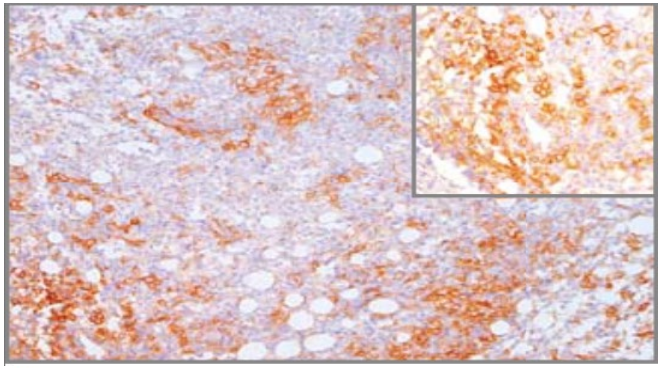


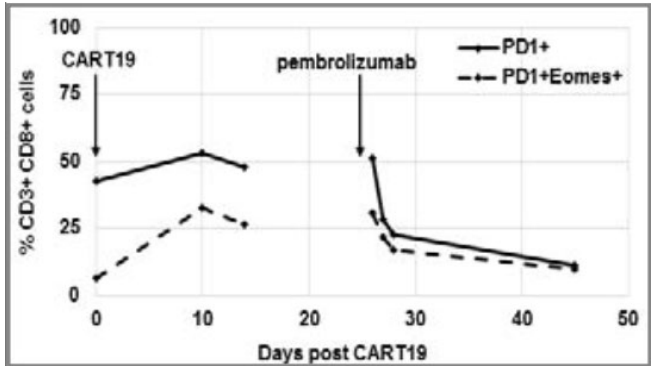
Sterner ASH 2018

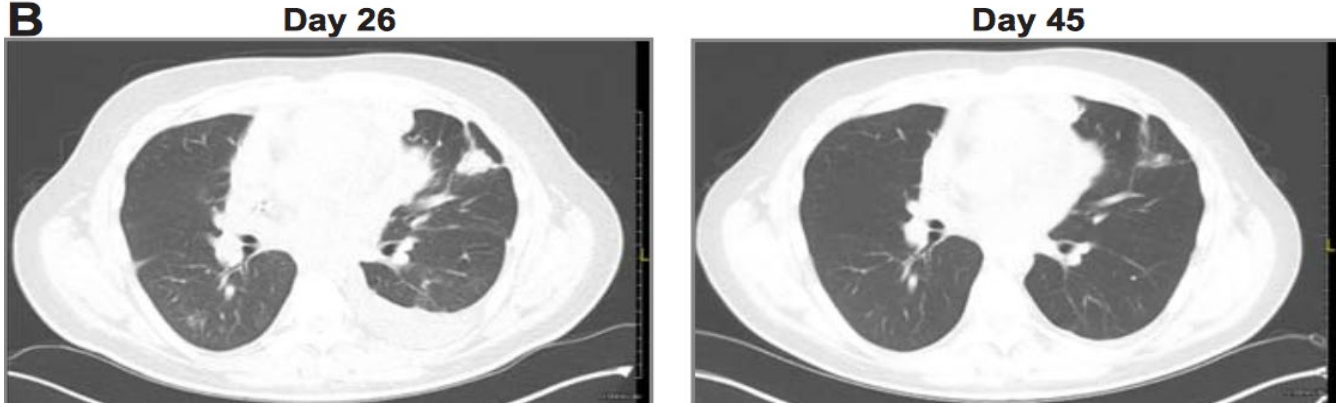
How to manage DLBCL relapsed after CART?

- Poor performance status and cytopenias may limit available options: expect <25% survival
- Consider clinical trial
- Immune check-point blockade
- Rituximab and lenalidomide
- TKI: Ibrutinib, ?PI3K inhibitors
- Allo-transplant for fit patients with limited disease burden

Anti-PD1 Pembrolizumab therapy in a PDL1+ NHL patient relapsing after CART infusion

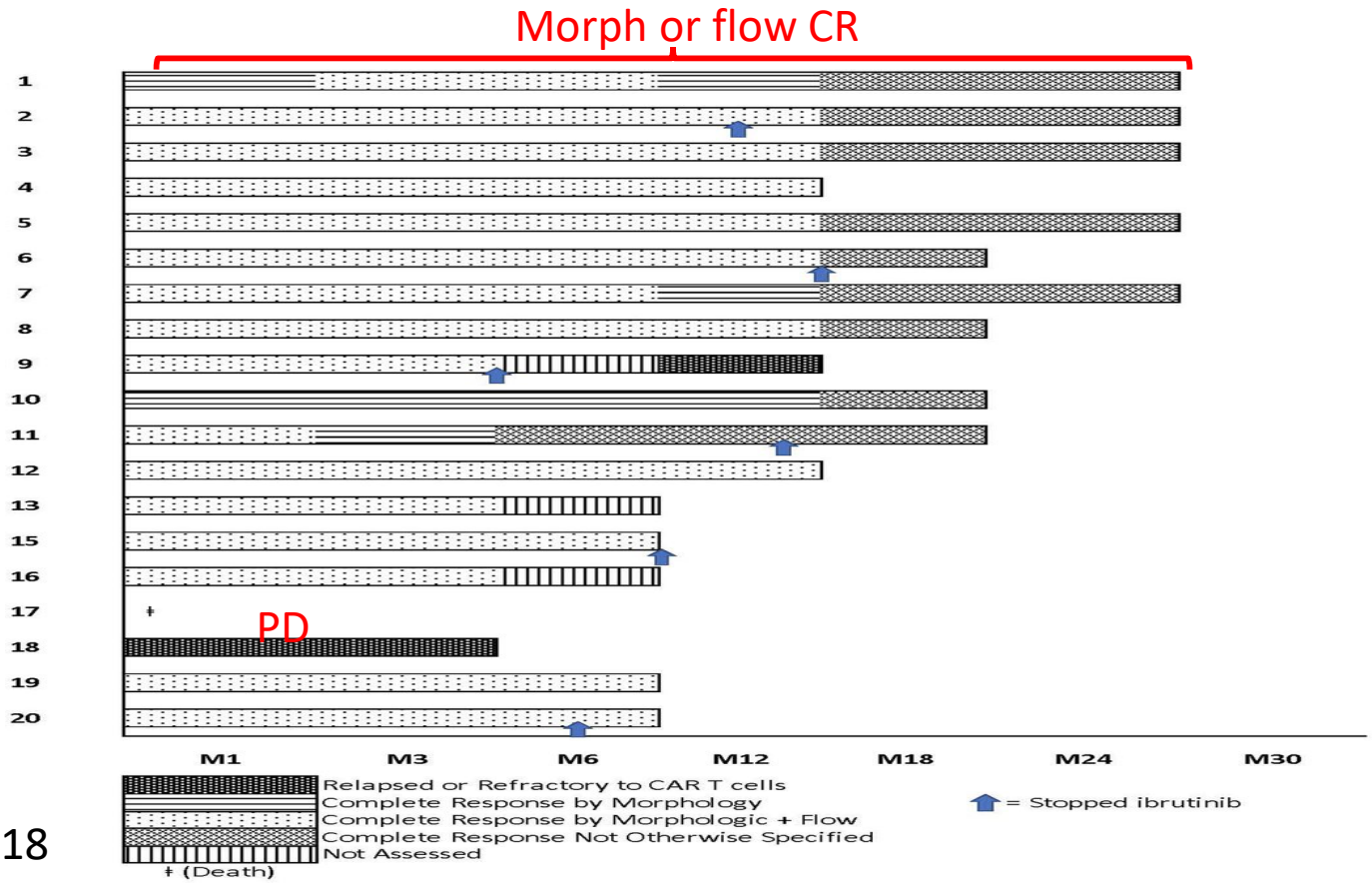






Chong 2016 Blood

Prospective Clinical Trial of Anti-CD19 CAR T Cells in Combination with Ibrutinib for CLL

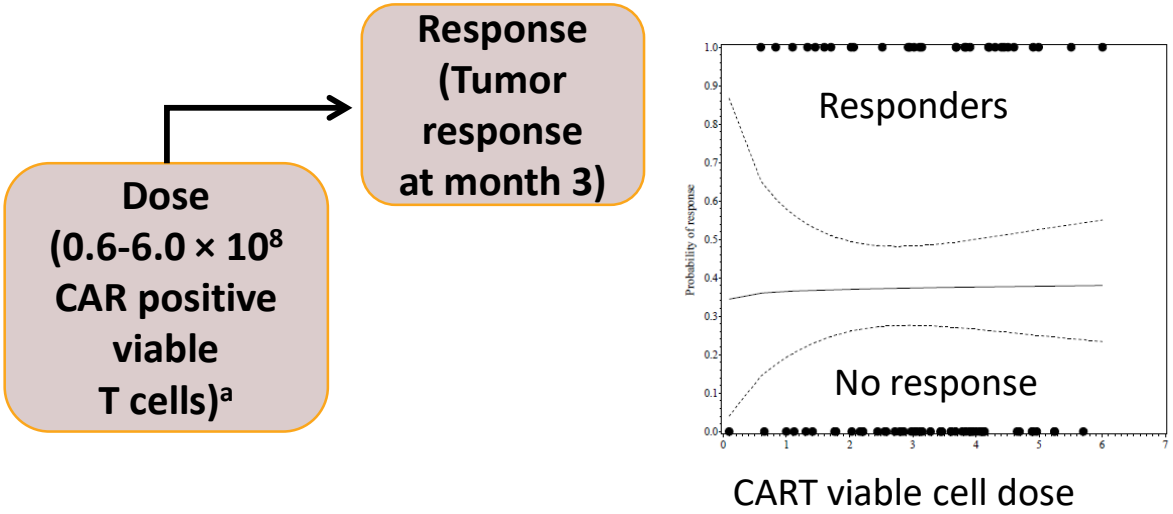


Gill ASH 2018

What can be done to increase the cell-intrinsic activity of CART therapy?

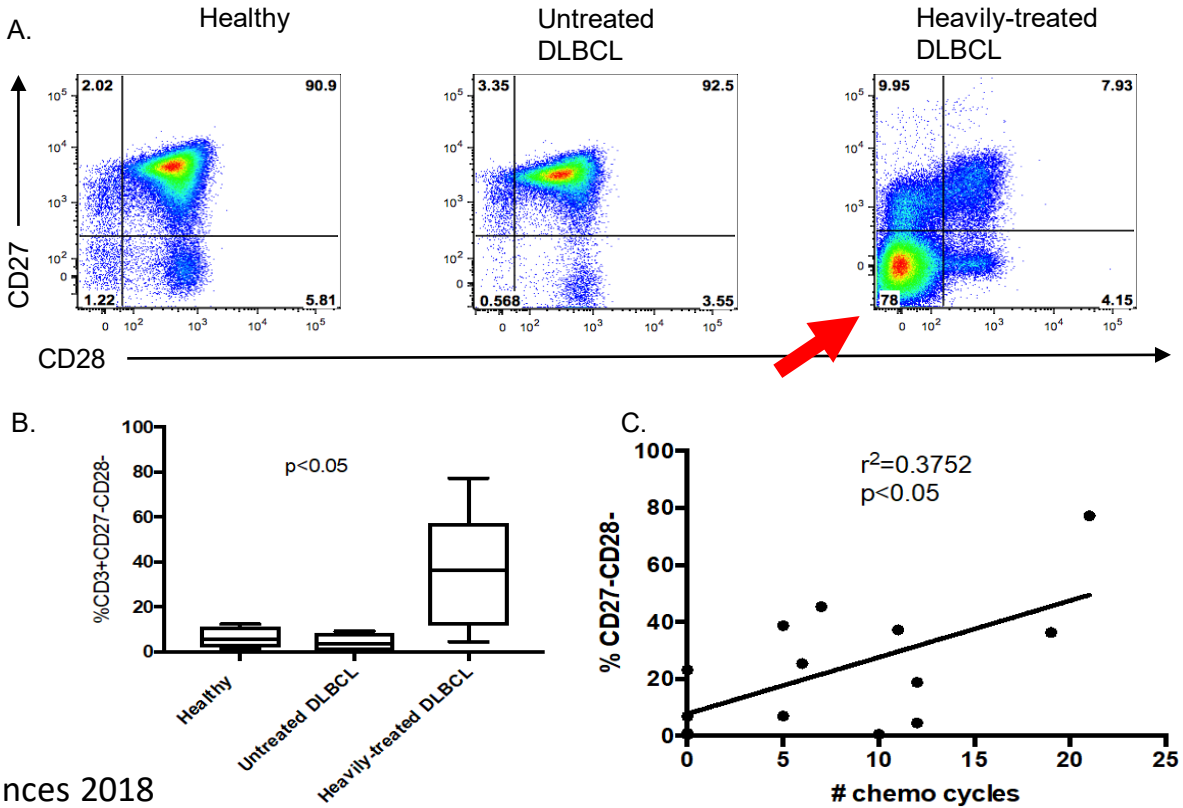
- Give more CART (with split dose to limit toxicity)
- Obtain patient T cells earlier in the disease course, before they become senescent (Belinda and Transform trials)
- Improve manufacturing process- shorter expansion cultures with less senescence
- Immune check-point drugs to block co-inhibitory pathways
- TKI treatment to change metabolic profile of CART *in vivo*
- Next generation of dual CAR T, armored CART, etc…

Infusing larger numbers of Tisagenlecleucel did not increase *in vivo* expansion or response



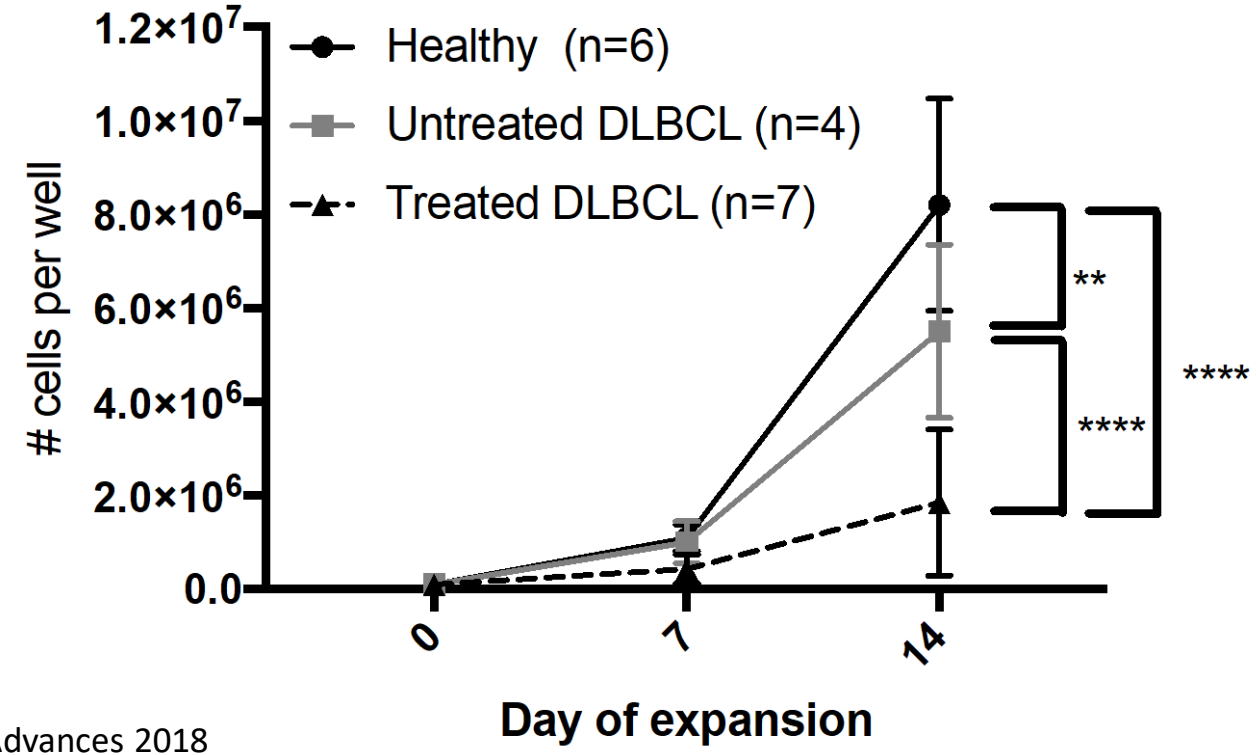
Responses were observed across full range of doses

T cells from DLBCL patients show loss of CD27 and CD28



Petersen Blood Advances 2018

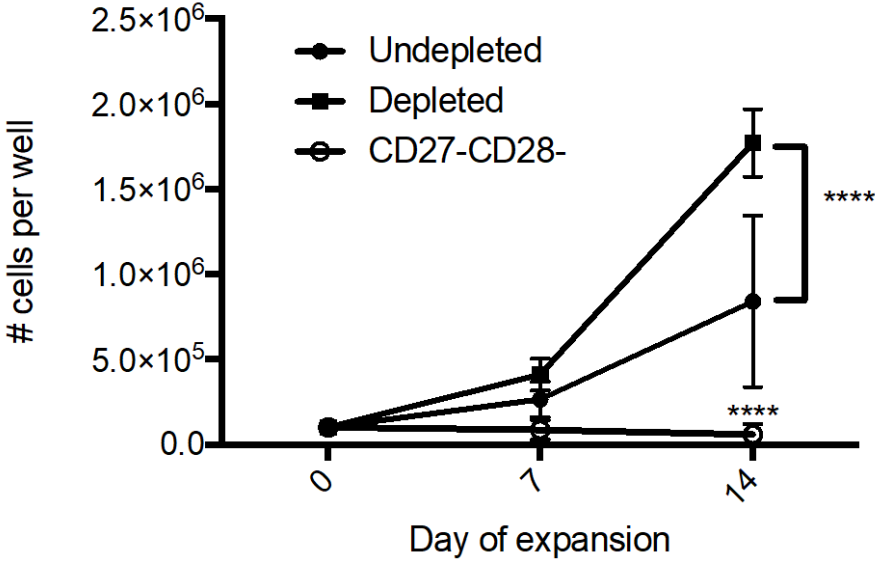
T cells from heavily pre-treated DLBCL patients have decreased ex vivo growth



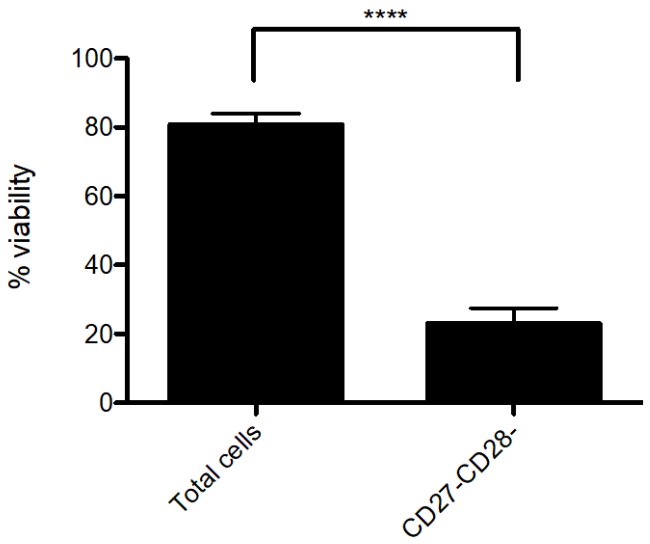
Petersen Blood Advances 2018

How might manufacturing of CART be improved?

Depletion of CD27-CD28- cells improves the expansion of T cells from DLBCL patients

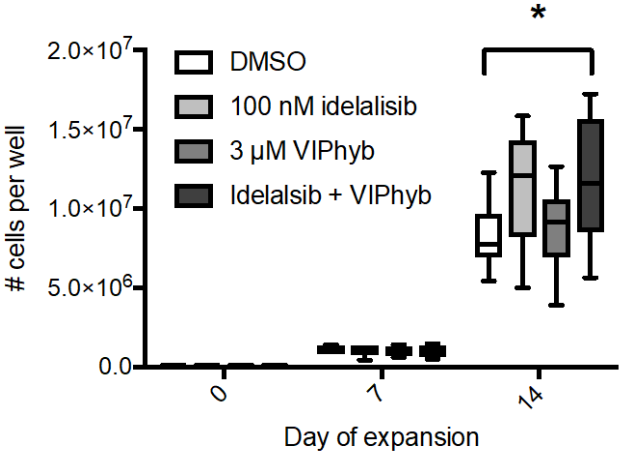


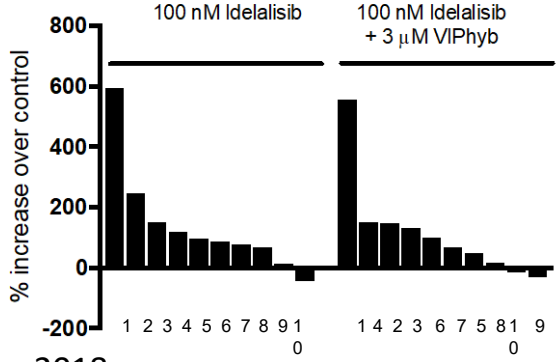
Viability after 14 days of culture

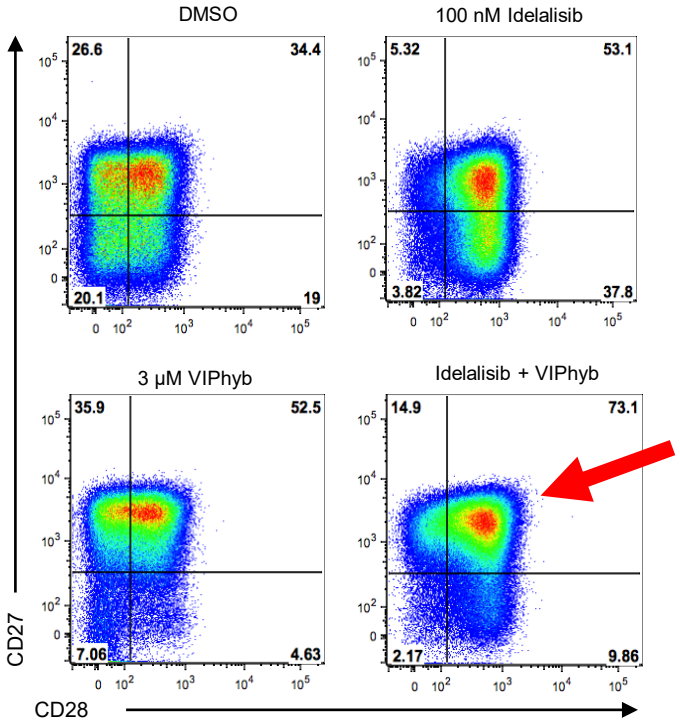


Petersen Blood Advances 2018

Combined pharmacological blockade of PI3Kδ and VIP antagonist increases CD27+CD28+ T cell expansion

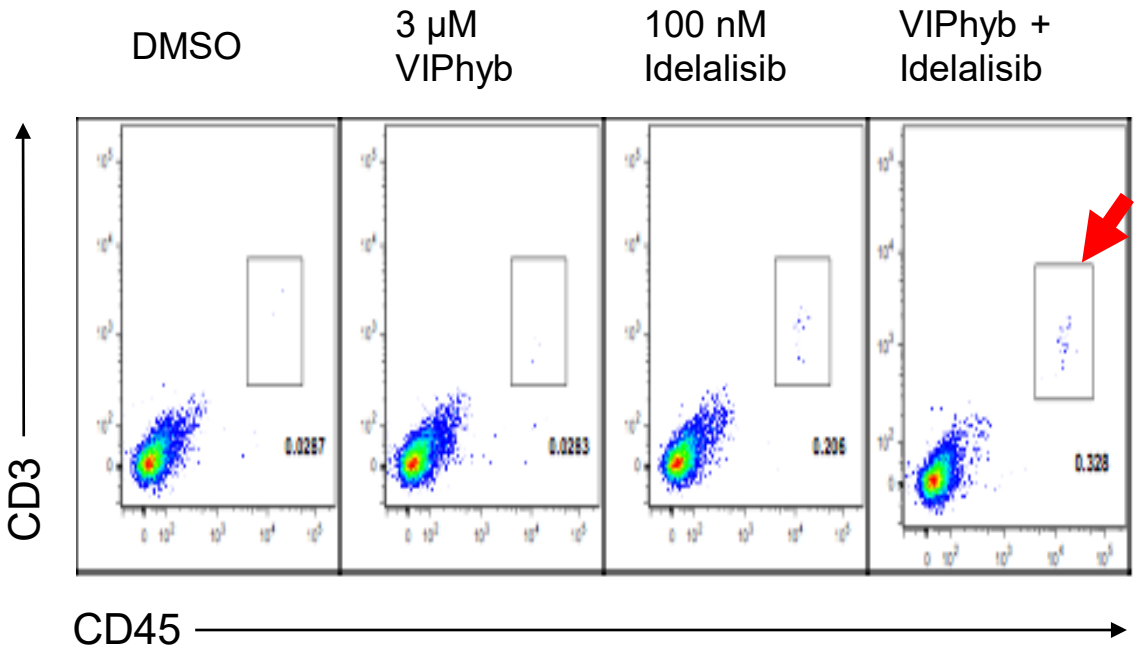


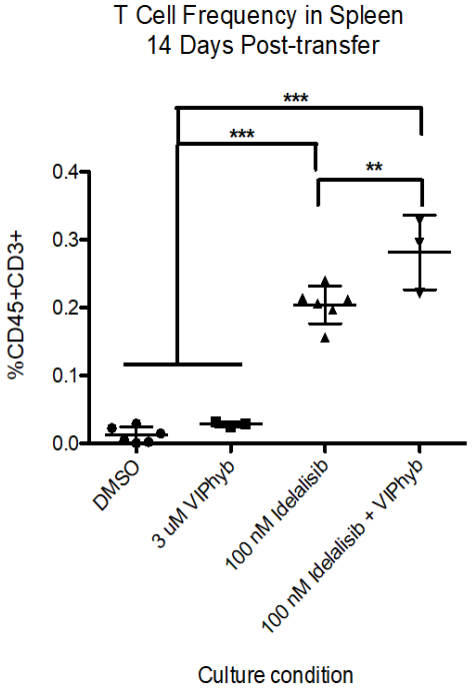




Petersen Blood Adv. 2018

Improved *in vivo* persistence of human T cells from DLBCL patient expanded with Idelalisib and VIP antagonist





Petersen Blood Advances 2018

How to prepare your center for CART

- Identify CART experts/champions among physicians, intake coordinators and nurses
- Develop SOP for CART ordering and handling, pre- and post CART patient evaluation, CART infusion, follow-up
- Assemble and educate multi-disciplinary team that includes cell therapists, ICU, ER, neurology, nursing, social worker
- Develop standardized treatment algorithms for management CRS and neurotoxicity
- Track your institutional experience with different clinical targets, CAR constructs

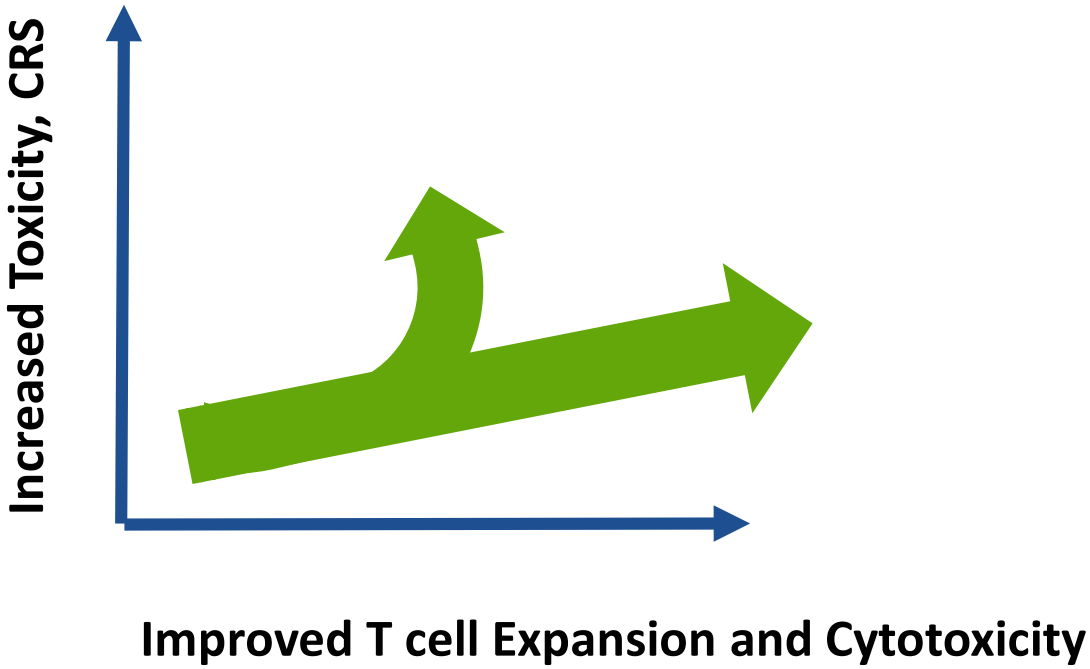
General points on managing CART patients

- Identify patients to identify those who will benefit and tolerate possible complications
- Expect lower responses in patients with rapidly growing disease, high LDH, ferritin pre-treatment
- Avoid CART infusions during acute inflammation/infections
- Work-up early fevers as infections, low threshold for tocilizumab
- Work-up altered neurological status to r/o infection, stroke, relapse
- Monitor Ig and blood B cell levels, give replacement IVIG

Future Directions for CART

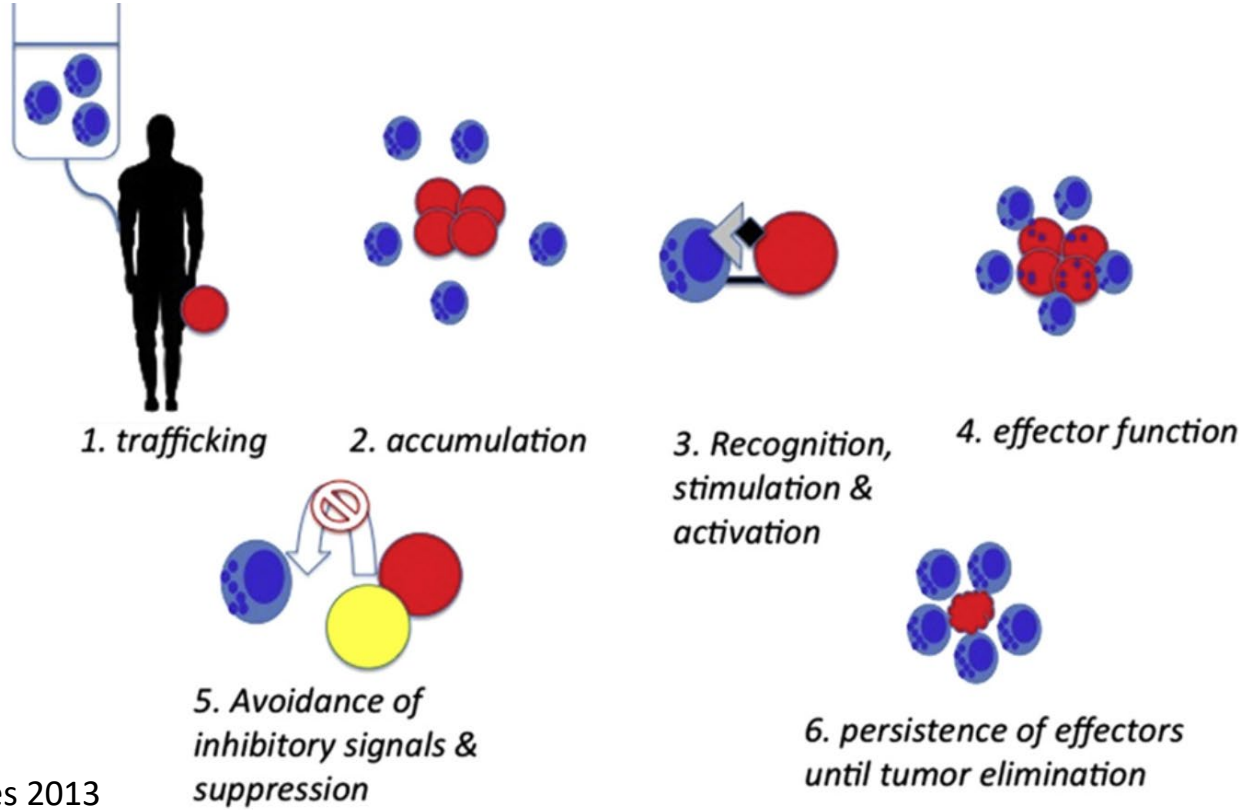
- Improved functionality of CART
- Adjuvant drugs to enhance in vivo efficacy
- Dual CAR to avoid antigen escape
- Improved supportive care and CAR constructs to reduce toxicities.

A warning on increasing CART efficacy



ewaller@emory.edu

What are the requirements for successful adoptive T-cell therapy?



Gill and Kalos Trans Res 2013

Cytokine Release Syndrome (CRS)

- Clinical diagnosis with fever and tachycardia as the presenting symptoms followed by hypotension, hypoxemia and multi-organ failure

- Symptoms occur 1 to 14 days after cell infusion (median of 2 days after axi-cel; 3 days after CTL019), lasts a median of a week

- Laboratory evaluations show marked elevations in cytokines particularly IL-6, interferon gamma and less intensely TNF. CRP and ferritin elevated, but clinical signs of CRS preceded the laboratory abnormalities that are routinely measured.

Immune effector cell-associated neurotoxicity syndrome (ICANS); CAR-T-cell-related encephalopathy syndrome (CRES)

- Manifests as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema

- Usually appears after CRS (median 5 axi-cel; 6 days CTL019), lasts up to 2 weeks

- Treated with initially with steroids (most patients have already had tocilizumab for CRS)