

Toxicities of CAR-T and CAR Treg Cells

aka Renal Risks and Rewards of Cell Therapy



Dana-Farber
Cancer Institute

HMS Onconeurology Symposium
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Disclosures

Sarah Nikiforow declares participation in ad hoc Advisory Boards and/or Educational opportunities for A2 Bio, Atara, Iovance, Johnson & Johnson, Pierre Fabre, and Sobi

Presentation Overview

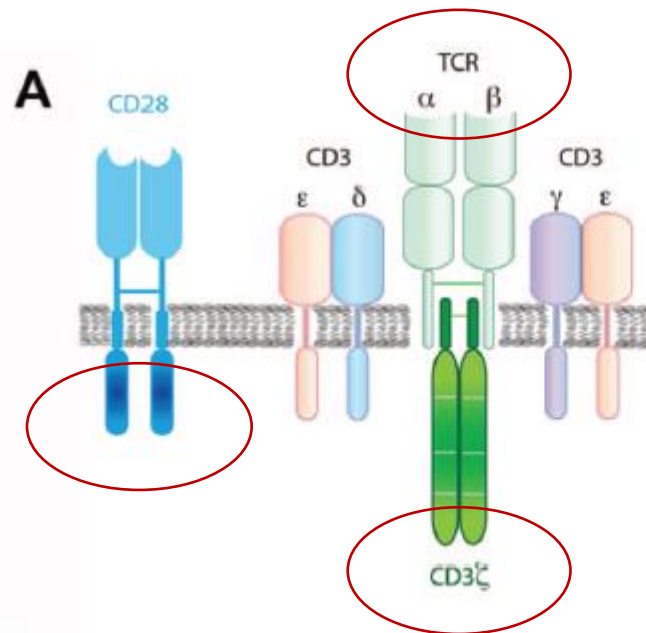
- Background of Chimeric Antigen Receptor Therapy
- Cytokine Release Syndrome and CAR-T Renal Toxicities
- Mitigation Strategies and Expanding Eligibility
- Applications of Cell Therapy to Kidney Disease
 - Autoimmune Conditions
 - Tolerance in Organ Transplant
 - Renal Cancer

T-cell Recognition and Activation

1) Antigen specificity (peptide in HLA context)

2) Signal transduction/activation

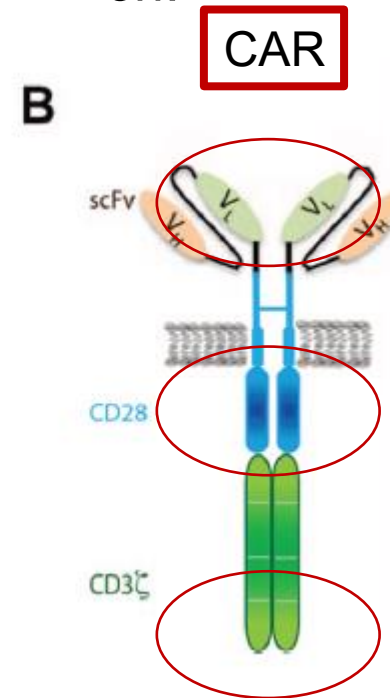
3) A double check – 2nd signal



1) Antigen specificity – Antibody domain

2) Signal transduction/activation

3) A double check – 2nd signal turned on!

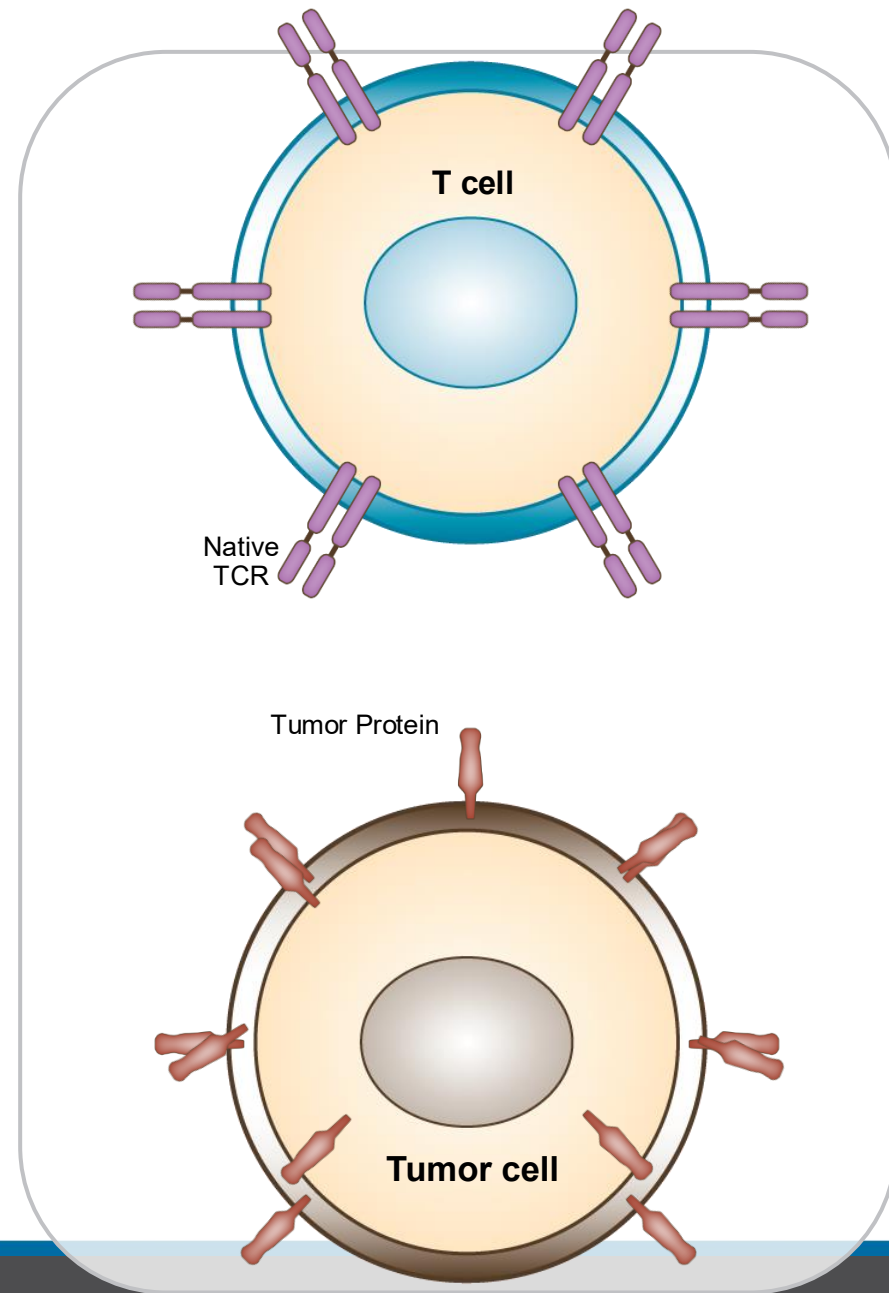


Sadelain, Park ASH Educ Program, 2015

Chimeric Antigen Receptor T Cells

- These T cells exploit native antibody or T cell recognition and signaling pathways
- Genetic engineering and introduction of unique combinations of proteins through viral vectors allows generation of T cells recognizing a particular tumor protein
- These cells are a “living drug”, expanding dramatically after infusion, and effectively killing tumor cells
- After initial trials proving the targeted efficacy in B cell malignancies, other targets, cancers and molecular constructs are being explored

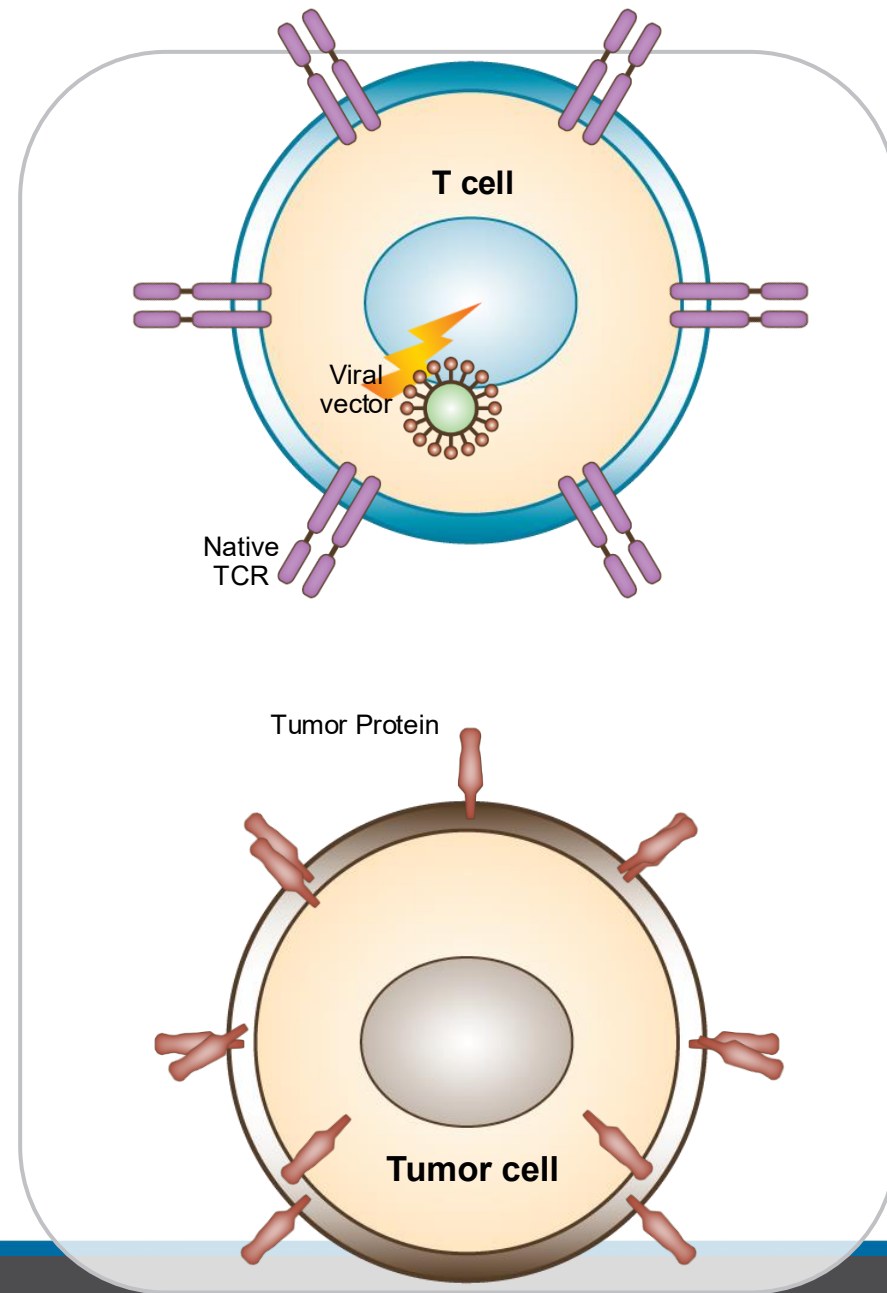
Image courtesy of Stephan Grupp, UPenn



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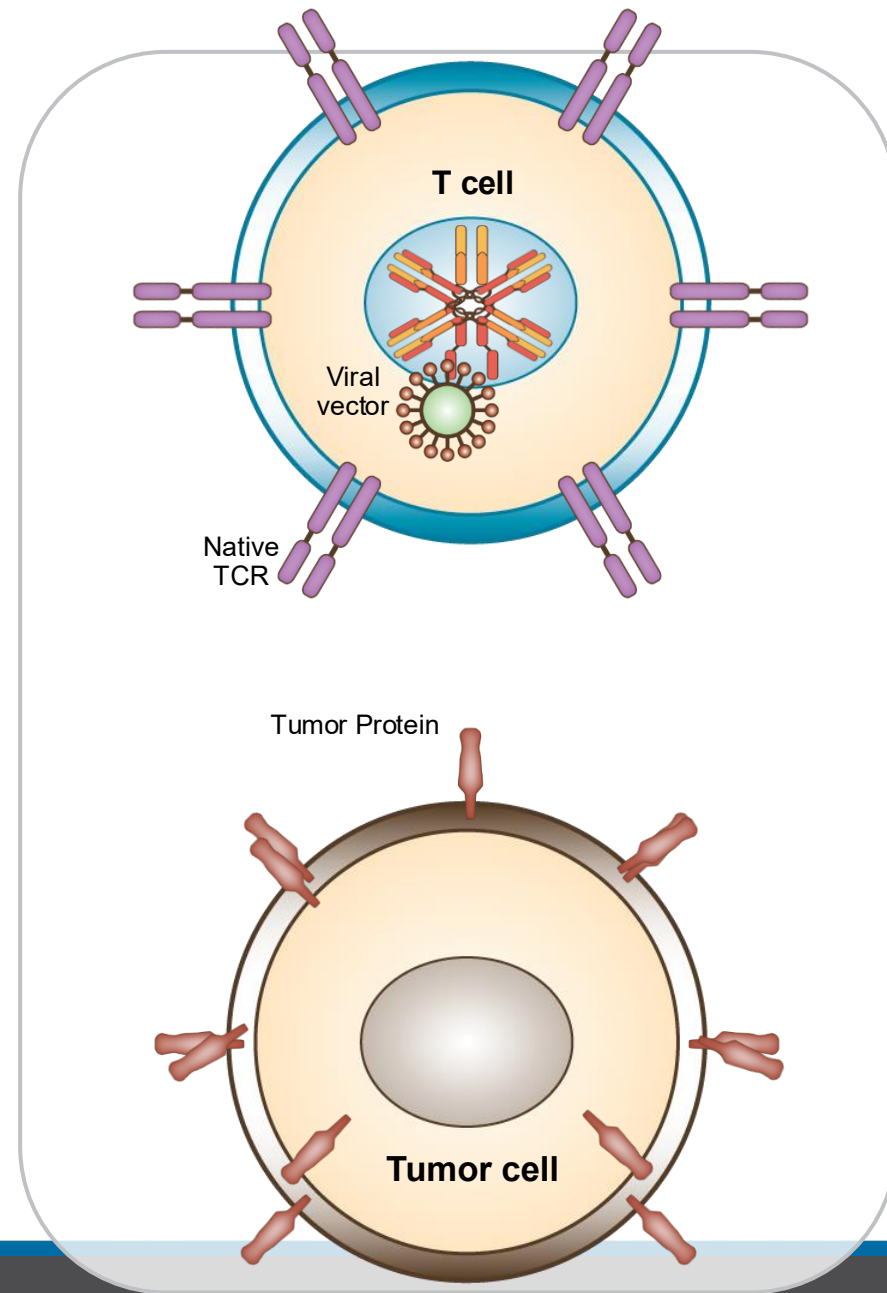
Image courtesy of Stephan Grupp, UPenn



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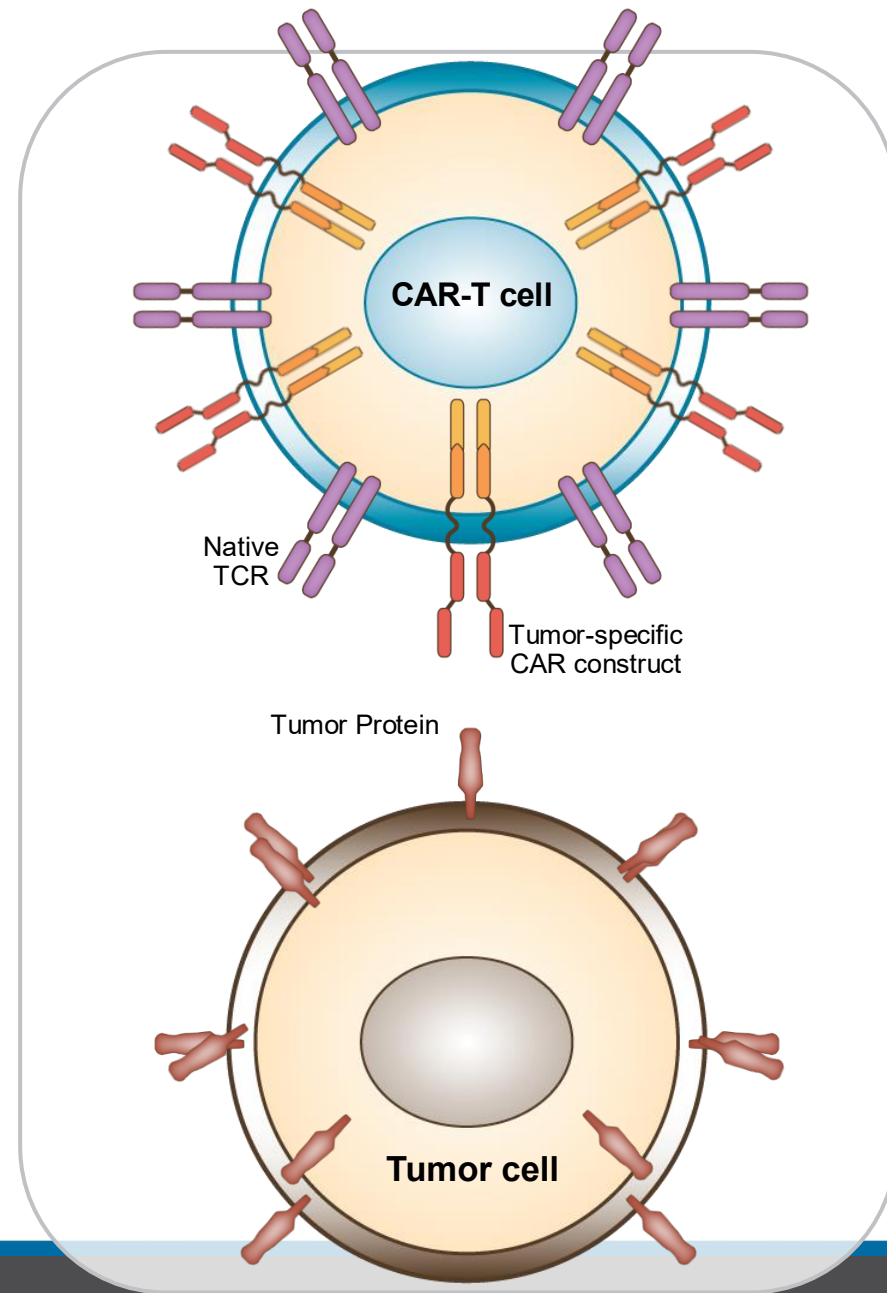
Image courtesy of Stephan Grupp, UPenn



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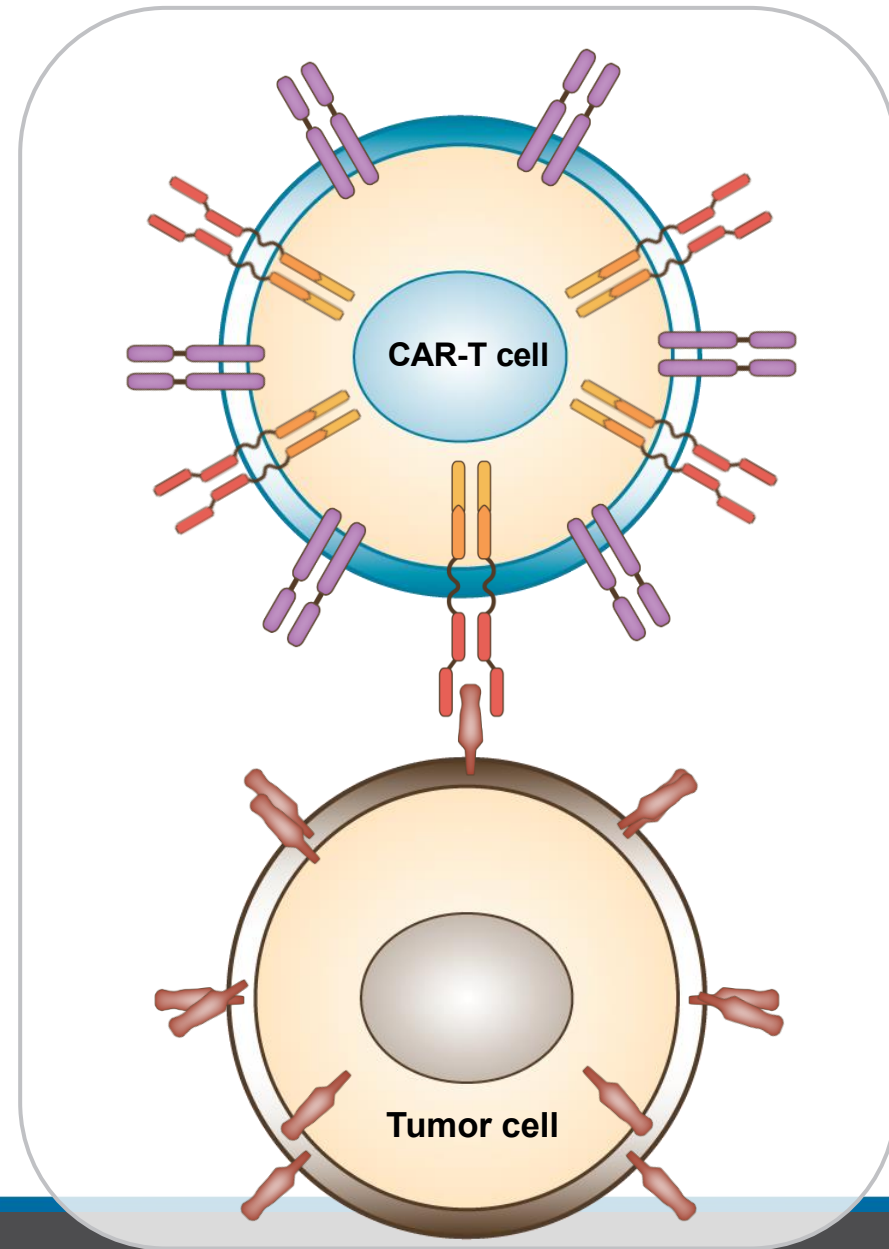
Image courtesy of Stephan Grupp, UPenn



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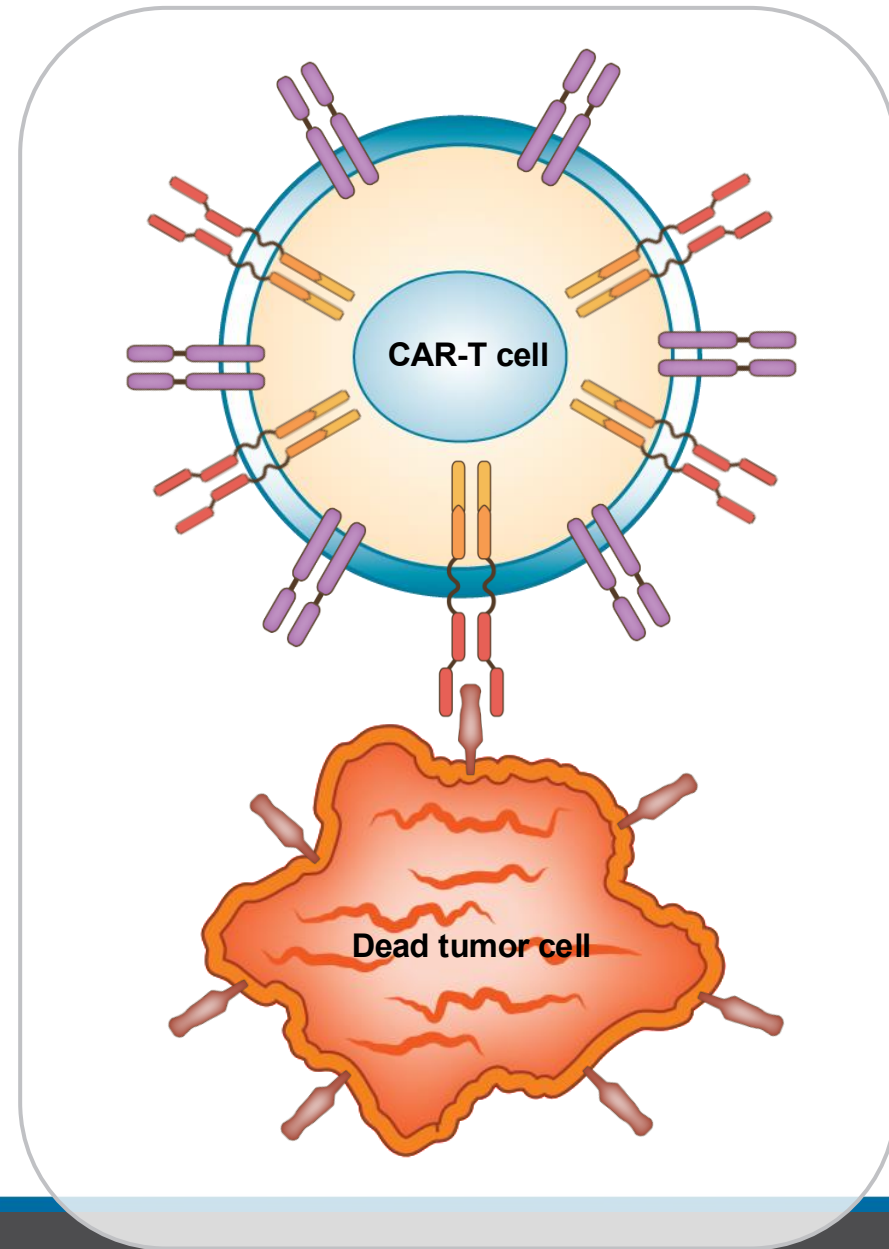
Image courtesy of Stephan Grupp, UPenn



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Image courtesy of Stephan Grupp, UPenn



Second Generation Chimeric Antigen Receptor (CAR) T cell

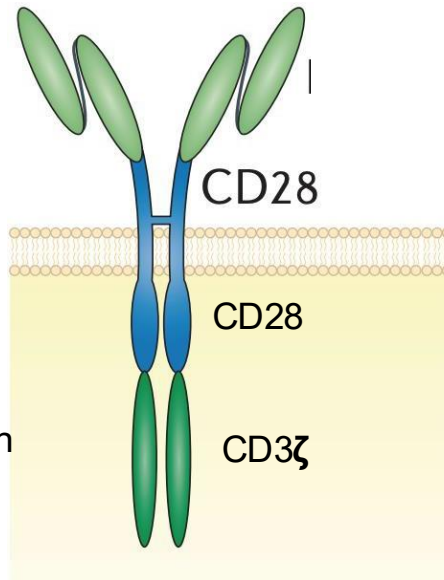
– all commercially approved are 2G

Antigen Recognition

Hinge Transmembrane

Costim

Primary activation



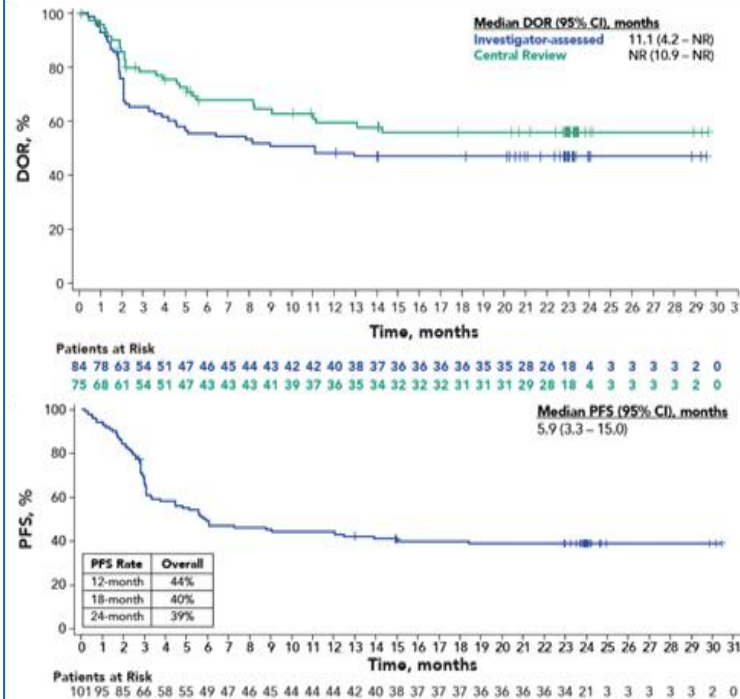
Variations in:

- Antigen recognized (CD19, BCMA)
- Hinge region
- Costim domain – CD28 vs 41BB
- Modifications of CD3z or different signaling domain entirely

R/R Lymphoma Registration Studies

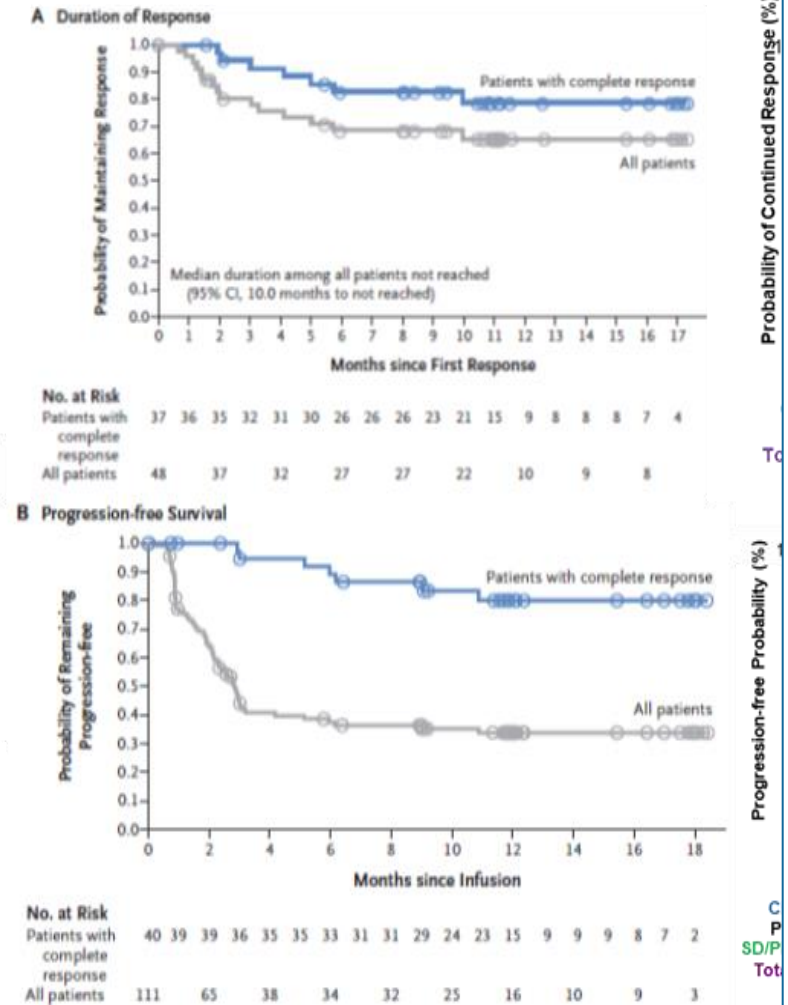
Yescarta (axi-cel) Kymriah (tisa-cel)

ZUMA-1

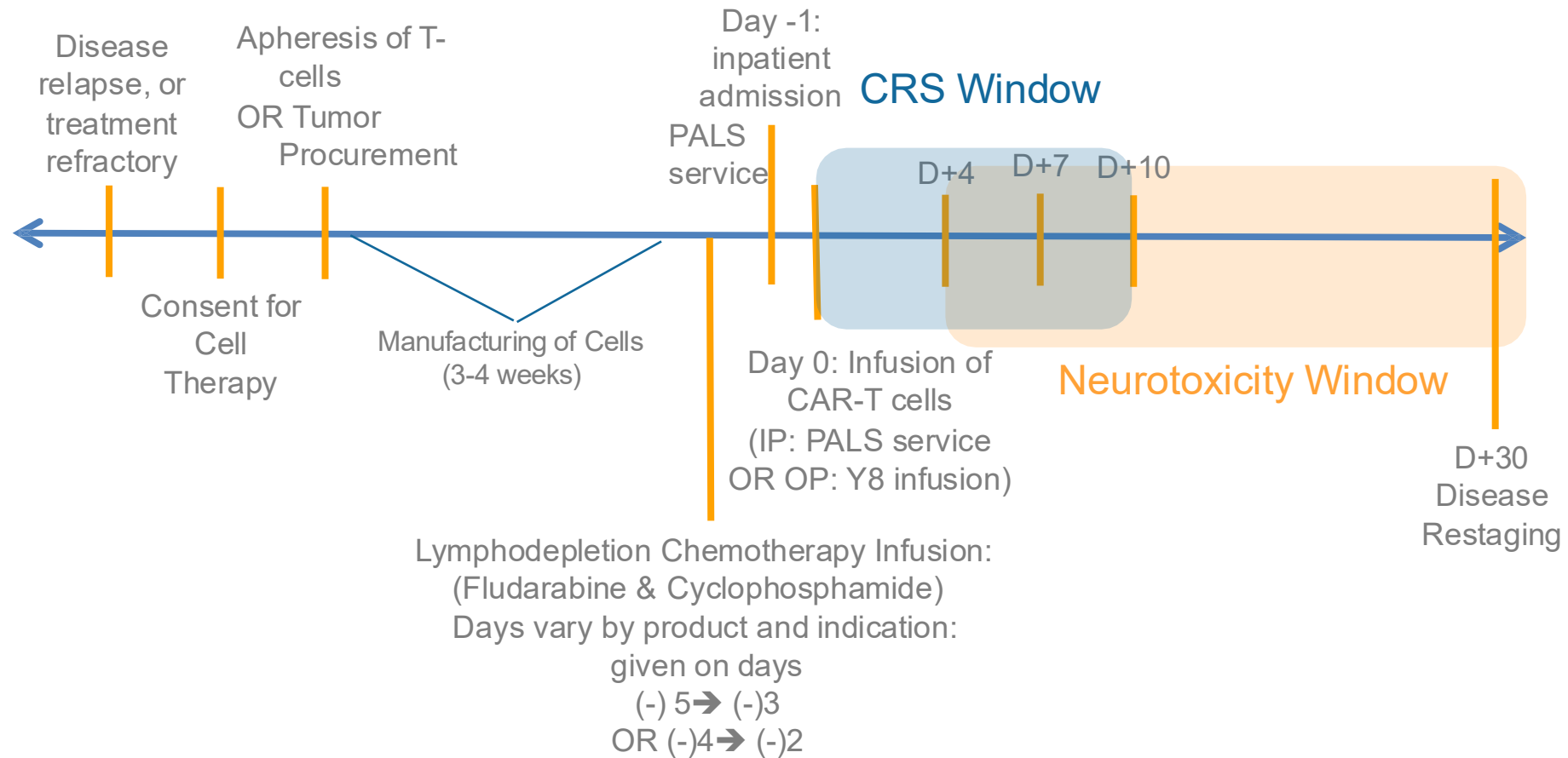


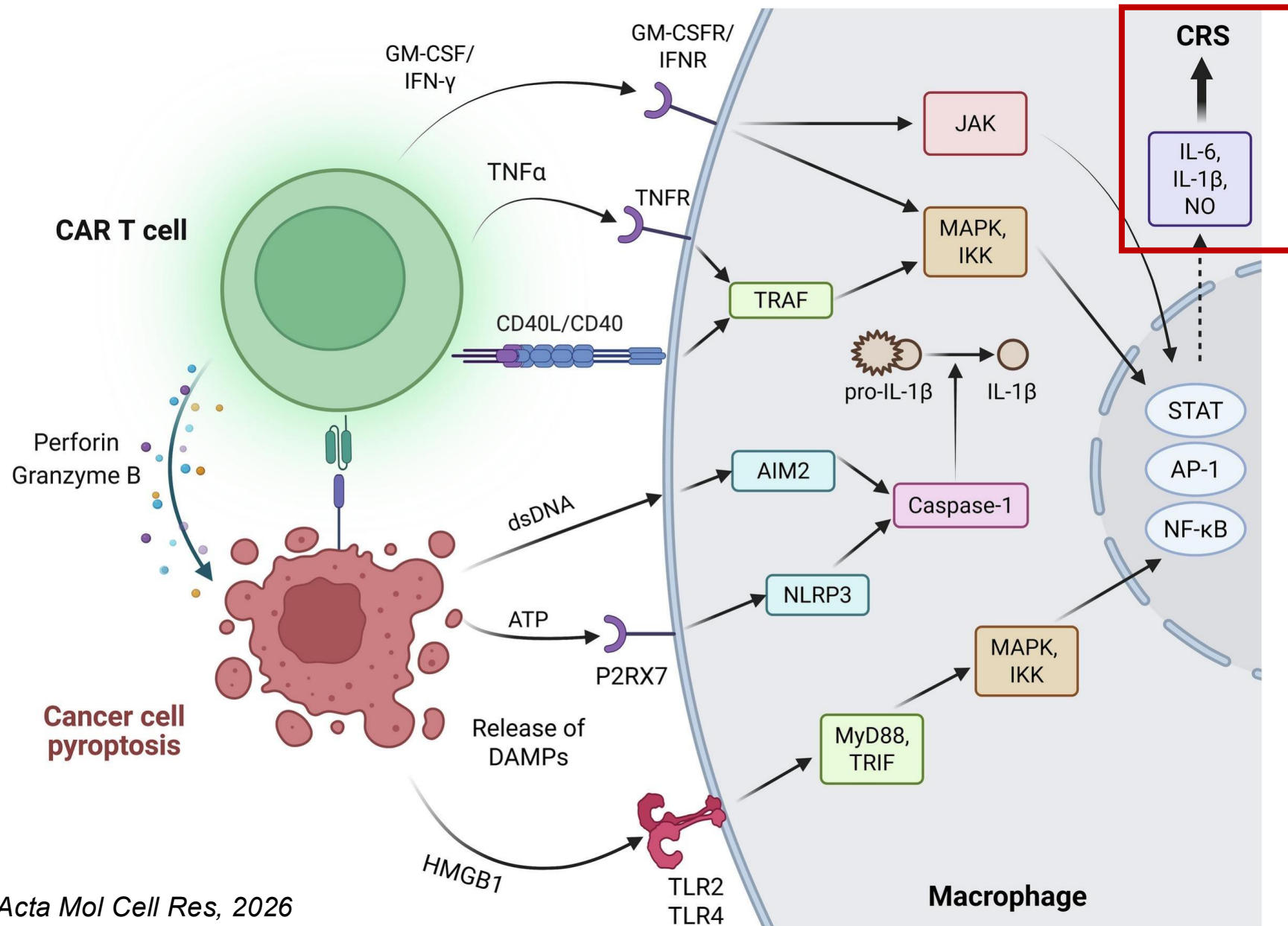
Locke et al Lancet Oncology 2019;20:31
Schuster et al NEJM 2018
Abramson et al ASH 2019

JULIET



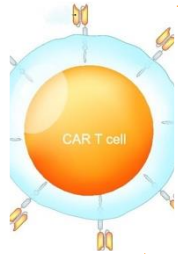
Treatment Trajectory



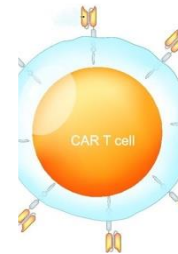


Gabriel, Biochim Biophys Acta Mol Cell Res, 2026

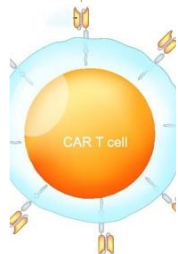
Cytokine Release Syndrome (CRS)



CRS is a result of activation of immune cells, driven by the release of IL-6 by activated macrophages and monocytes



Risk factors for development: High disease burden, higher CAR T cell dose, CARs with a CD28 costimulatory domain



Presentation: Typically, presents with constitutional symptoms such as flu-like symptoms with fevers, malaise, headache, rigors, nausea but *can progress to more serious symptoms* such as: Capillary Leak Syndrome, Hypotension, Hypoxia, Multiorgan Failure, MAS/HLH



Work Up:

CRS we will see elevated serum inflammatory markers (CRP, ferritin, IL-6), these should be repeated

Febrile Neutropenia/Sepsis: w/u with pan culturing (blood cultures, u/a, urine culture, CXR) and possibly CT scans if clinically indicated.



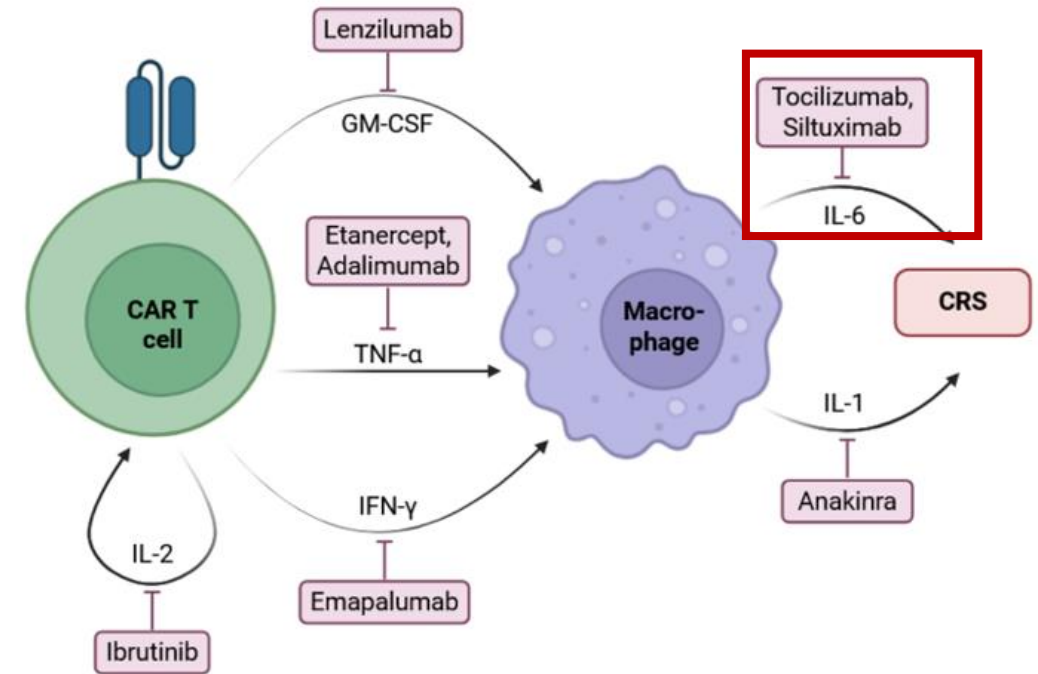
TREATMENT: We don't treat based off rising inflammatory markers alone, but look at the whole clinical picture. Since CRS can mimic sepsis we may also treat for possible sepsis

- CRS: Toci +/- Steroids → discuss with oncologist prior to ordering/administering
- Febrile Neutropenia: IV Ceftazidime
- Sometimes, CAR T cell patients will require ICU level of care for pressors or intubation → patients receiving an anti-CD 19 CAR (Lymphoma patients) should be admitted to the neuro ICU if needed ICU level care due to risk of Neurotoxicity, regardless of reason for ICU transfer.

CRS Grading and Management

ASTCT CRS Consensus Grading*

CRS parameter	Grade 1 CRS	Grade 2 CRS	Grade 3 CRS	Grade 4 CRS
Fever	Temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>is the distinguishing symptom</i> . If patients who have CRS receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, then fever is no longer required, and grading is driven by hypotension or hypoxia.			
<i>With either</i>				
Hypotension*	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥ 2 vasopressors (excluding vasopressin)
<i>and/or</i>				
Hypoxia*	None	Requiring low-flow nasal cannula at $\leq 6\text{ L/minute}$, or blow-by, <i>not as a comfort measure</i>	Requiring high-flow nasal cannula at $> 6\text{ L/minute}$, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)



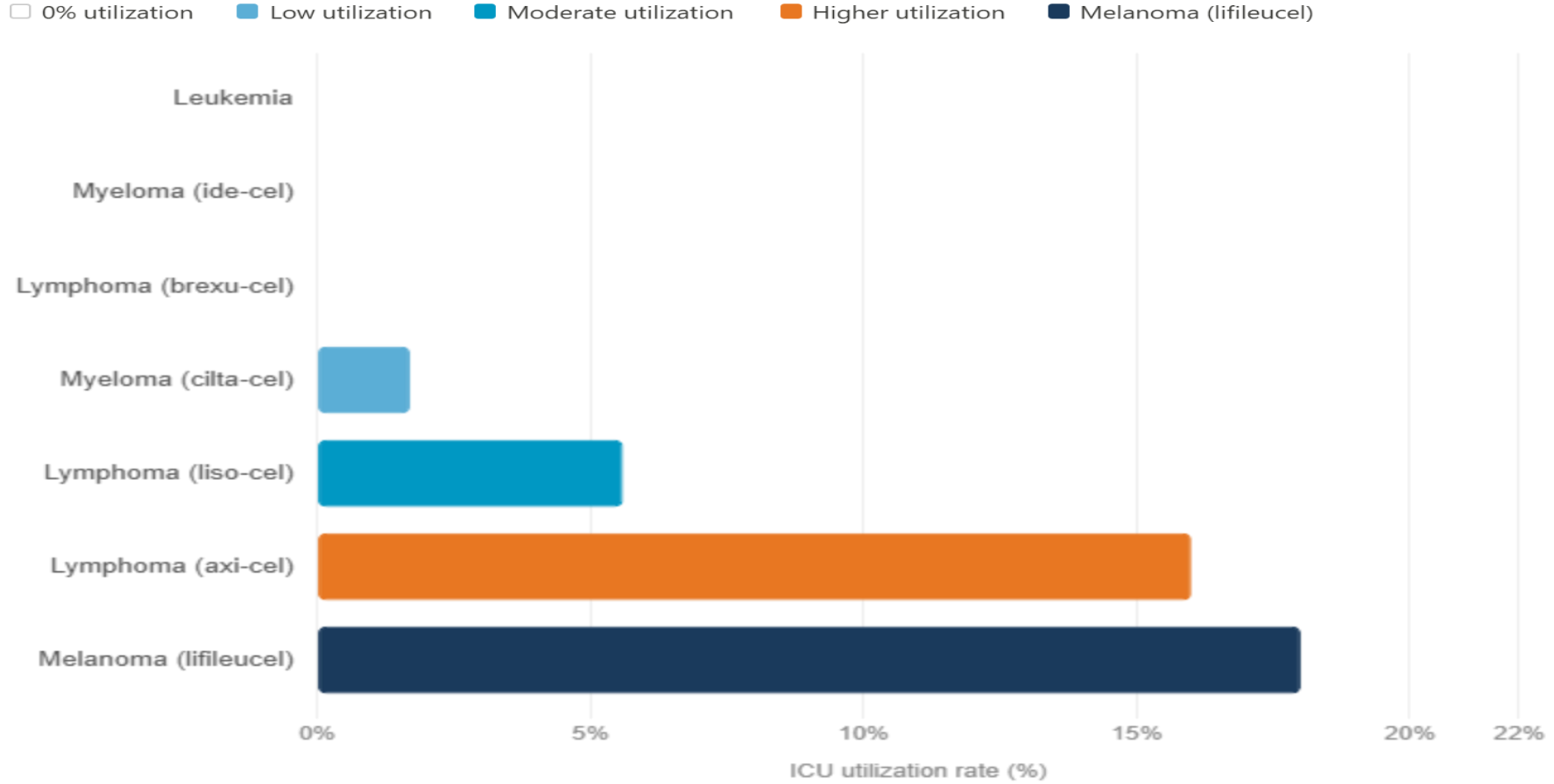
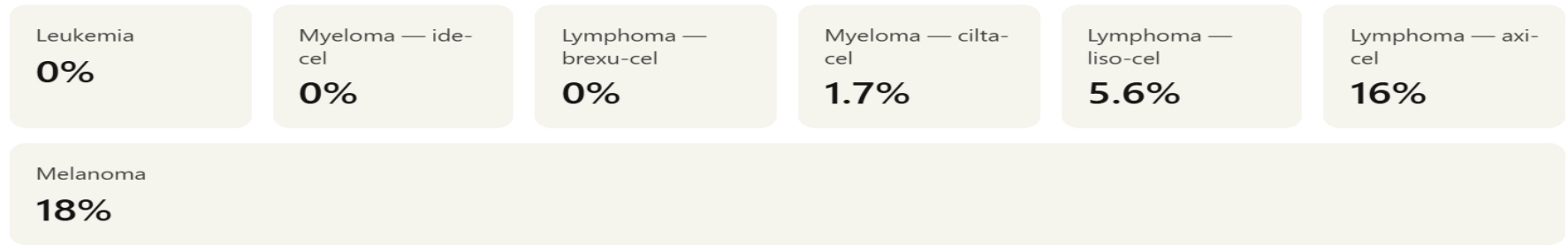
FDA APPROVED Anti-CD19 CAR T CELLS

	YESCARTA (Axicabtagene ciloleucel)	KYMRIAH (Tisagenlecleucel)	BREYANZI (Lisocabtagene maraleucel)	TECARTUS (Brexucabtagene autoleucel)	Aucatzyl (obecabtagene autoleucel)
ORR / CR	LCL: 82% / 54% FL: 91% / 60%	LCL: 52% / 40% B-ALL: 100% / 83%	LBCL: 73% / 53% CLL/SLL: 45%/ 20% FL: 95%/ 73% MCL: 85%/67%	MCL: 87% / 62% B-ALL: 71% / 56%	CR/CRi: 63%
CRS Overall; Grade 3/4	LCL: 94%; 13% FL: 81% ; 8%	LCL: 58% ; 23% ALL: 79% ; 49%	LBCL: 42% ; 2% CLL/SLL: 83%/ 9% FL: 59%/ 0.9% MCL: 61%/ 1.1%	MCL: 91% ; 18% B-ALL: 92% ; 24%	75%/ 3%

FDA APPROVED Anti-BCMA CAR T CELLS

	ABECMA (Idecabtagene vicleucel)	CARVYKTI (Ciltacabtagene autoleucel)
ORR / CR	72% / 28% sCR	98% / 78% sCR
CRS Overall; Grade 3/4	85% ; 9%	94% / 4%

ICU Utilization Across Disease centers in 2025



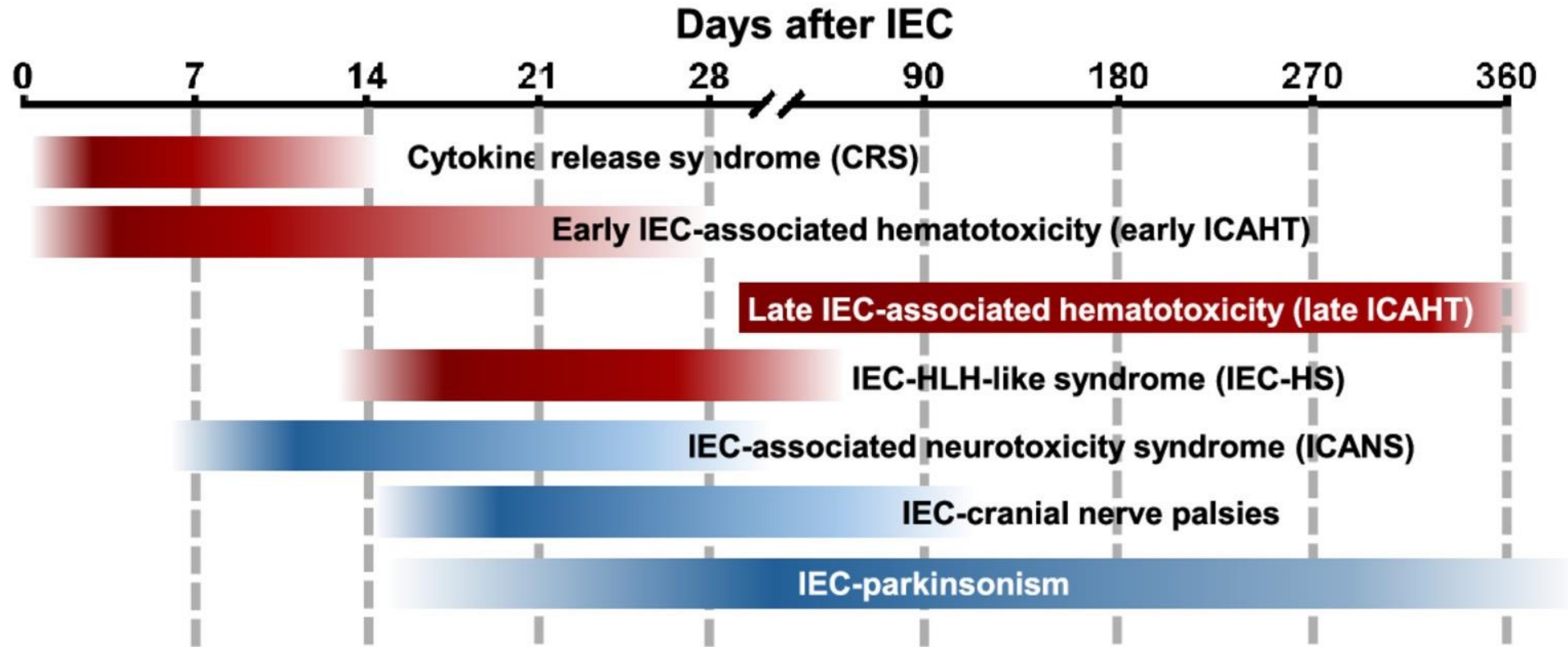
DFCI IEC Program · 2025 · ICU transfer rate by therapy

Early Toxicities

< 30 days after IEC infusion

Late Toxicities

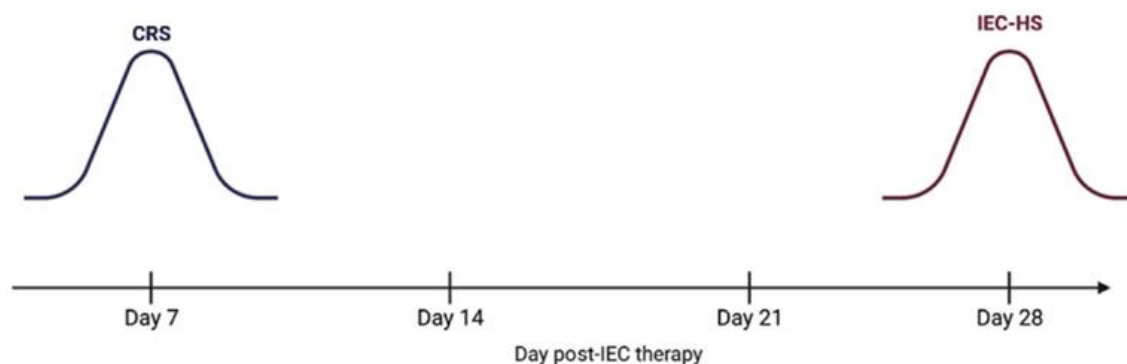
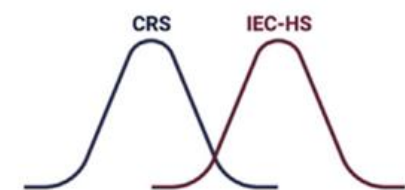
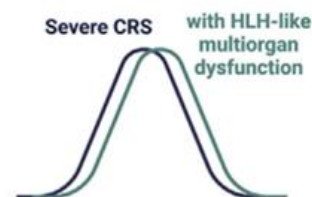
> 30 days after IEC infusion



Abbreviation: IEC, immune effector cell

Tumor Inflammation-Associated Neurotoxicity
IEC-Enterocolitis
On-Target, Off-Tumor Toxicity
Secondary Malignancies (CAR-associated T-cell Lymphoma)

Grading Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-like Syndrome



Description and timing	Grade 1 IEC-HS	Grade 2 IEC-HS	Grade 3 IEC-HS	Grade 4 IEC-HS
IEC-HS not attributable to other causes and is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and hepatic transaminitis ($>5 \times \text{ULN}$). While HLH-like manifestations are frequently seen in patients with severe CRS (as defined by ASTCT), IEC-HS is often delayed in onset and manifests as CRS is resolved/resolving.	Asymptomatic or mild symptoms; requires observation and/or clinical and diagnostic evaluation. Intervention not indicated.	Mild to moderate symptoms, with intervention indicated (eg, immunosuppressive agents directed at IEC-HS, transfusions for asymptomatic hypofibrinogenemia)	Severe or medically significant but not immediately life-threatening (eg, coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress)	Life-threatening consequences: urgent intervention indicated (eg, life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury)

Note: This table has been adapted with permission from Hines et al. [30].

CRS indicates cytokine release syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome.

Acute Kidney Injury after CAR-T therapy (DLBCL)

- 78 patients receiving axi-cel or tisa-cel
- Baseline eGFR 109 +/- 17 mL/min/1.73m2
 - 85% CRS (13% $\geq$ Gr 3)
 - 62% tocilizumab, 49% Dexamethasone
- 15 (19%) developed AKI
 - 8 decreased perfusion, 6 ATN, 1 urinary obstruction 2/2 disease
 - ATN and obstruction => longer hospital stay and 60-day mortalities
- Electrolyte abnormalities common (>50%)

Decreased kidney perfusion (n = 8)

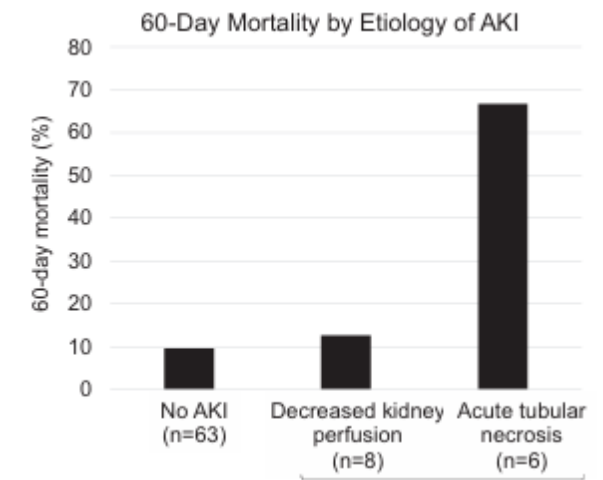
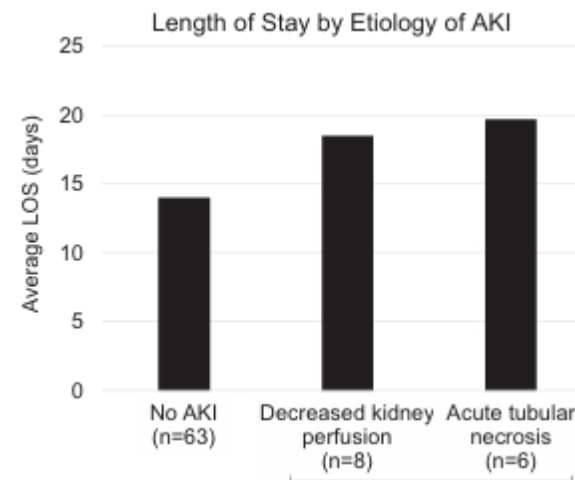
No cytokine release syndrome	1/8
Cytokine release syndrome stage 1	3/8
Cytokine release syndrome stage 2	3/8
Cytokine release syndrome stage 3	1/8

Acute tubular necrosis (n = 6)

Cytokine release syndrome stage 1	0/6
Cytokine release syndrome stage 2	1/6
Cytokine release syndrome stage 3	2/6
Cytokine release syndrome stage 4	3/6

Urinary obstruction (n = 1)

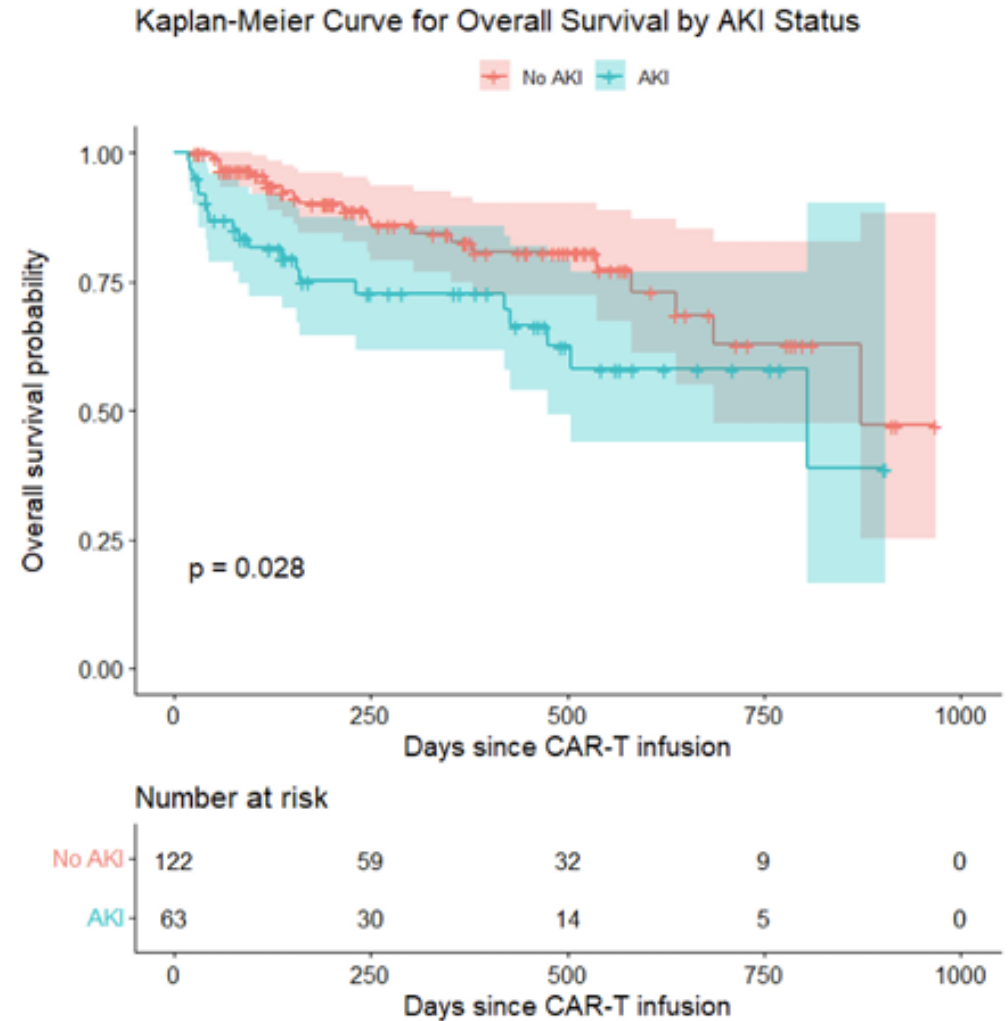
No cytokine release syndrome ^c	1/1
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Gupta, Am J Kidney Dis, 2020

Acute Kidney Injury after CAR-T therapy (Mult Dzs)

- 186 patients
- 34% developed AKI (95% CI: 27-41%)
 - 78% within 3 weeks of CAR
 - Most Grade 1 (69.8%) and reversible
 - 71.4% recovered baseline function (1HD)
- More common among:
 - African American (57.7%)
 - Older age (67 vs 62 yo)
 - Prior CKD (50.8% vs 25.6%)
- No association with CRS
 - Gr 1 33.9% AKI, Gr2 37.9%, Gr 3 42.9% (p=0.83)
- AKI => OR death 2.57 (p=0.019)
 - HR mortality 2.59 (95% CI: 1.33-5.04)
- No associate with CAR product type



Jazieh, Transplant Cell Ther, 2026

Prospective evaluation of CAR-T cell therapy-related proteinuria and kidney dysfunction

Characterization of renal complications in patients receiving CAR-T cell therapy, including proteinuria, acute kidney injury (AKI), and associated electrolyte abnormalities.

Cohort and Methods



63 patients treated with
CAR-T therapy
June 2020–December 2023



Urine samples on
day 0, +7, and +14



AKI: 12 (19%) patients



uPCR ≥ 0.5 g/g on day +7:
23 (37%) patients

Results

Proteinuria measured on day +7 after CAR-T infusion

Renal and clinical events

Proteinuria associated with:



AKI before day +7 ($P = .004$)



CRS grade ≥ 3 ($P = .03$)



ICANS grade ≥ 3 ($P = .04$)

Electrolyte disorders



Hypophosphatemia (78%)



Hypokalemia (70%)



Hyponatremia (59%)

$\uparrow$ uPCR — $\downarrow$ P, K and Na ($P < .05$)

Prognostic impact: high proteinuria at infusion day linked to:

$\uparrow$ Risk of progression (HR 3.30, 95% CI 1.46–7.44, $P = .004$)

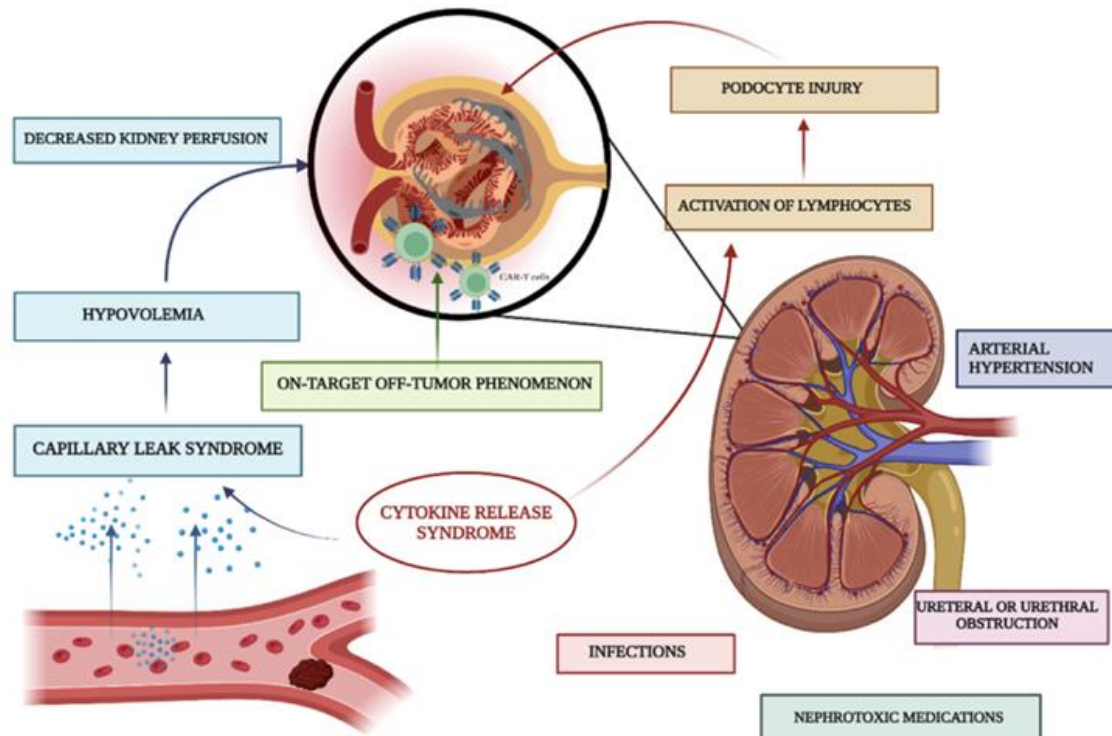
$\uparrow$ Risk of mortality (HR 4.51, 95% CI 2.00–10.19, $P < .001$)

No impact of AKI in progression or mortality

Conclusion: CAR-T cell therapy is associated with transient renal adverse effects, including proteinuria, AKI, and electrolyte disorders. Proteinuria may serve as a marker of early complications.

Moncho Francés, F., Hernani, R.
Clinical Kidney Journal (2025)
fmoncho@incliva.es
@CKJsocial

Etiology for Acute Kidney Injury after CAR-T therapy?



Review of studies specifically reporting on CAR nephrotoxicity

- Incidence 3-33%
- Lymphodepletion chemotherapy
- Hypovolemia and decreased perfusion
- Vasoconstriction 2/2 CRS => ATN
- Podocyte injury from excessive cytokine production
- Accumulation of inflammatory cells
- Rat models – increased sulfation of glomerular basement membrane => proteinuria
- ? Direct CAR T targeting?

Sadowski, Transplant Cell Ther, 2025

But we soldier on....

- Current DFCI eGFR eligibility for CAR
 - 30% for Myeloma
 - 40% for Lymphoma
 - 55% for Leukemia
- 87 myeloma patients (*Grieb, Transplant Cell Tx, 2026*)
 - 33 Mod/sev CKD => 45.5% standard Flu/Cy
 - CKD status alone no impact on OS or PFS across all products in survival analysis
- 900 CAR patients (*Br J Haematol, 2026*)
 - HR 1.108 per 10mL/mL/1.73m² decrease predicted
 - Grade ≥ 2 CRS
- 223 myeloma patients (*Habib, Curr Oncol, 2026*)
 - Renal Insuff (CrCL<45 mL.min) no impact on PFS or OS. Higher rates of ICANS and infections
- Real world” 1272 Myeloma patients
 - GFR <60 associated with inferior OS
 - HR 3.66 (cilta-cel, p<0.001)
 - HR 1.73 (ide-cel, p=0.003)
 - (*Filippatos, Cancers (Basel), 2026*)
- Report on 8 hemodialysis patients receiving CAR (*Zolotov, Curr Oncol, 2026*)
 - LD – bendamustine or dose-reduced Flu/Cy only Gr 1 CRS
 - 1 death from fungal PNA – TRM 12.5%
 - Appears feasible

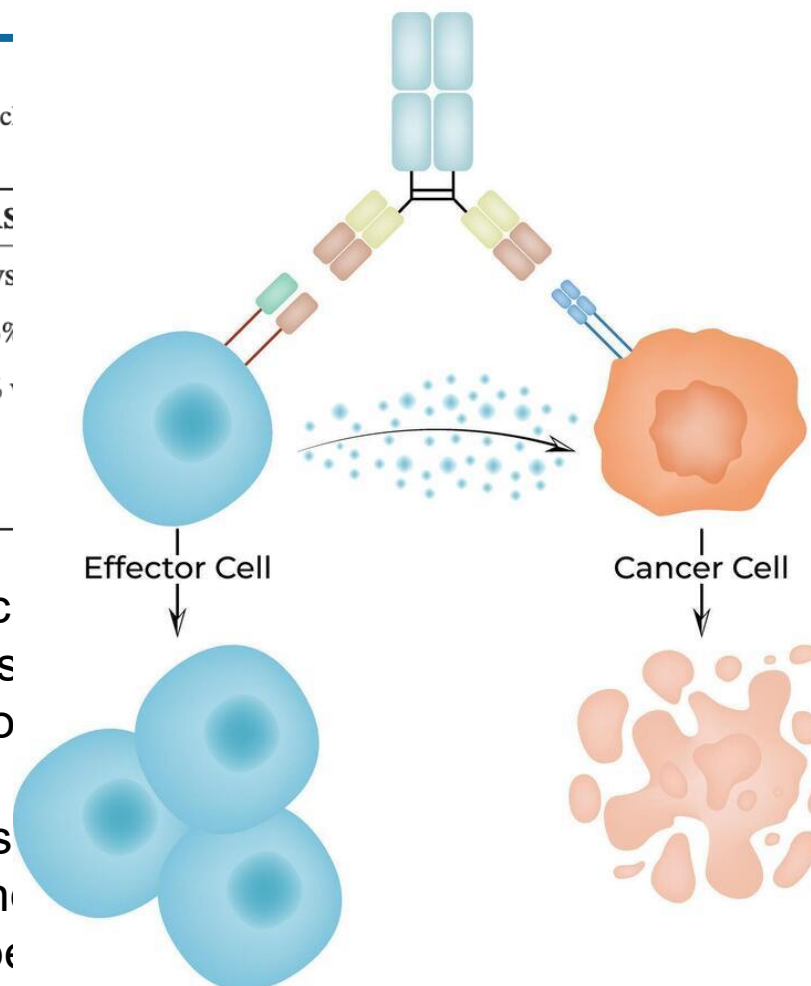
Bi-specific antibody

TABLE 3 | Study-level analysis of treatment-related toxicities including severe events (grade ≥ 3), with corresponding *p*-values.

Author (year)	CRS (<i>p</i>)	CRS
Joiner et al. (2025)	63% vs. 56% (0.21)	6% vs
Ali et al. (2025)	66.7 vs. 66.7	8.3%
Dima et al. (2025)	50.6% vs. 58.7% (0.23)	1.2%
Habib et al. (2024)	57.1% vs. 42%	
Parekh et al. (2025)	23% vs. 23.6% (0.8)	

- CRS > Grade 3 is seen after bispec
- Rates of severe toxicities in patients with thrombocytopenia across registratio
- In propensity score-matched analysis, moderate RI was associated with in
- Higher rates anemia, thrombocytop

Bispecific Antibody



st CRS&ICANS

ed neurotoxicity syndrome (ICANS), and infections, as well as

Infections (<i>p</i>)	Infections > G3 (<i>p</i>)
39% vs. 40% (0.65)	N/A
8.3% vs. 16.7% (0.65)	N/A
33% vs. 46% (0.06)	20% vs. 19% (0.9)
100% vs. 0% (<0.001)	57% vs. 0% (<0.001)
N/A	N/A

with step up dosing.
ased except for

sAb patients, neither severe nor

Ntanasis-Stathopoulos, Am J Hematol, 2026
Muddasani, Cancers (Basel), 2026

Bi-specific antibody therapies also manifest CRS&ICANS

TABLE 3 | Study-level analysis of treatment-related toxicities including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infections, as well as severe events (grade ≥ 3), with corresponding *p*-values.

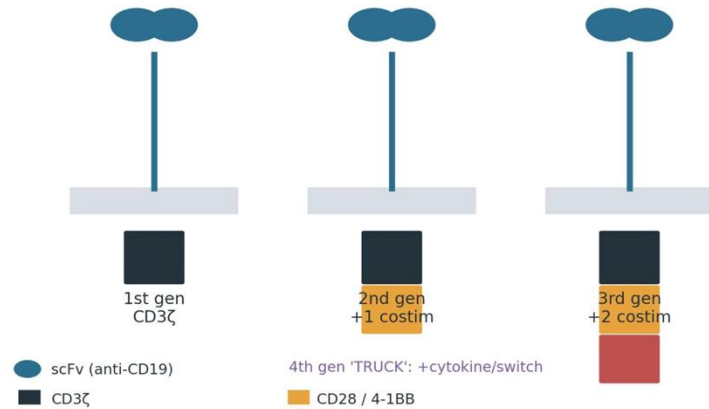
Author (year)	CRS (<i>p</i>)	CRS > G3 (<i>p</i>)	ICANS (<i>p</i>)	ICANS > G3 (<i>p</i>)	Infections (<i>p</i>)	Infections > G3 (<i>p</i>)
Joiner et al. (2025)	63% vs. 56% (0.21)	6% vs. 2% (0.02)	20% vs. 14% (0.21)	4% vs. 4% (0.97)	39% vs. 40% (0.65)	N/A
Ali et al. (2025)	66.7 vs. 66.7	8.3% vs. 8.3%	16.7% vs. 20.8% (1.0)	8.3% vs. 12.5% (1.0)	8.3% vs. 16.7% (0.65)	N/A
Dima et al. (2025)	50.6% vs. 58.7% (0.23)	1.2% vs. 1% (0.9)	16% vs. 13% (0.6)	2.5% vs. 2.6% (0.9)	33% vs. 46% (0.06)	20% vs. 19% (0.9)
Habib et al. (2024)	57.1% vs. 42%	N/A	7.1% vs. 10%	0% vs. 1% (0.5)	100% vs. 0% (<0.001)	57% vs. 0% (<0.001)
Parekh et al. (2025)	23% vs. 23.6% (0.8)	N/A	8.7% vs. 16.9% (0.04)	N/A	N/A	N/A

- CRS > Grade 3 is seen after bispecific antibody therapy, despite mitigation with step up dosing.
- Rates of severe toxicities in patients with renal impairment were NOT increased except for thrombocytopenia across registration studies.
- In propensity score-matched analysis, of 2716 CAR-T patients and 3376 BsAb patients, neither severe nor moderate RI was associated with increased mortality , CRS or ICANS.
- Higher rates anemia, thrombocytopenia and AKI were seen.

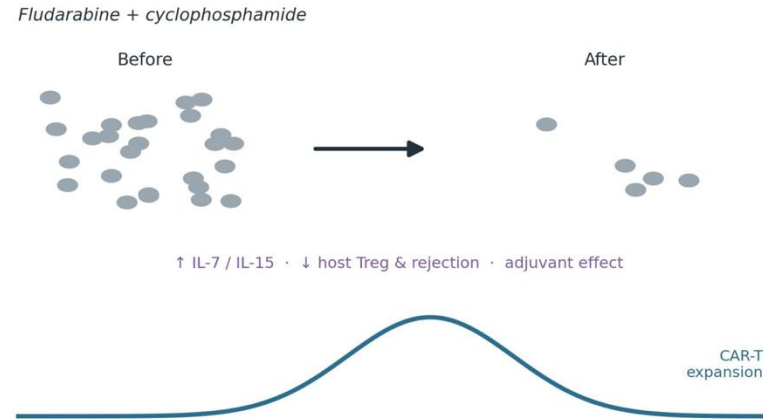
Ntanasis-Stathopoulos, Am J Hematol, 2026
Muddasani, Cancers (Basel), 2026

There is still good in this cell therapy world!!

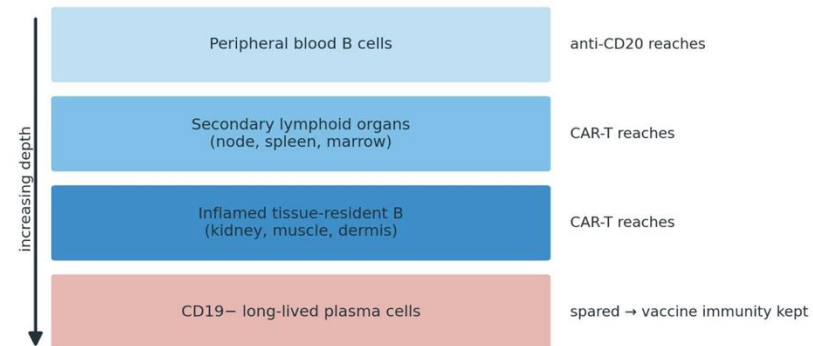
A Chimeric antigen receptor architecture



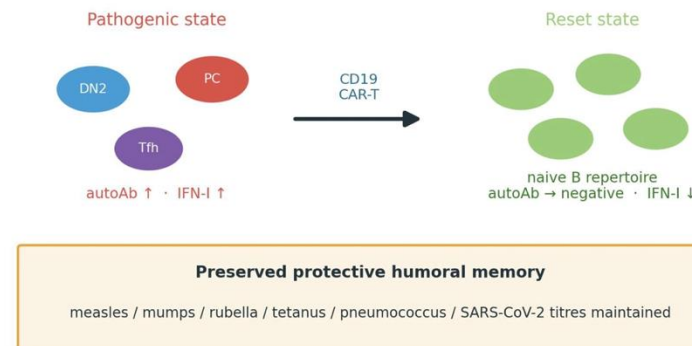
B Lymphodepletion creates a permissive niche



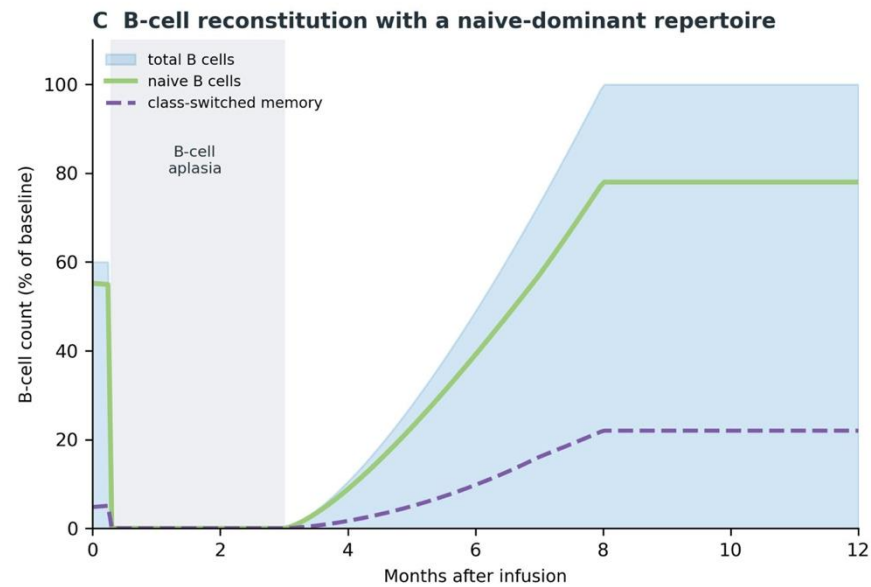
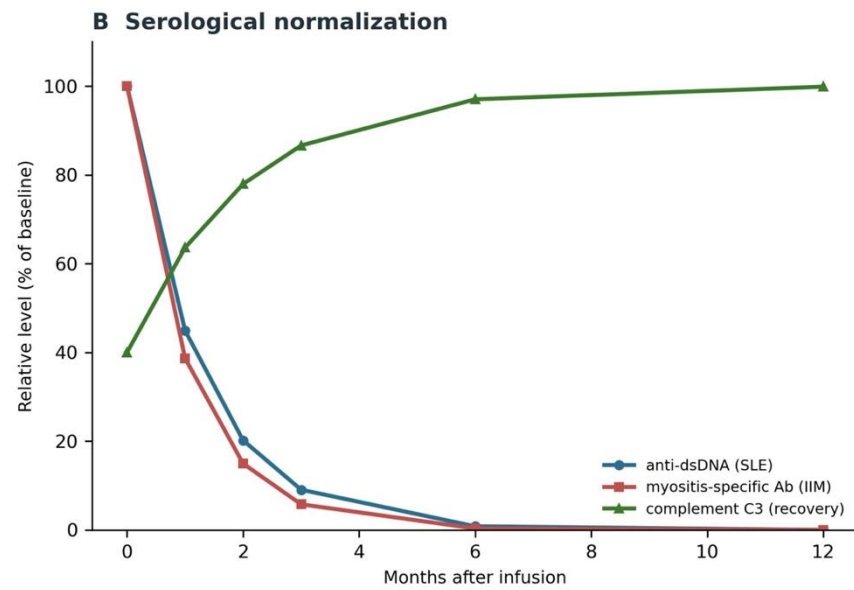
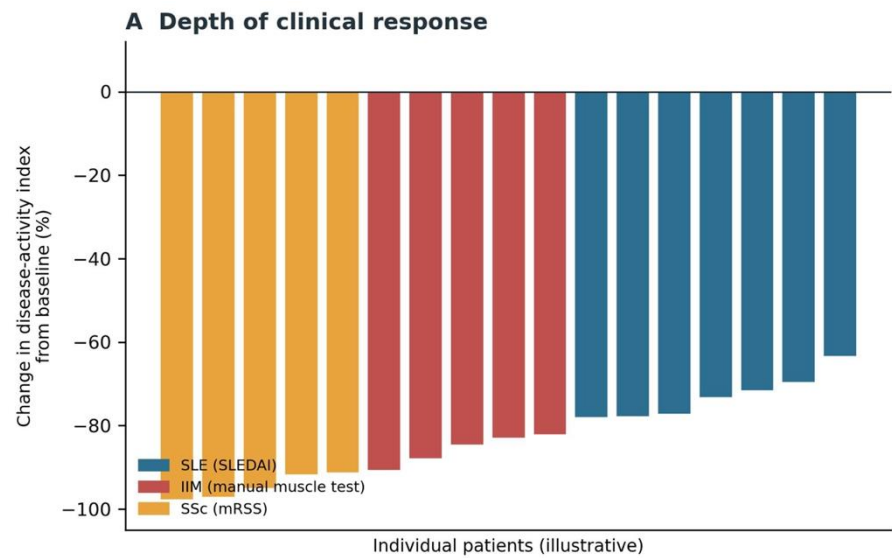
C Anatomical depth of B-lineage depletion



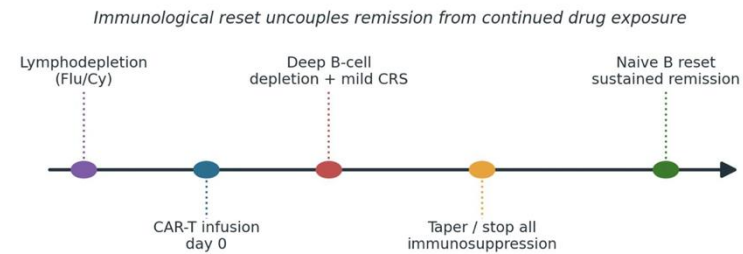
D Deep depletion → immune reset



Zhan, *Frontiers Immunol*, 2026



D Trajectory toward drug-free remission



Zhan, *Frontiers Immunol*, 2026

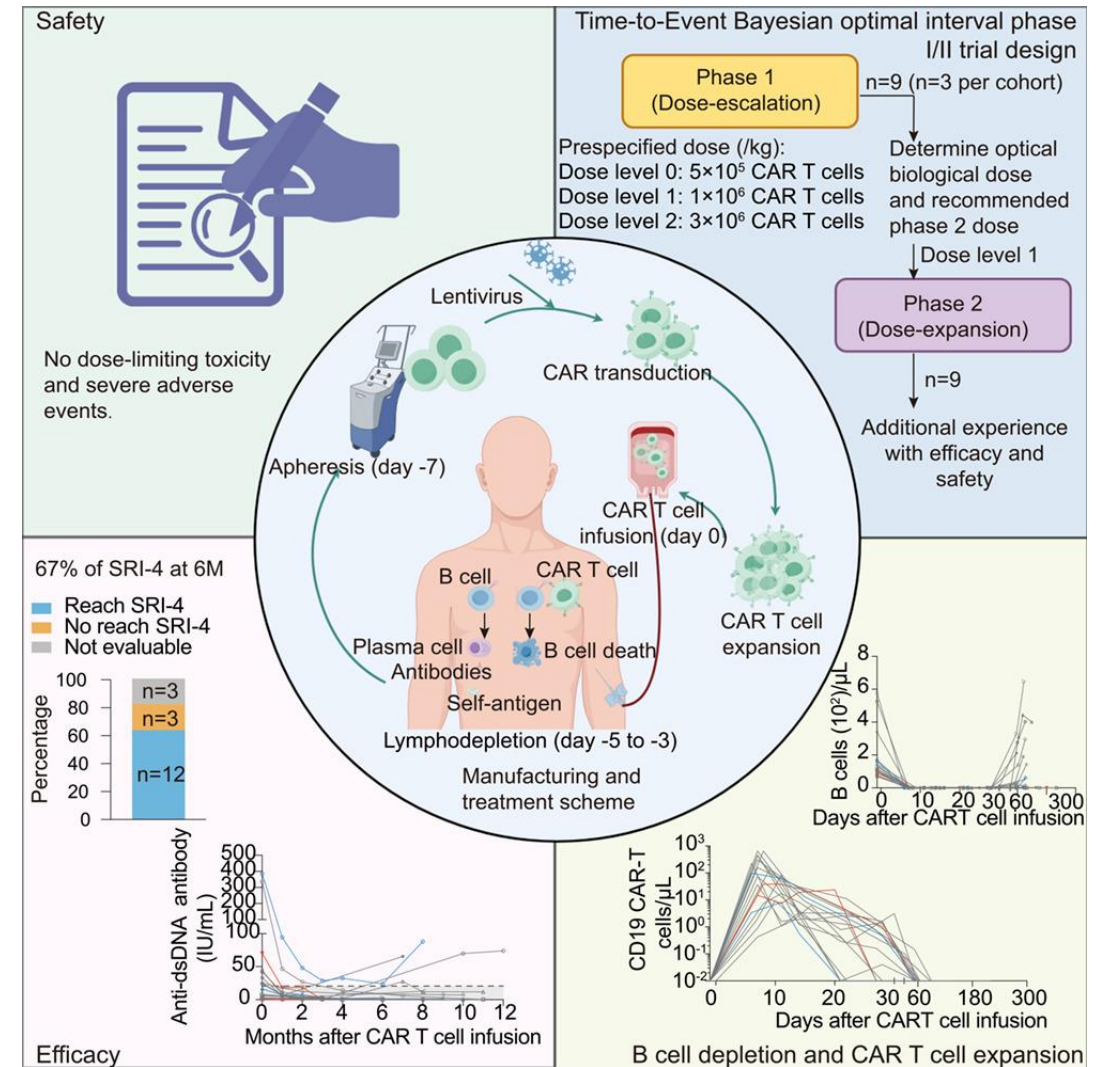
Phase 1/2 CASTLE basket study of CD19 CAR-T Cells in Autoimmune Diseases

- 24 patients – 10 SLE, 9 SSc, 5 IIM
- Max Grade2 CARS, no ICANS
- 9/10 SLE patient – DORIS remission
- 9/9 SSc patients without progression
- 4/5 IIM patients with ACR major/mod response
- All patients free of steroids/IS treatment

Observation period 24 weeks

Muller, Nat Med, 2026

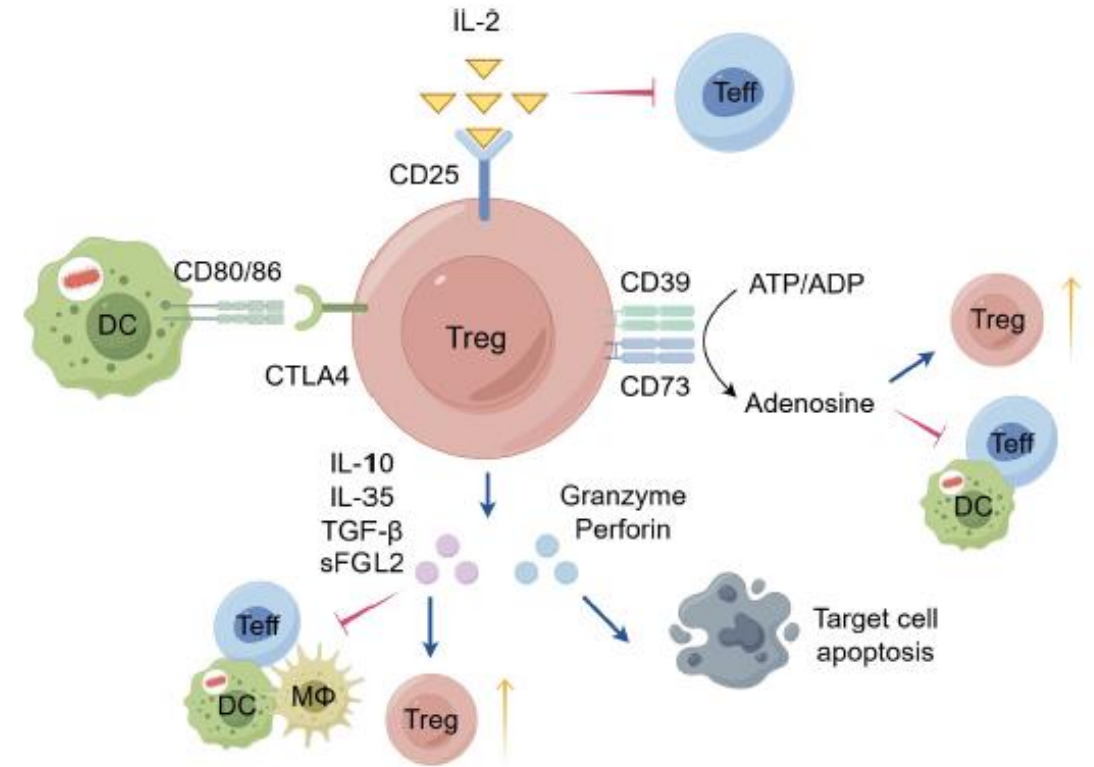
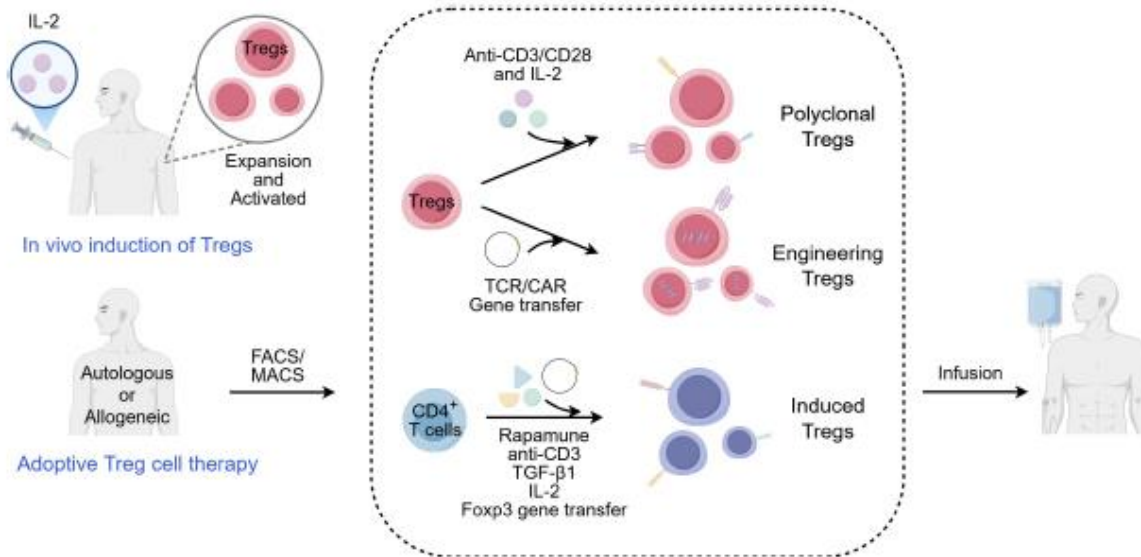
Phase 1/2 SLE CD19 CAR – all ages



Shan, Mol Ther, 2026

There is still good in this cell therapy world!!

- CD19 and BCMA CARs in autoimmune disease
- CAR Tregs in autoimmune disease
- Tregs and CAR Tregs in Allograft Organ Tolerance

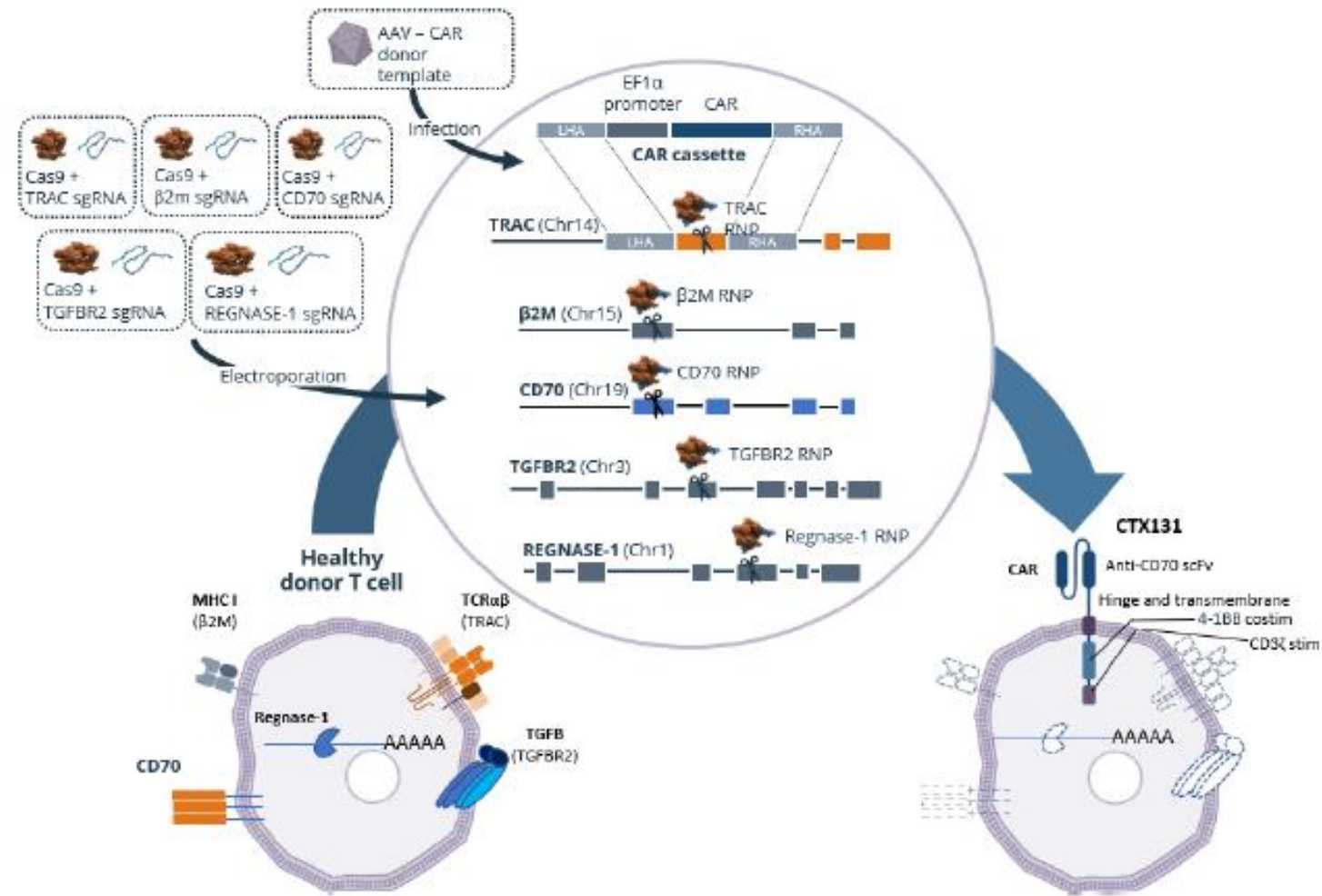


Duan, Frontiers Immunol, 2026

Example of an **allogeneic** off the shelf CAR for **RCC** with multiple genetic engineering steps

GU: CRISPR Allo antiCD70 CAR
6 total genetic changes

1. **CAR inserted**
2. Into **TCR locus** so no TCR to mediate GvHD
3. **Down-regulate B2 microglobulin** – less HLA expression in cells....resists rejection
4. Delete CD70 target on T cell so **no fratricide**
5. Knock out TGFb R2 and Regnase to help with robust **T-cell expansion** and function



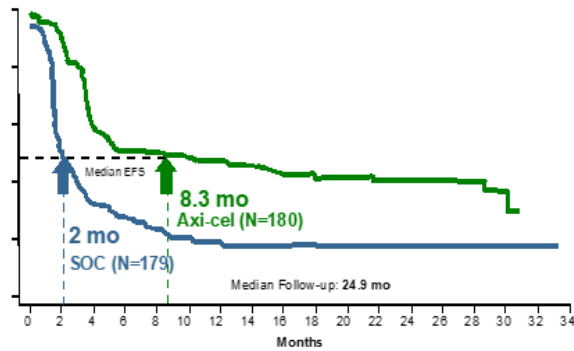
2nd Line Lymphoma

Yescarta (axi-cel)

Breyanzi (liso-cel)

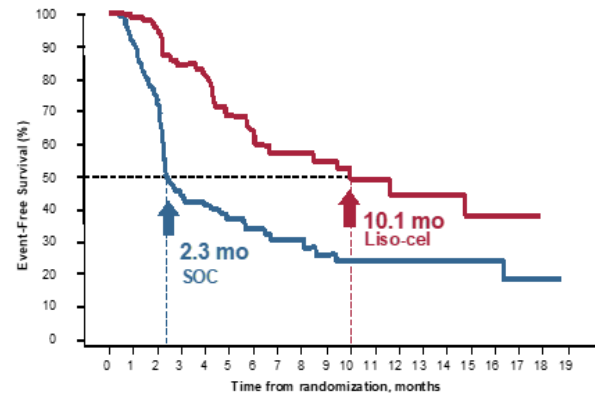
ZUMA-7¹

HR 0.398 (95% CI, 0.308–0.514); $P < 0.0001$



TRANSFORM²

HR 0.349 (95% CI, 0.229–0.530); $P < 0.0001$



Trials in first line therapy – Zuma 23 ongoing

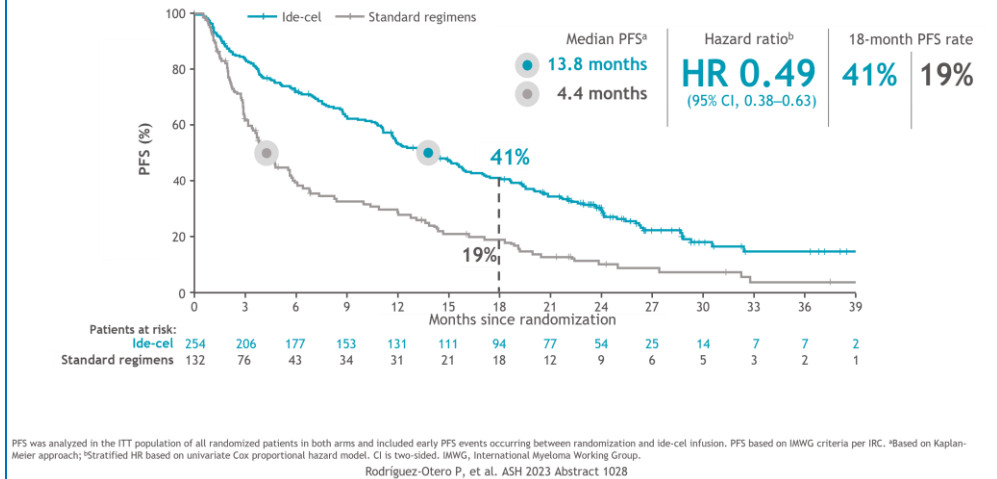
=> Fewer auto stem cell transplants occurring

=> Interesting clinician/patient discussions about 2nd line CAR versus Bi-specific Antibody or other immune therapies

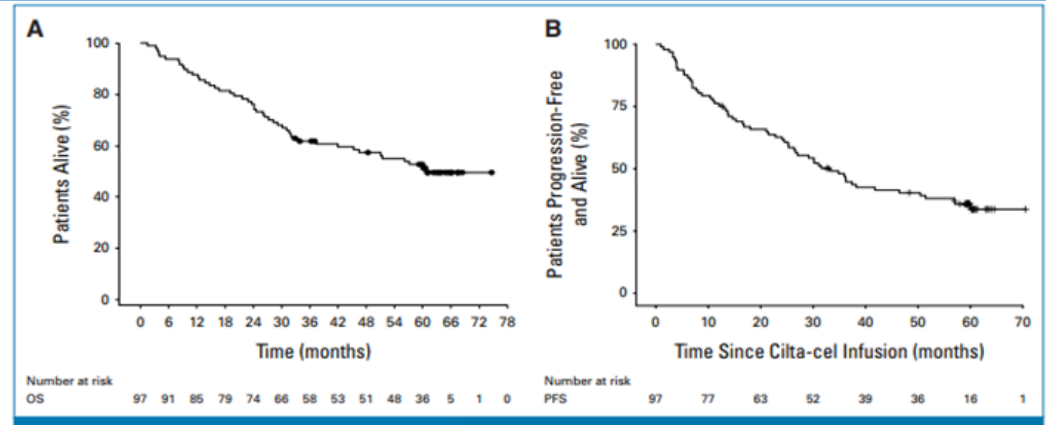
***** More patients receiving CAR therapies**

R/R Myeloma Abecma (ide-cel)

Abecma vs Standard Regimens



R/R Myeloma Carvykti (Cilta-cel)





Summary

- CAR T cell therapy entails risk of AKI and likely increased risk of toxicity/mortality for those with pre-existing renal disease
- However, benefits are such that we continue to push the envelop
- Early toxicity detection/management and improvements in CAR constructs are mitigating these risks
- CARs, CAR Tregs and other types of cell therapies have increasingly broad applications – including SLE, organ transplant and RCC

Welcome to the fray!!

And if you found the CAR world daunting, hang on for the TIL cell therapy experience!!



Questions ?

