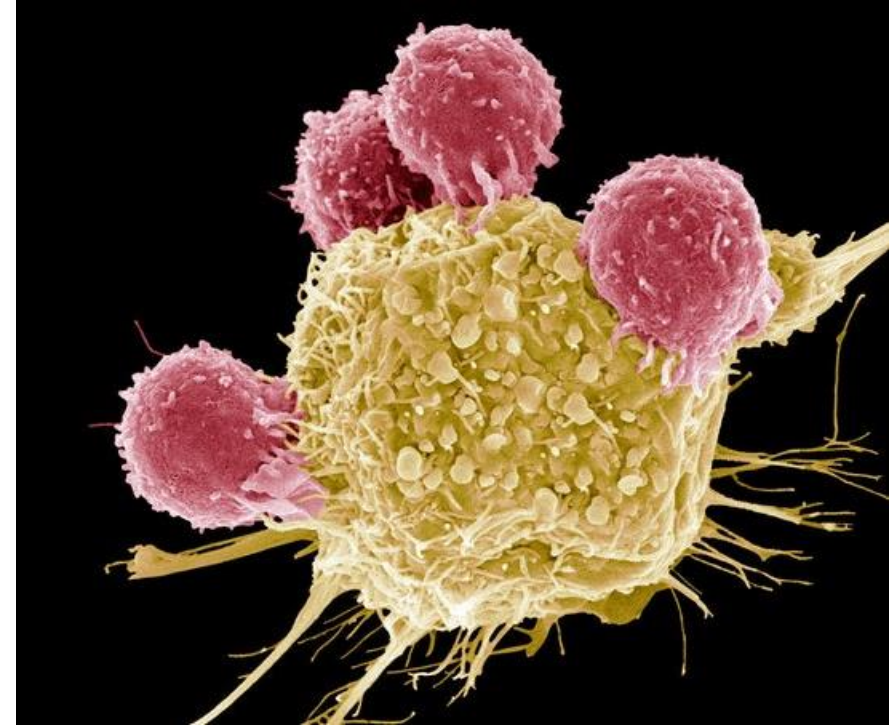


Post-Kidney Transplant Lymphoproliferative Disorders: Perspectives from a Transplant Nephrologist

Chris Blosser

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Conflict of Interest Disclosure

- Research funding - Kuni Foundation, WA CARES Foundation, Natera, NIDDK
- Advisory Board Member – Pierre Fabre Pharmaceuticals, Apellis/Biogen
- Editorial Board Member - *American Journal of Transplantation*

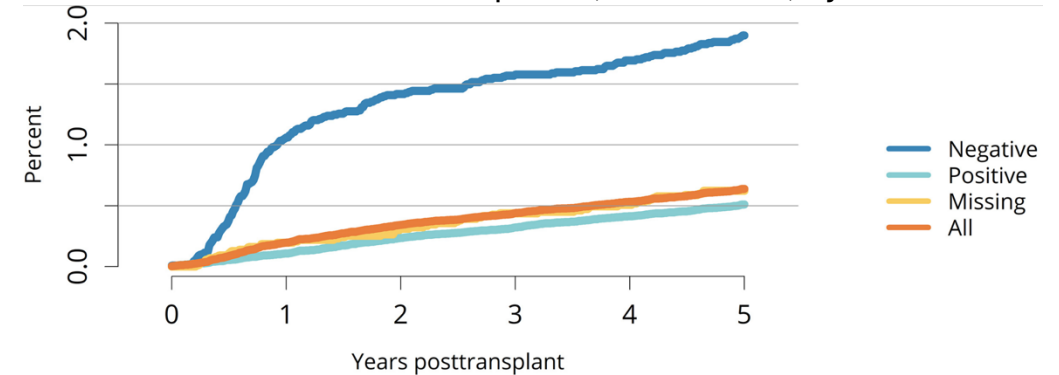
Learning Objectives

1. Reflect the knowledge of epidemiology and risks of PTLD
2. Describe symptoms and signs of PTLD and initial evaluation.
3. Discuss management of PTLD and future directions.

Post-transplant Lymphoproliferative Disorder

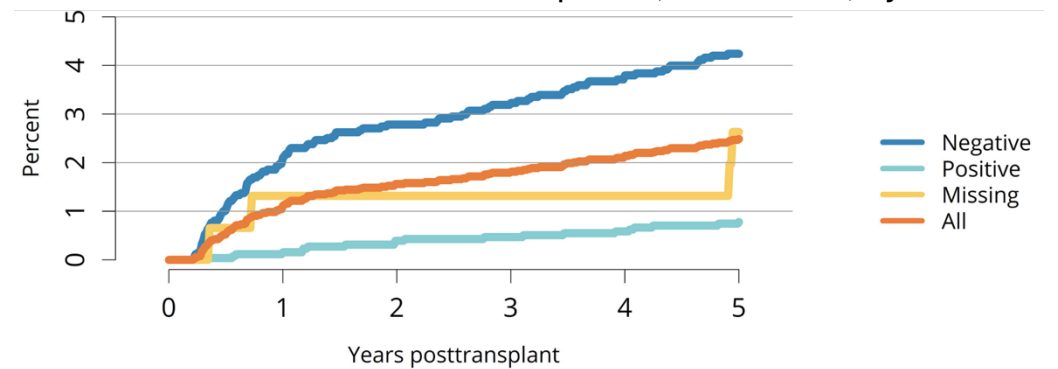
- **PTLD is the leading cancer cause of death among KTRs¹**
- Lifelong incidence of PTLD 2-20%²
 - No change in incidence over time, despite improved SOTR survival³
 - DLBCL incidence 12x greater than general population⁴
- Contemporary management: median PFS 4.0 years and OS 6.6 years⁵

Incidence of PTLD in Adult Recipients, 2012-2018, by EBV Status



OPTN/SRTR 2023 Annual Data Report

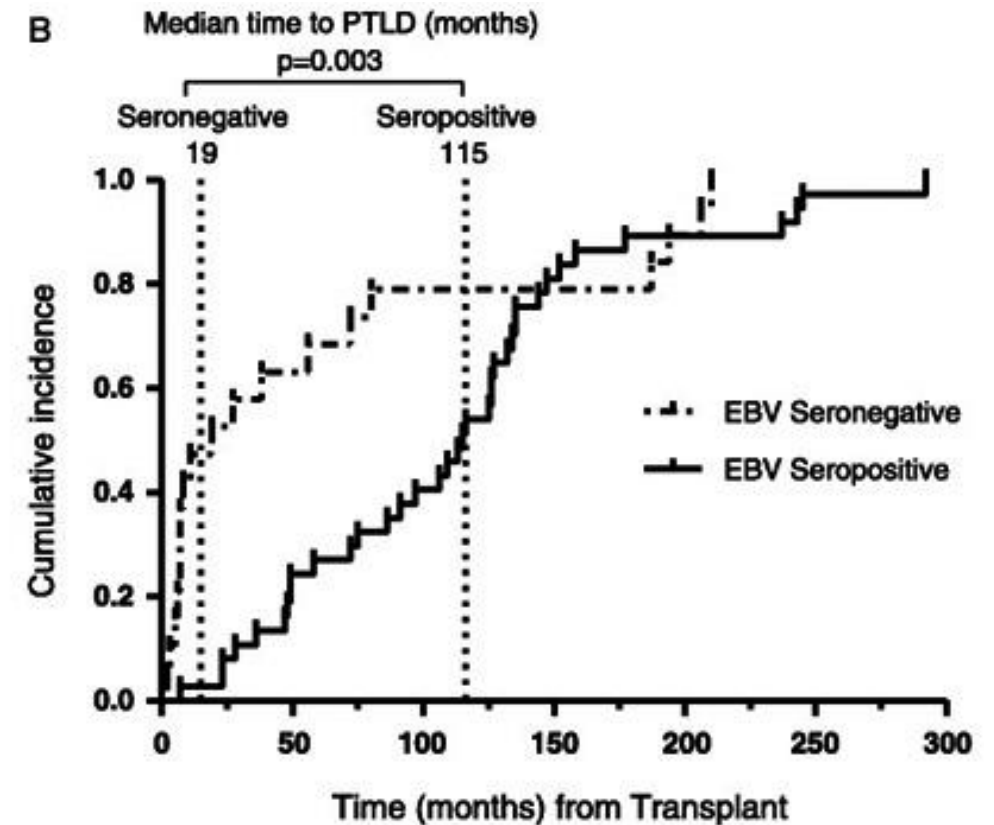
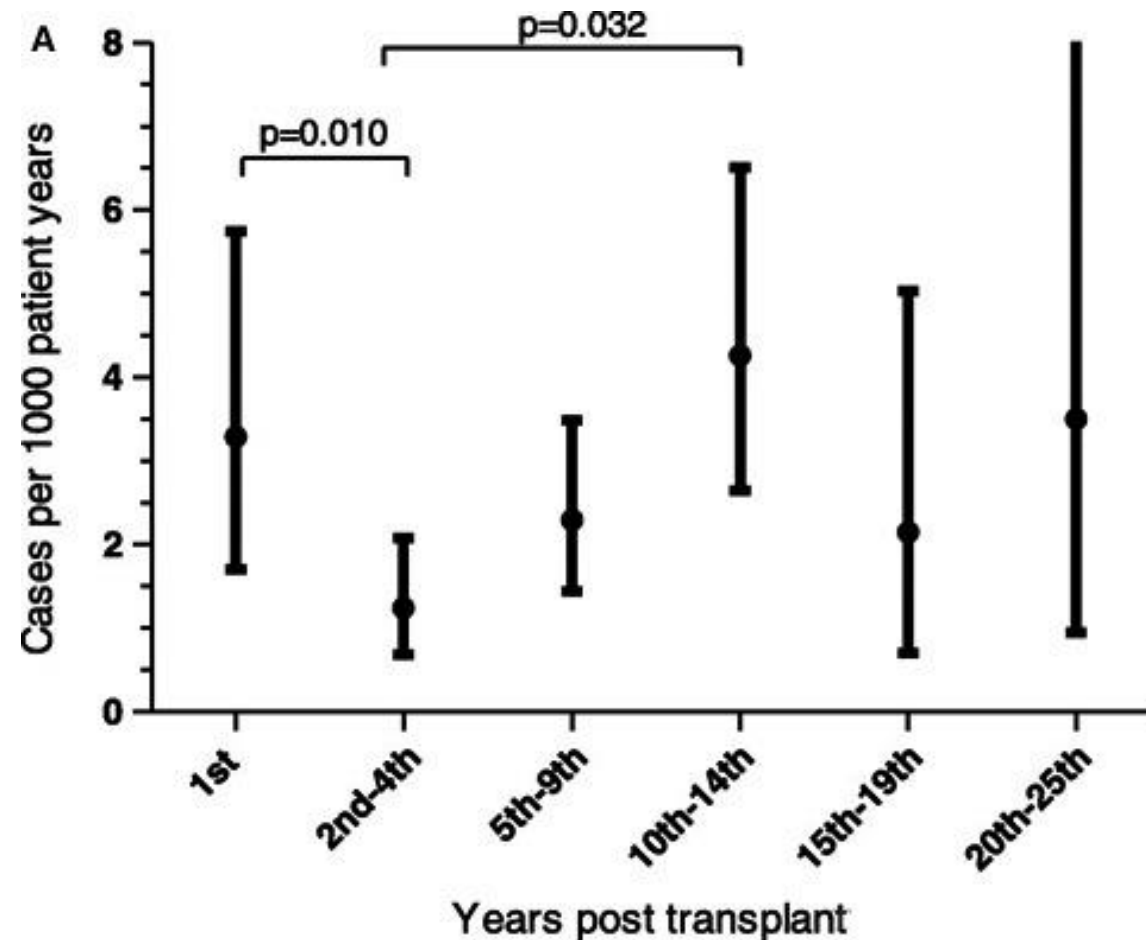
Incidence of PTLD in Pediatric Recipients, 2012-2018, by EBV Status



OPTN/SRTR 2023 Annual Data Report

1. Acuna SA, et al. JAMA Oncol 2016;2(4):463-9. DOI: 10.1001/jamaoncol.2015.5137.
2. Morscio J, et al. Clin Dev Immunol 2013;2013:150835. DOI: 10.1155/2013/150835.
3. Blosser CD, et al. Kidney Int. 2021 Jun;99(6):1430-1438. doi: 10.1016/j.kint.2020.10.018.
4. Gibson TM, et al. Am J Hematol 2014;89:714-20.
5. Trappe R, et al. Lancet Oncol 2012;13(2):196-206. DOI: 10.1016/S1470-2045(11)70300-X.

PTLD Incidence Rate Post-Transplant



Risk Factors for PTLD

Risk factors

EBV seronegativity at the time of transplantation

Active primary EBV infection at the time of transplantation

Variants of *LMPI* gene sequence

T-cell depletion

Immunosuppressive drug regimen and intensity

Type of transplanted organ

Age (children and older patients)

CMV coinfection

Acute or chronic graft versus host disease

Second transplant

Prior splenectomy

HLA type

Extent of HLA mismatch

Abbreviations: CMV, cytomegalo virus; EBV, Epstein–Barr virus; HLA, human leukocyte antigen; LMPI, latent membrane protein I; PTLD, posttransplant lymphoproliferative disease.

Type of transplant

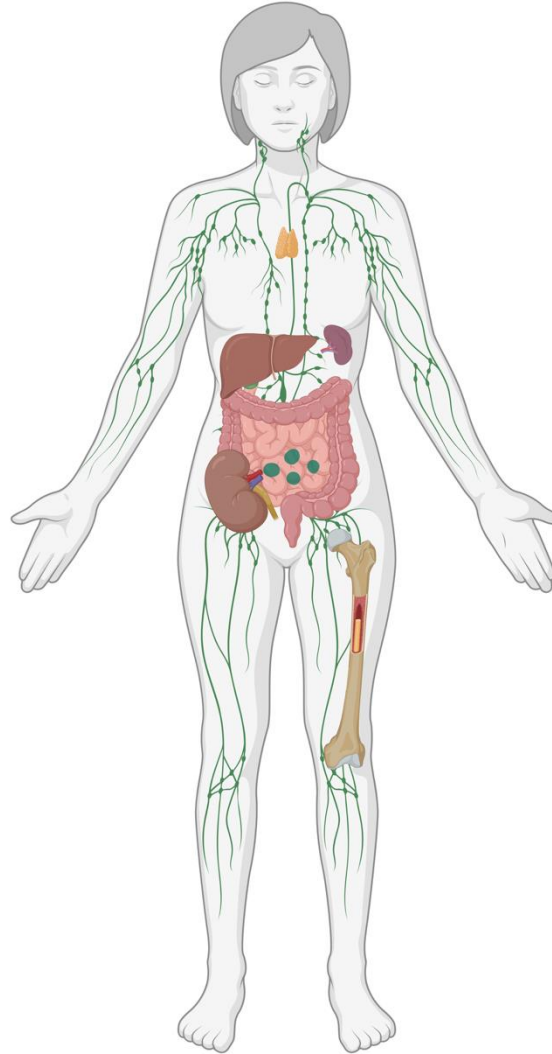
- Multi-organ and intestinal transplants: >20%
- Lung transplants: 3–10%
- Heart transplants: 2–8%
- Liver transplants: 1–5.5%
- Pancreatic transplants: 0.5–5%
- Kidney transplants: 0.8–2.5%

Diagnostic Sites (Percent of Incidence) and Symptoms of PTLD

Sites of PTLD:

- Lymph Nodes 10-33%
- CNS 9-13%
- Lung 4%
- Liver 5-12%
- GI Tract 10-29%
- Organ Transplant 10-15%

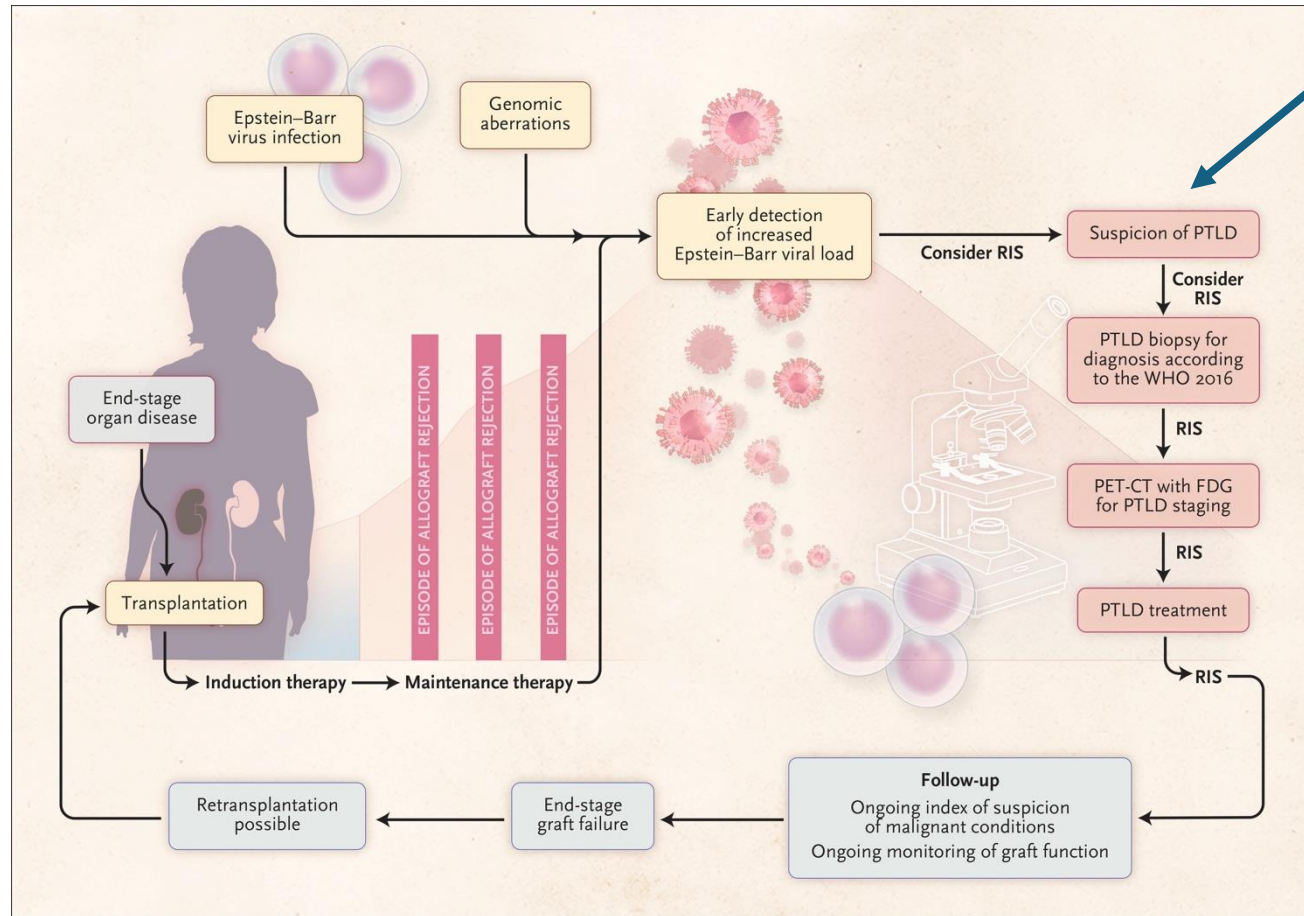
Extra-Nodal



PTLD Symptoms:

- B Symptoms
 - Fever
 - Night Sweats
 - Weight Loss
- Lymphadenopathy
- Extranodal
 - GI or CNS Symptoms
 - Abd/Back Pain
 - Transplant organ pain/swelling

Initial Evaluation for PTLD

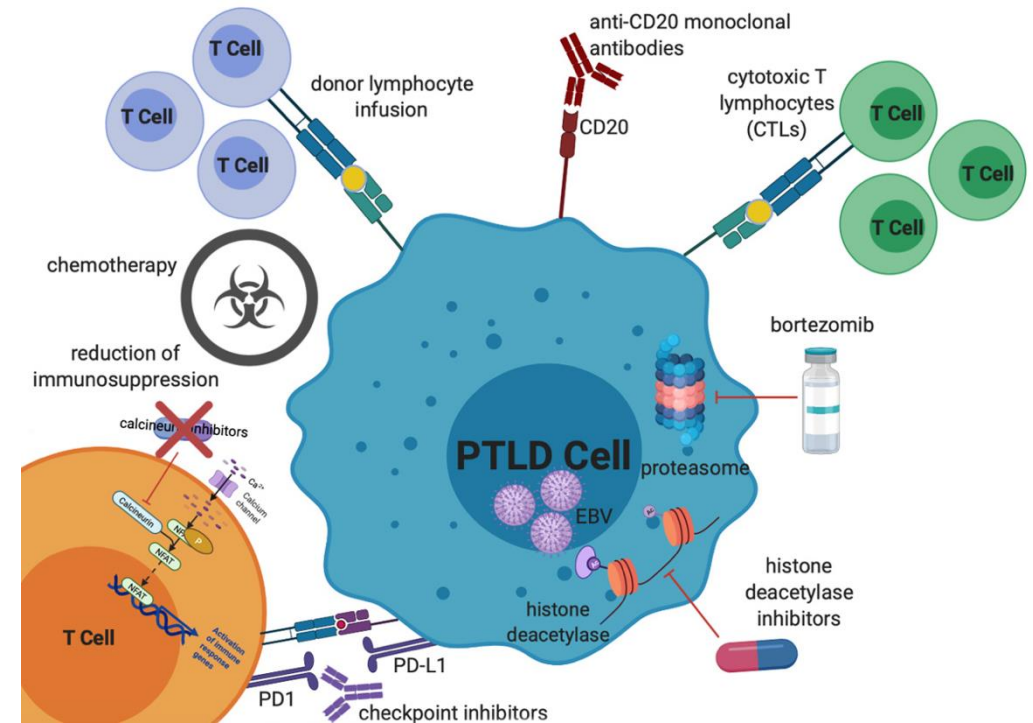


Dierickx D, Haberman TM. NEJM 2018

Routine	Select Patients
CBC with Differential	EGD and/or colonoscopy
Complete Met Panel	
LDH	CT-head/MRI-brain
Uric Acid	Lumbar puncture
EBV PCR	
CT-C/A/P with contrast	Bone Scan
Biopsy (excis/needle) for histology, flow of lymphs, EBER & CD20 IHC	Bone marrow biopsy

PTLD Treatment

1. Reduction of IS
2. Rituximab-based chemotherapy regimens
 - **PTLD-1** and **PTLD-2** studies (multicenter phase II trials) support sequential use of rituximab → CHOP chemotherapy^{1,2}
 - PTLD-2: intensification to CHOP may be avoided in low-risk patients who achieve a remission after rituximab
- **~50% will not achieve cure with Rituximab/R-CHOP = Refractory/Resistant (R/R) PTLD³**
3. No consensus on salvage therapy for R/R PTLD⁴
4. CAR-T? VSTs? BiTEs?

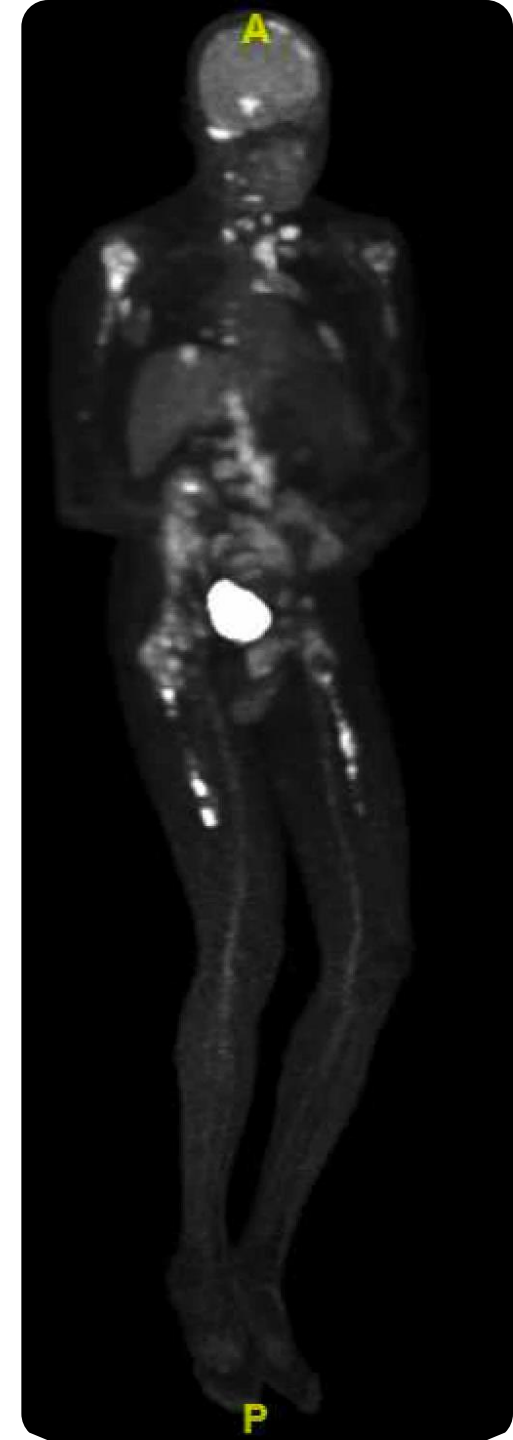


modified with permission by S Shahid and SE Prockop, Cancer Drug Resist. 2021; 4:646-64.

1. Trappe R, et al. Lancet Oncol 2012;13(2):196-206. DOI: 10.1016/S1470-2045(11)70300-X.
2. Zimmermann H, et al. Leukemia 2022;36(10):2468-2478. DOI: 10.1038/s41375-022-01667-1.
3. Bishop MR, et al. N Engl J Med. Feb 17 2022;386(7):629-639. DOI:10.1056/NEJMoa2116596
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Clinical Case

- 47-year-old male with a history of lupus nephritis (dx age 13) s/p 3 kidney transplants (most recent 2013)
- Immunosuppression: Tacrolimus (5-7), MMF, Prednisone
- Summer '21: back pain, night sweats, 15 lb weight loss
- MRI: diffuse bony disease and extensive adenopathy
- Ann Arbor stage IV monomorphic PTLN, DLBCL type (IPI 2, EBV-negative, germinal center subtype)
- Stop MMF
- R-CHOP x6 cycles → PR
- 2 months later: B symptoms returned
- Progressive disease on PET/CT
- Salvage **R-ICE** x2 cycles → PR
- NOT a candidate for auto-HSCT due to progressive disease
- New recommendation: **CD19 CAR-T therapy**



Chimeric Antigen Receptor T cell (CAR-T)

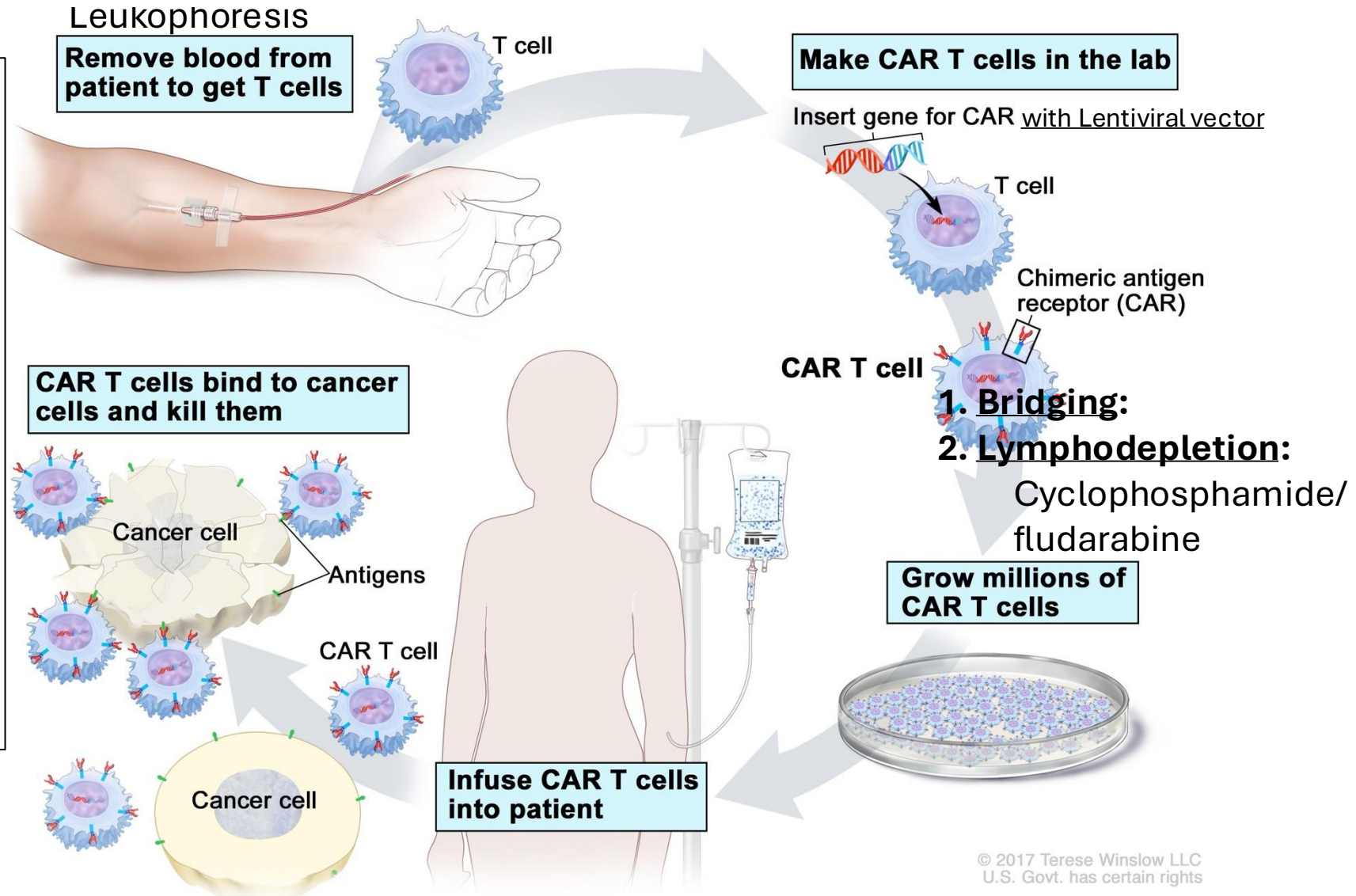
FDA Approved Treatments:

CD19-targeted CAR T:

- Relapsed and/or refractory B cell lymphoma
- B cell acute lymphoblastic leukemia
- Mantle cell lymphoma

B cell maturation antigen-targeted (BCMA) CAR T:

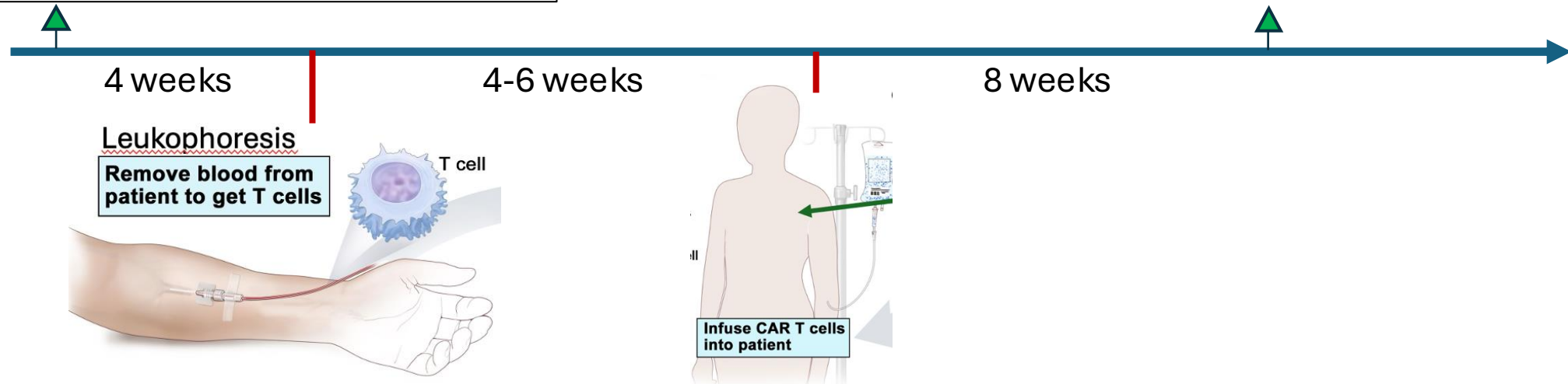
- Relapsed and/or refractory multiple myeloma.



Immunosuppression Management with CAR-T

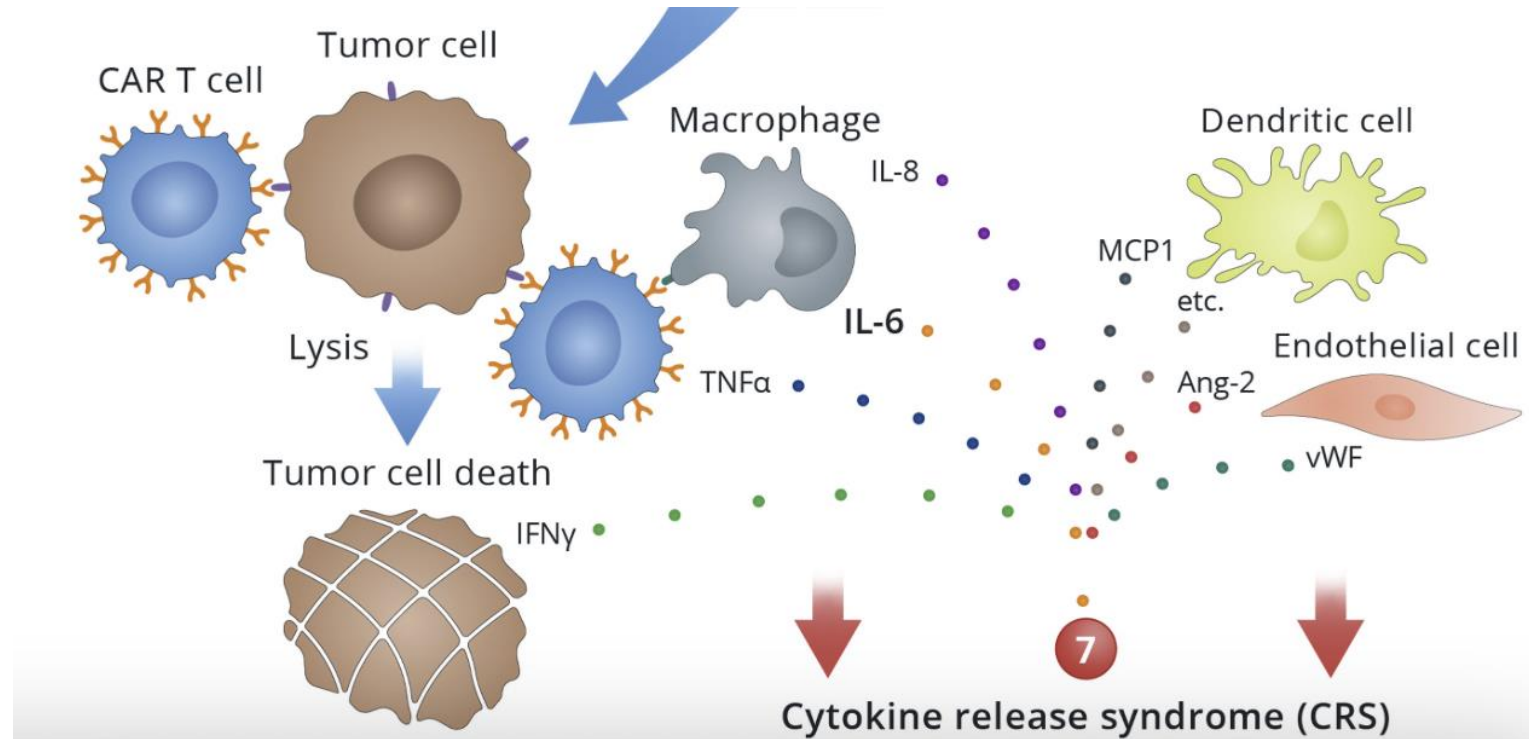
- Stop antimetabolite & CNI/mTOR/Belatacept over >4 weeks.
- Goal to be off CNI >2 weeks prior to Leukapheresis.
- Continue Prednisone 5-10mg daily, goal to minimize.

- >8 weeks post-infusion with PTLD control, restart Tacrolimus (or Everolimus, re: PMID: 35835450, 36832496), (goal 3-6)
- Would not restart antimetabolite

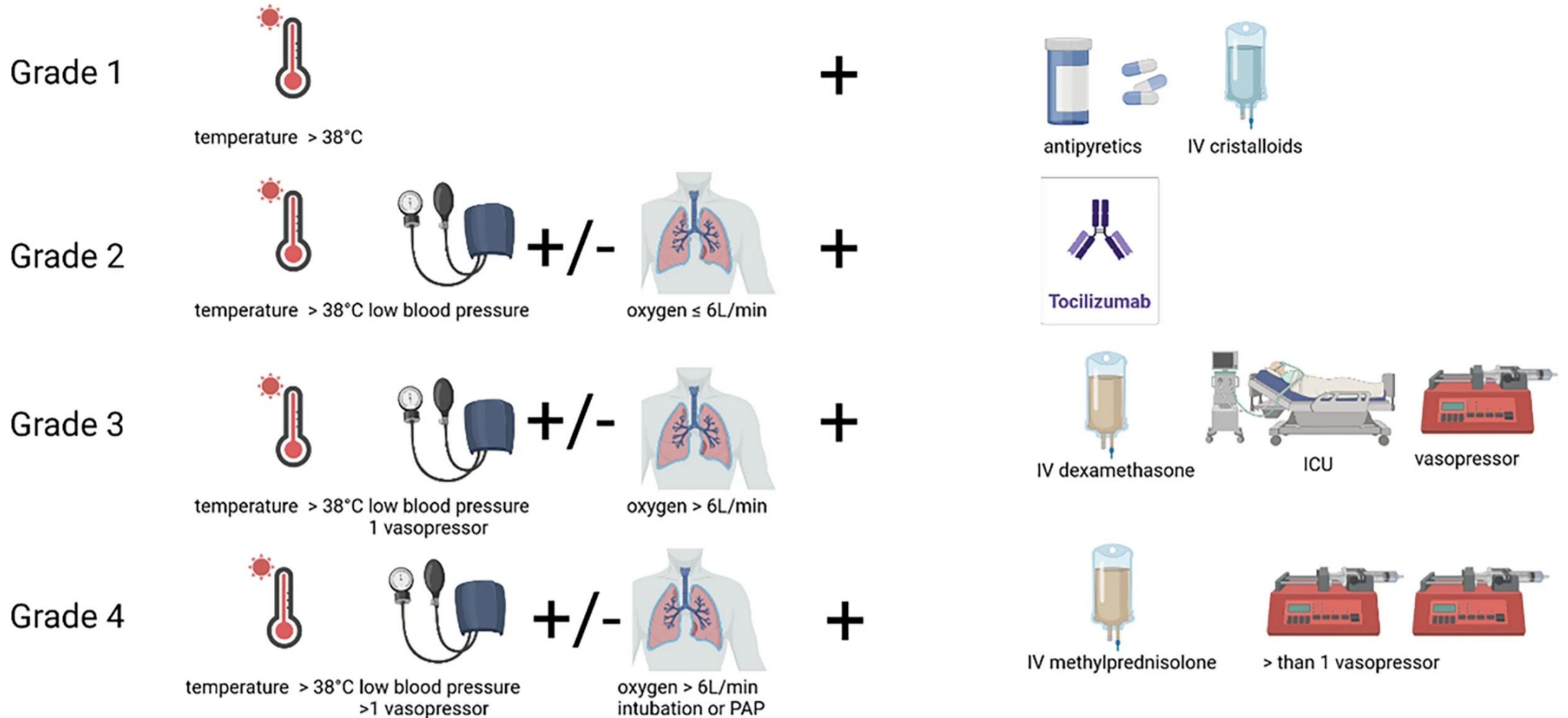


Cytokine Release Syndrome (CRS)

- Malaise
- Fevers
- Tachycardia
- Hypotension
- Hypoxemia -> ARDS
- Cardiomyopathy
- Liver Injury (AST/ALT, Bili)
- Acute Kidney Injury
- Capillary Leak Syndrome



Cytokine Release Syndrome (CRS)



Hemoadsorption for Severe CRS

- 4/48 patients treated with Continuous venovenous hemodiafiltration with an AN69ST hemofilter and a CytoSorb cartridge 5.2 $\pm$ 1.7 days after CAR-T Infusion
- After Tocilizumab, Corticosteroid and Anakinra (IL-1R Ab) therapy failure
- 3 experienced CRS resolution with reduced inflammation and improved hemodynamic stability, without treatment-related complications. 1 died of CM after day 1.

Table 1. Main Clinical and Laboratory Characteristics at Baseline (Day of CAR-T Infusion) in Patients Treated With Hemoadsorption

Patient	1	2	3	4
Clinical features				
Age, y	69	47	77	75
Sex	F	F	M	F
Hypertension	No	No	Yes	Yes
Diabetes	No	No	Yes	No
Charlson Index	4	2	6	6
Hematological Diagnosis	NOS-DLBCL	NOS-DLBCL	MCL	NOS-DLBCL
previous therapy lines	2	2	3	2
disease stage	4B	4A	3SB	4B
IPI/MIPI	High	High	High	High
ECOG	3	4	3	3
Laboratory				
LDH, U/L	992	3,059	470	647
CRP, mg/L	40	59.3	54.7	16.4
IL-6, ng/L	21	11	41	48
Ferritin, μ g/L	322	3,131	1,599	450
Platelets, $\times 10^9$ /L	56	51	19	168
sCr, mg/dL	0.6	1.5	0.7	0.7

Hemoadsorption for Severe CRS

Table 3. Operative Parameters and Laboratory and Clinical Characteristics of CAR-T Patients Treated With Hemoadsorption-Based Blood Purification

Patient	Days From CAR-T Infusion	Blood Purification Modality	Dialysis Membranes	Anticoagulation	No. HA cycles	CVVHDF Duration (d)	IL-6 at HA Start (ng/L)	IL-6 at HA Stop (ng/L)	Delta IL-6 (%)	NE at HA Start (µg/kg/min)	NE at HA Stop (µg/kg/min)	CRS Resolution
1	7	CVVHDF	modified AN69S + <i>CytoSorb</i>	RCA	2	6	>5,000 ^a	255	-95%	0.03	Stop	Yes
2	3	CVVHDF	AN69ST + <i>CytoSorb</i>	RCA	3	11	4,842	559	-88%	0.4	Stop	Yes
3	6	CVVHDF	modified AN69S + <i>CytoSorb</i>	RCA	4	5	4,575	1,477	-67%	0.14	Stop	Yes
4	5	CVVHDF	AN69ST + <i>CytoSorb</i>	No	1	1	2,452	1,997	-18%	0.5	0.7	No ^b

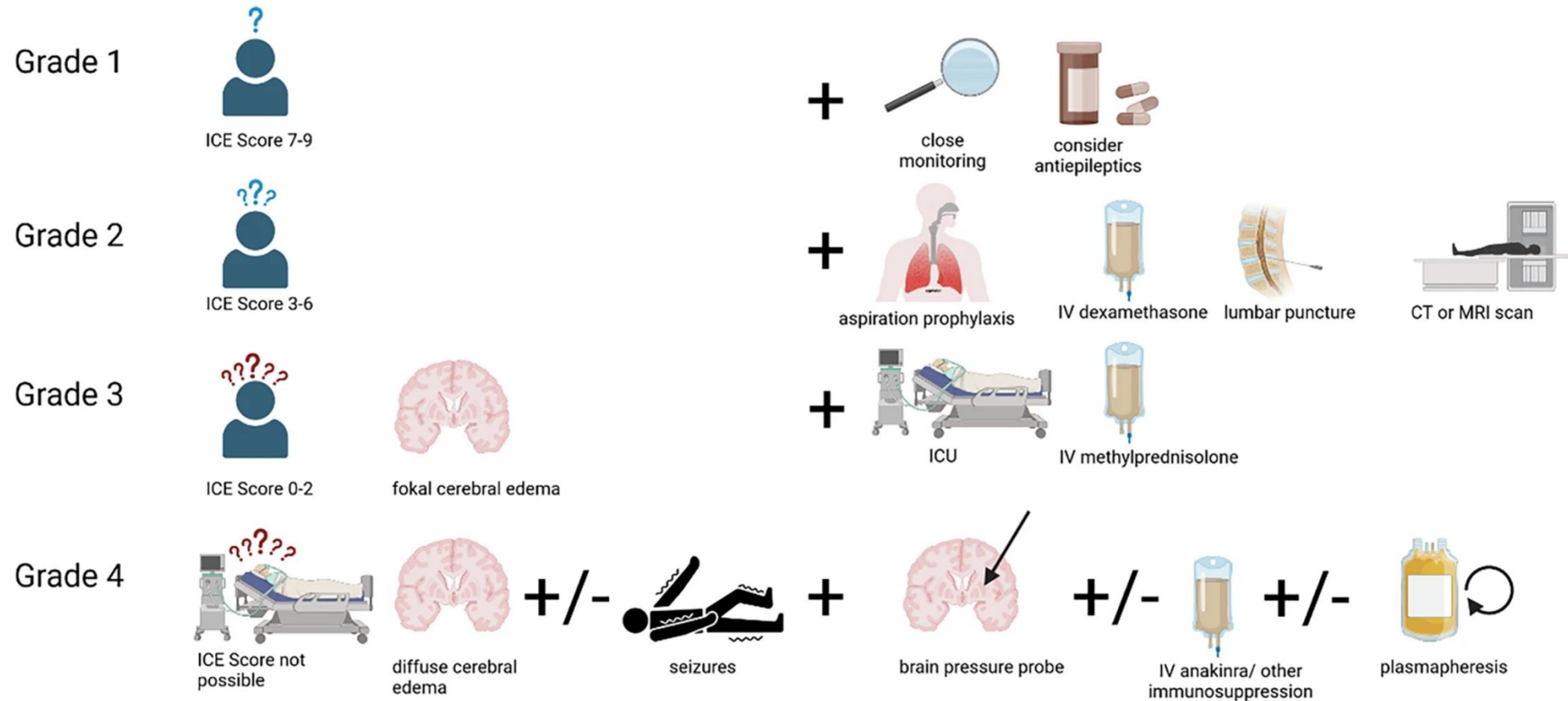
Abbreviations: CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; CVVHDF, continuous venovenous hemodiafiltration; HA, hemoadsorption; IL-6, interleukin-6; NE, norepinephrine; RCA, regional citrate anticoagulation.

^aAbove laboratory limit.

^bPatient with concomitant severe cardiomyopathy.



Immune effector cell–associated neurotoxicity syndrome (ICANS)



Clinical Case #2

- **CAR-T course**

- **LD chemotherapy** (red)
- **Outpatient infusion of liso-cel**
- Day 7: **admitted for grade 1 CRS and elevated serum creatinine (yellow)**
 - No additional IS given
- Day 16: Donor-derived cell-free DNA (dd-cfDNA) elevated (7.96%; NL <1%)

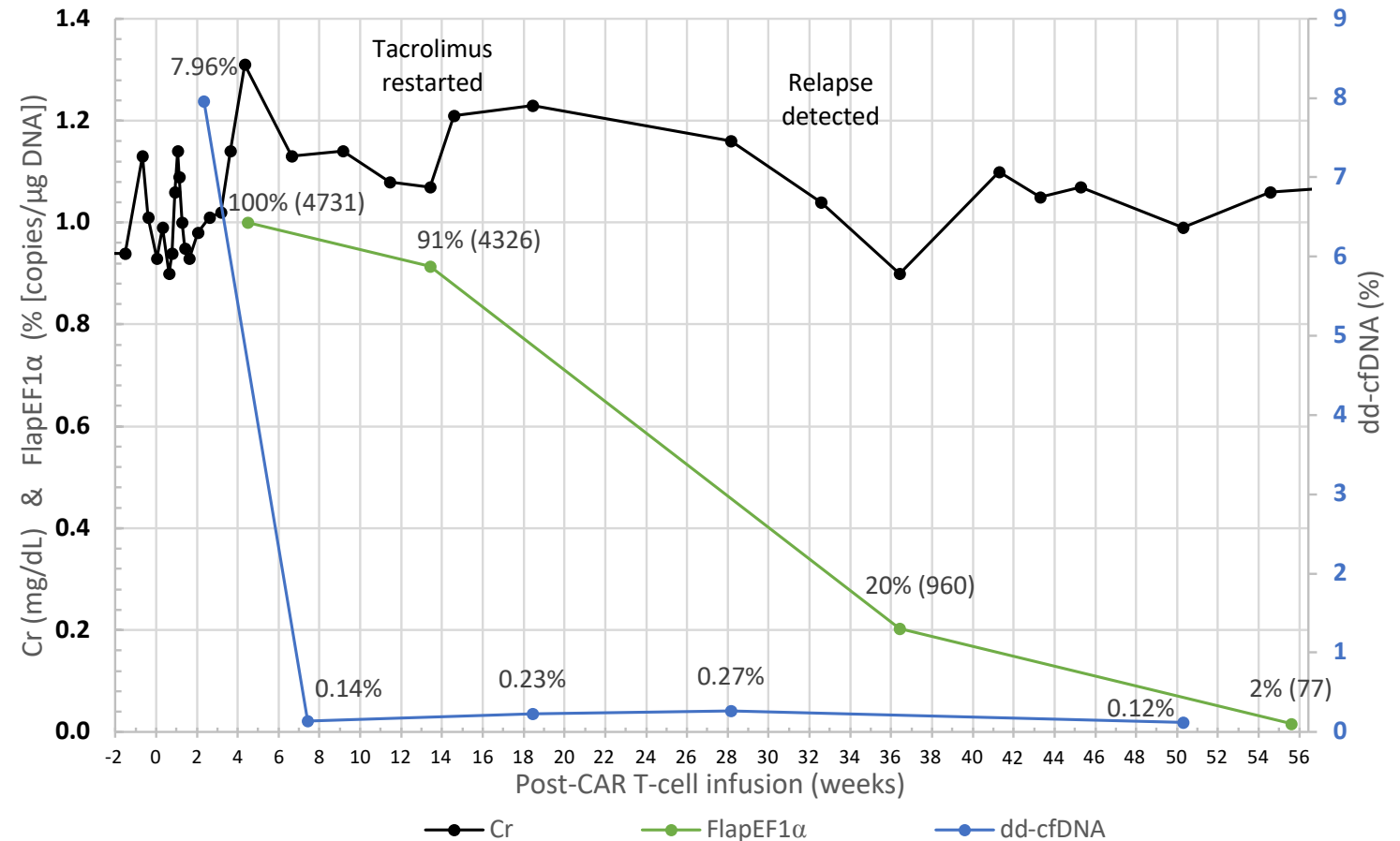
- **Response assessment**

- 1-month PET: PR
- 3-month PET: **CR** → tacrolimus restarted

- Subsequent PET/CTs negative

- Stable Renal function

- dd-cfDNA <1%
- FlapEF1α down-trending

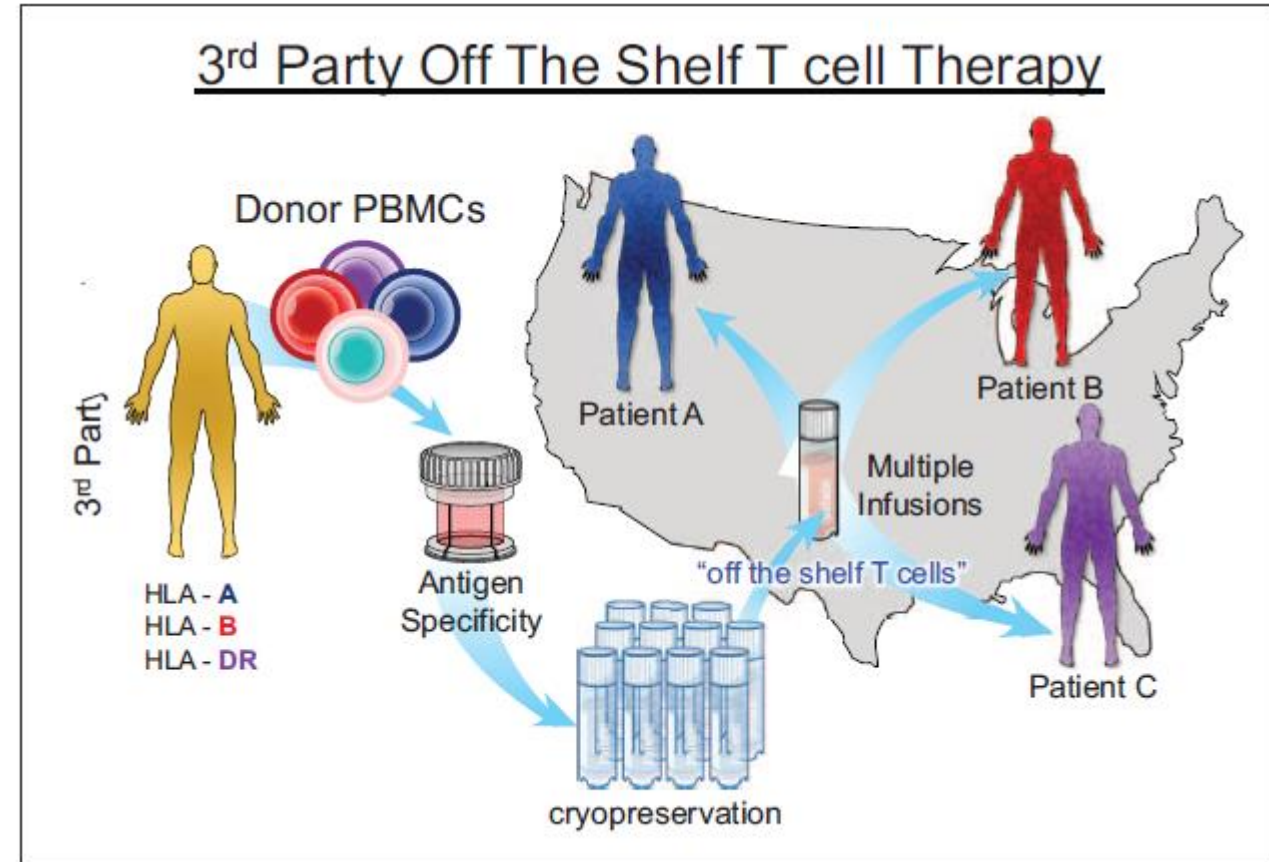
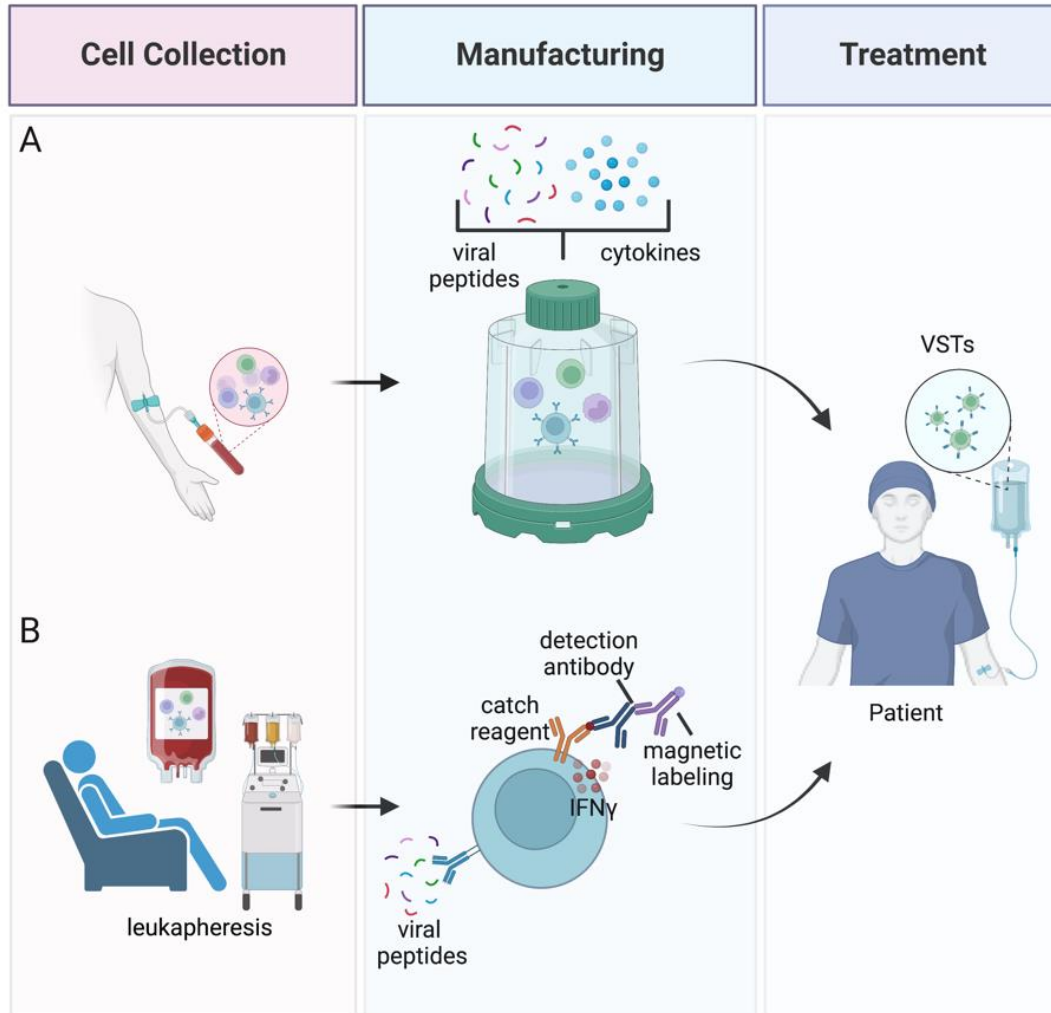


Summary: CAR-T in Organ Transplant

- Minimize Immunosuppression >4 weeks prior to leukapheresis
- Bridging and lymphodepletion can cause AKI, infections and endothelial injury (increased dd-cfDNA)
- CRS (40-90%) – Gr 1 80%, ICANS (20-70%), Hematotoxicity
- AKI (5-30%)
 - typically recoverable
- ORR Favorable,
but DOR is limited

	ZUMA-1	DLBCL PTLD cohort
Rejection		4/12 (25%), no GF
ORR	83%	82%
Median DOR (months)	11.1	6.5
CR	58%	59%
Median DOR (months)	NR (95% CI 12.9-NR)	7.7

Virus Specific T-cell Therapy (VSTs)



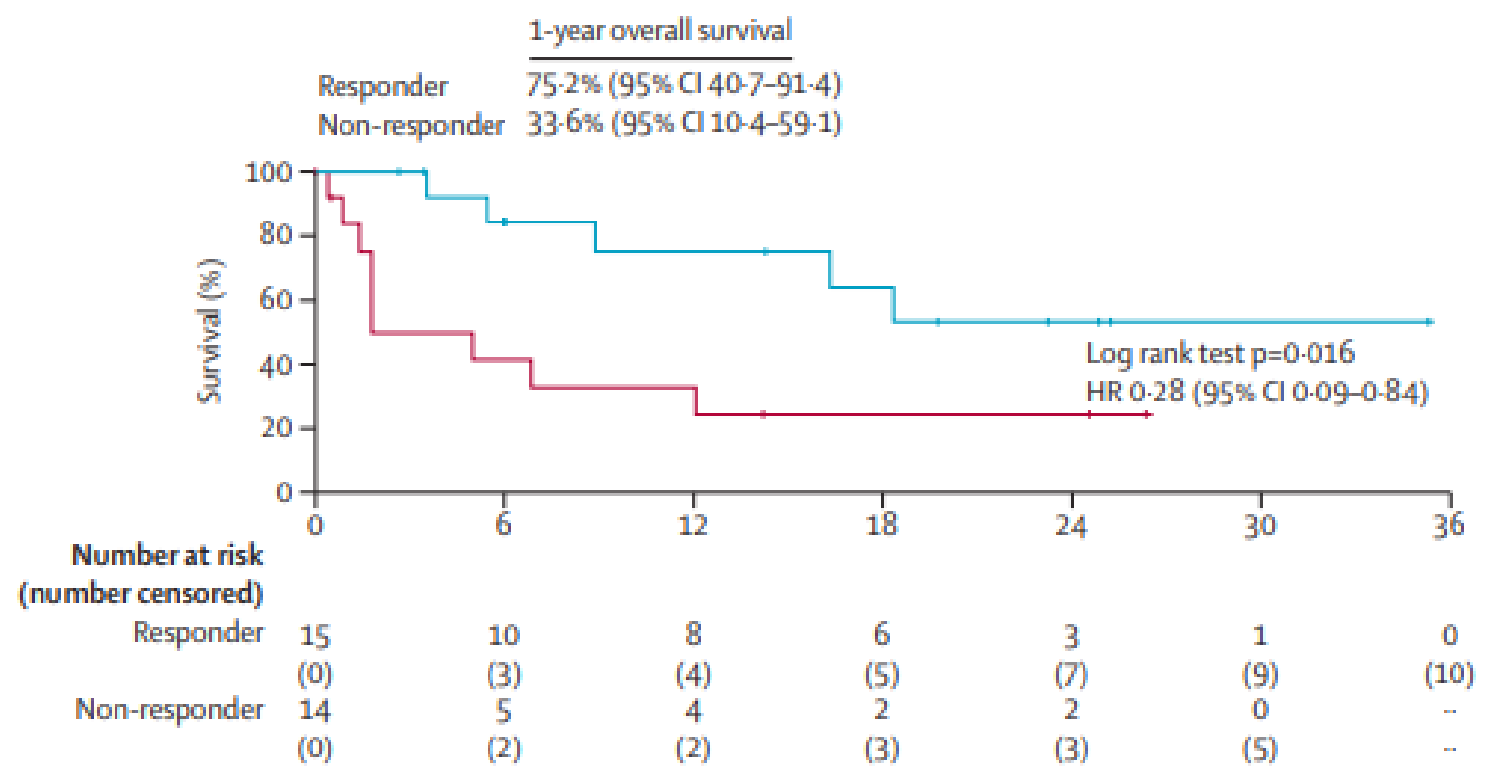
Baugh KA et al Curr Opin Infect Dis 2018
Green A et al, J Ped Inf Dis 2024
Wistinghausen et al Blood Adv 2024

Tabelecleucel for allogeneic haematopoietic stem-cell or solid organ transplant recipients with Epstein-Barr virus-positive post-transplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy (ALLELE): a phase 3, multicentre, open-label trial

	Haematopoietic stem-cell transplant group (n=14)	Solid organ transplant group (n=29)	All (n=43)
Objective response	7 (50%, 23–77)	15 (52%, 33–71)	22 (51%, 36–67)
Best overall response			
Complete response	6 (43%)	6 (21%)	12 (28%)
Partial response	1 (7%)	9 (31%)	10 (23%)
Stable disease	3 (21%)	2 (7%)	5 (12%)
Progressive disease	2 (14%)	7 (24%)	9 (21%)
Not evaluable	2 (14%)	5 (17%)	7 (16%)

Data are n (%; 95% CI) or n (%). Due to rounding, columns may not add to 100%. Response assessed per Lugano Classification with LYRIC modification by independent oncologic response adjudication in the full analysis set (consists of all patients who received at least one dose of tabelecleucel).

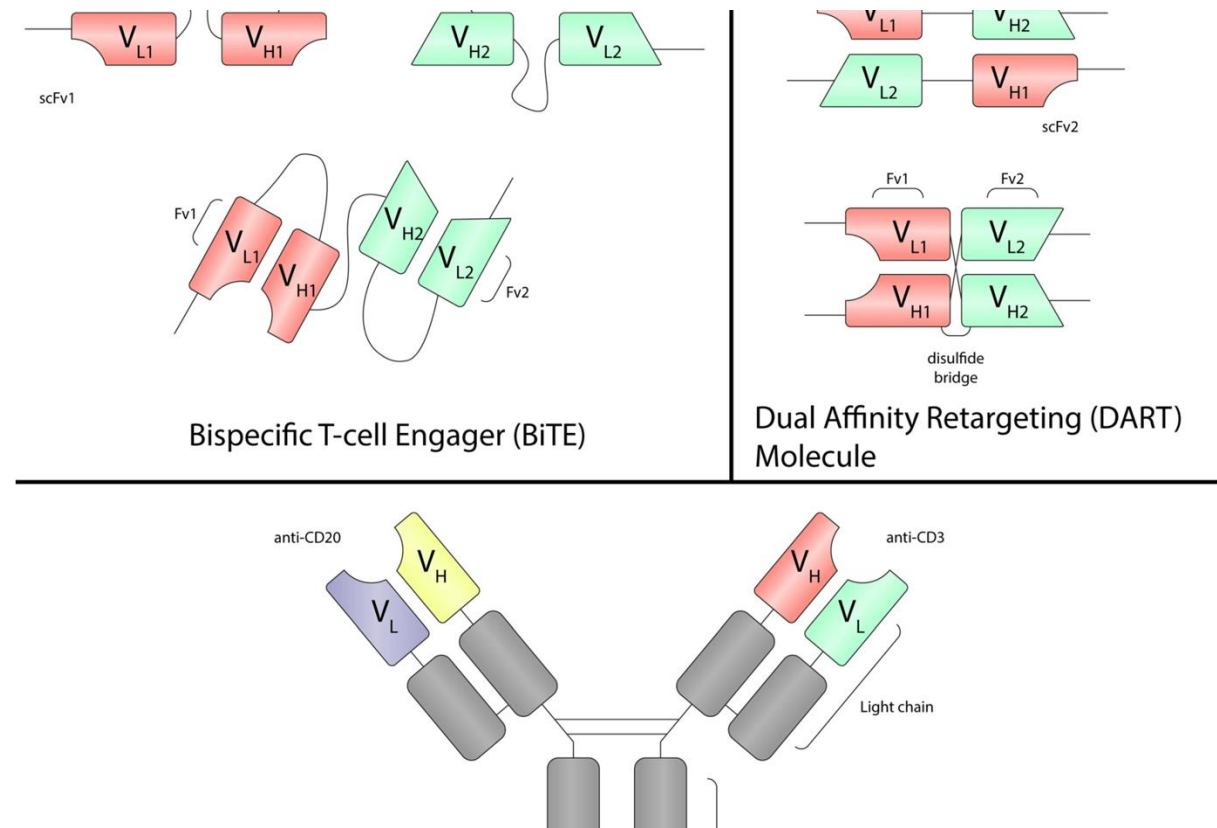
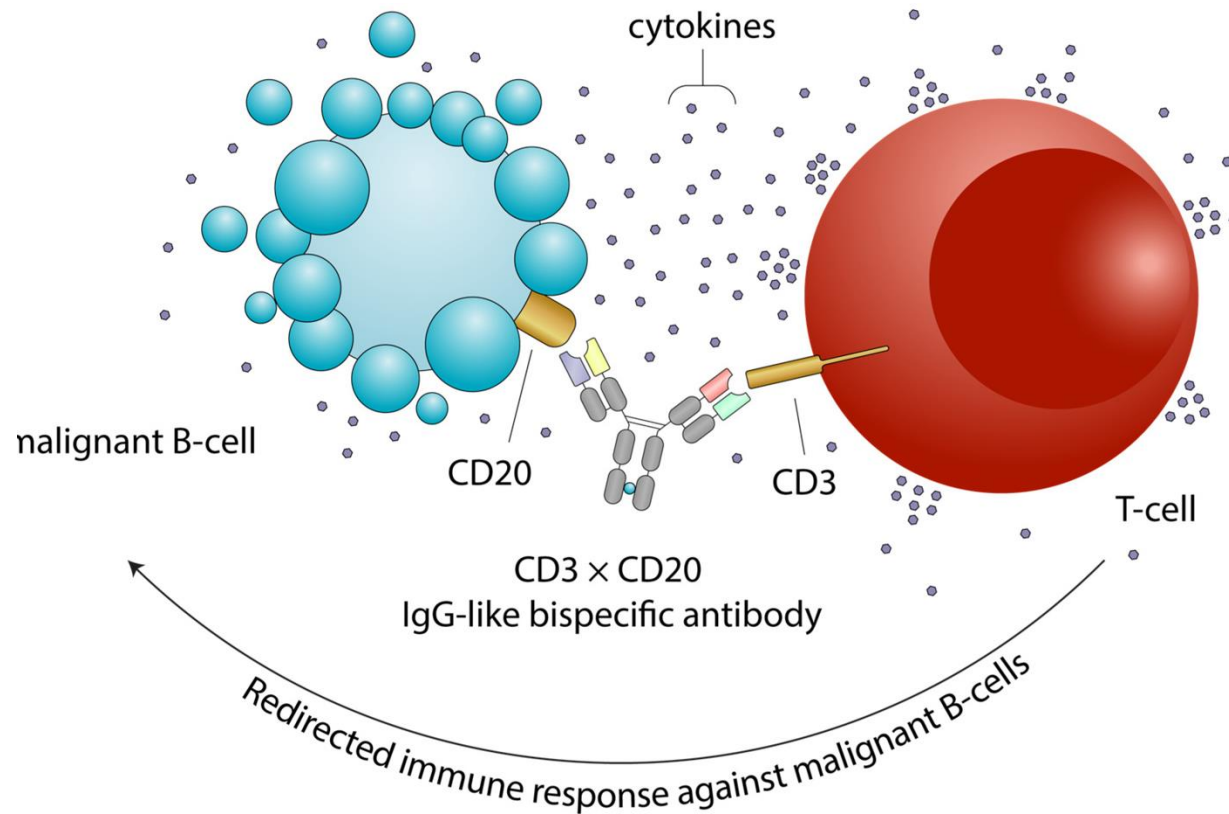
Table 2: Tabelecleucel efficacy endpoints



VST Conclusions

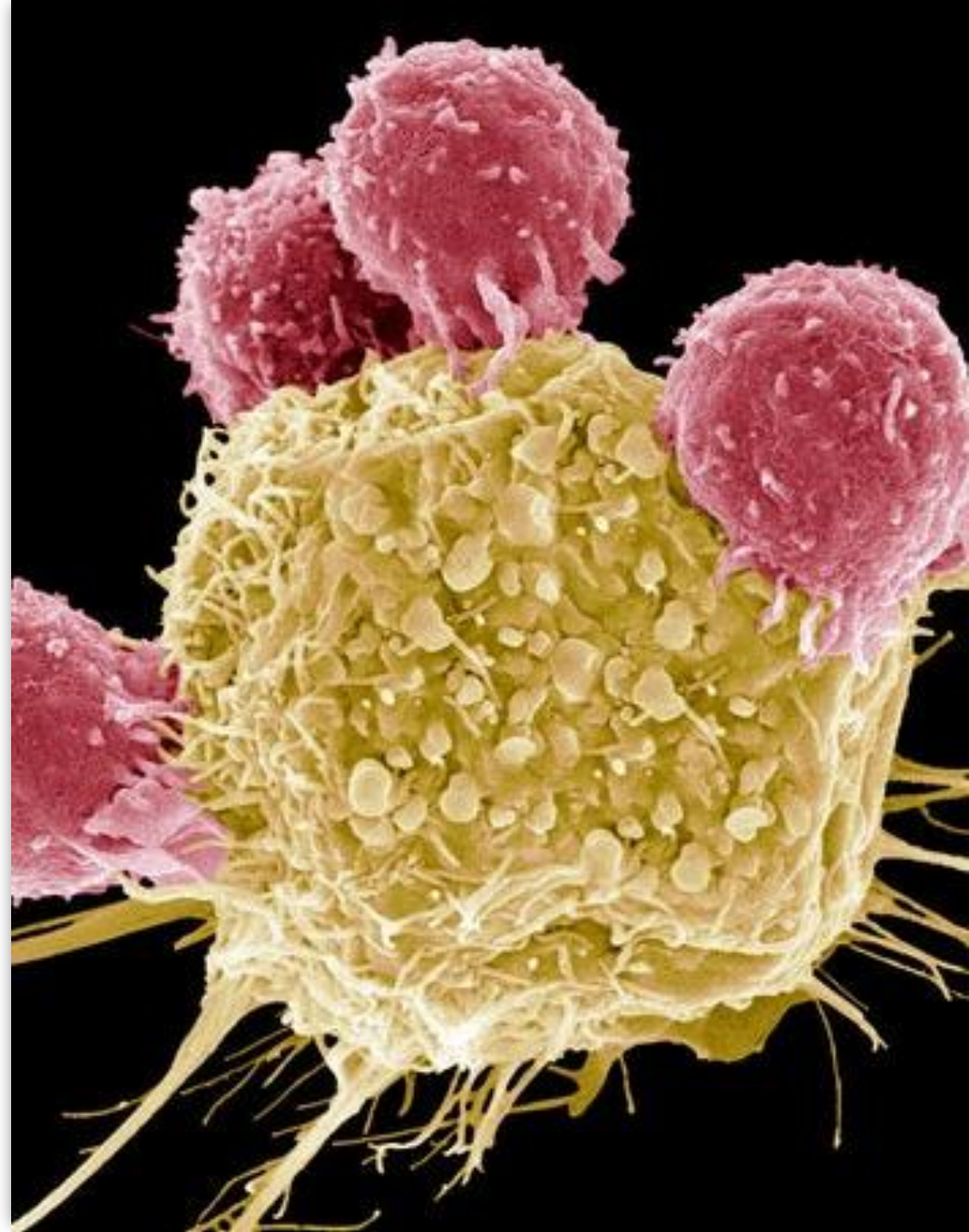
- VSTs increasingly used for EBV+ PTLD after SOT
 - Still difficult to obtain until Tab-cel FDA approved
 - Posaleucel trials halted for futility
- Safety profile: minimal rejection and no reported graft loss
- Moderate efficacy but not universal
- Potential trial in upfront setting in combination with rituximab
 - IIT preparation at CCHMC

PTLD Bispecific Antibodies



Summary

- PTLD is the leading cause of cancer death in KTRs
- Vague Symptoms are common: B symptoms, GI, Back pain or graft dysfunction
- Initial Eval: Labs (EBV PCR) + CT-C/A/P
- Reduce Immunosuppression followed by Ritux +/- CHOP
- R/R Disease = Poor Outcomes
- R/R Treatment: Chemo, VST, CAR-T, BiTEs
- New generation BiTEs & CAR-Ts to improve safety, efficacy & cost



Thank You!

- Patients
- UW Transplant Team
- COTC Team
- CICT Research Team
- FHCC, KRI & UW Nephrology
- Individual Donors

Email: Chrisbl@uw.edu



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