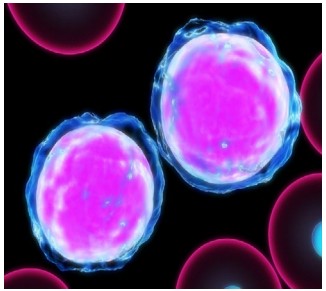

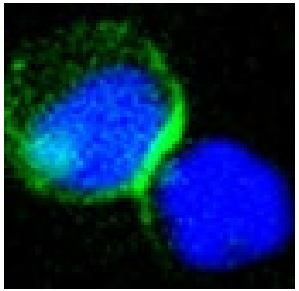

CAR T Cell Therapies

The State of the Science of Hematopoietic Stem Cell Treatment and Disability: A Workshop

David L Porter, MD
Director, Cell Therapy and Transplant
University of Pennsylvania
Abramson Cancer Center

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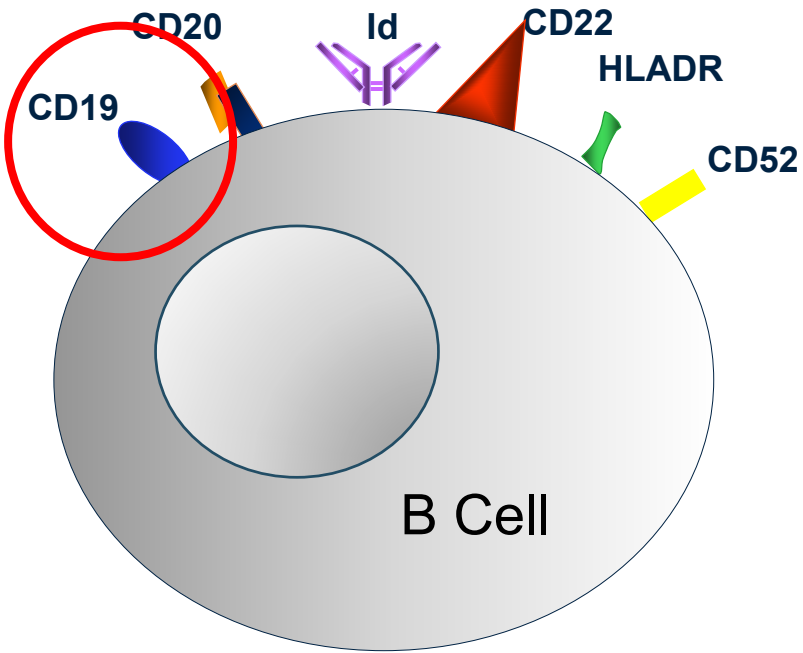
Disclosure Information: David L Porter

- Speaker and members of study team have financial interest due to potential upstream IP and patents and licensure to Novartis and Tmunity
  - COI managed in accordance with University of Pennsylvania policy and oversight
- Funding support for trials: ACGT, LLS, NCI, Novartis
- Advisory board (honorarium): Novartis, Kite, Incyte, Janssen, Jazz, DeCART
- Former member, ABIM Hematology Board exam writing committee (end Oct 2019)
- Employment: Spouse former employee Genentech (compensation included salary and stock)
- Member, Board of Directors, NMDP/Be The Match
- Some studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered preliminary until published in a peer-reviewed journal
- The views expressed in this presentation are those of the presenter

Cell-Surface Proteins are Targets for New Therapies



- Many cancer cells have well characterized surface proteins
- These proteins can be targeted to kill the cell with:
  - Monoclonal antibody
  - Engineered antibody
  - Immune (T) cells

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Adapted from Press O, et al. Cancer J Sci Am. 1998:4(suppl 2):s19–s26.

Targeting with Chimeric Antigen Receptors

- Antibody to target a specific protein on cancer cell.
- Sequences bring and keep protein on the surface of T cell
- Signals for T cell activation (killing), growth, and survival

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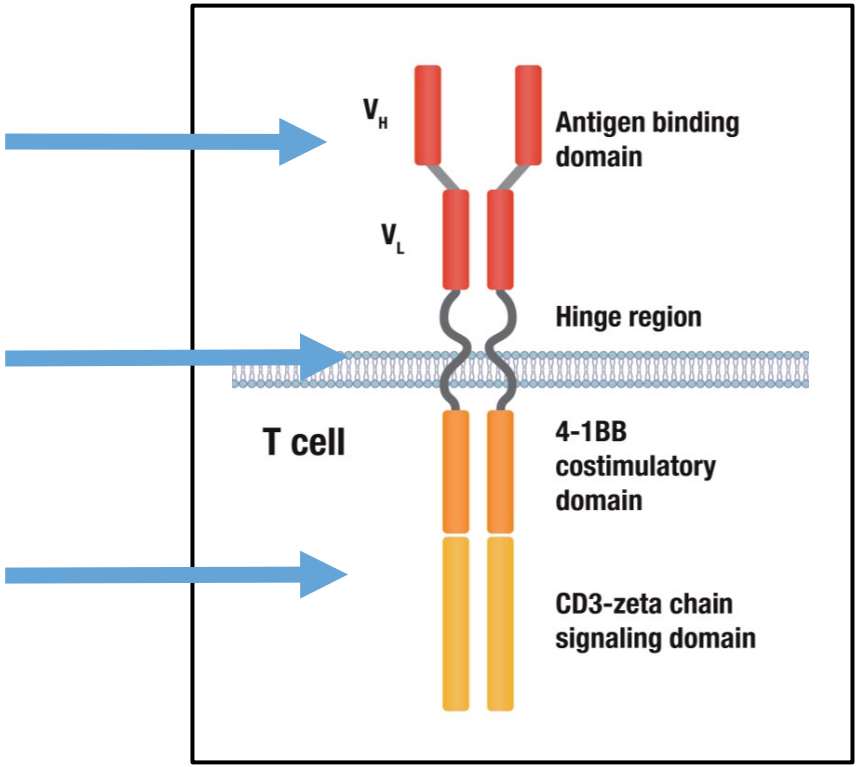
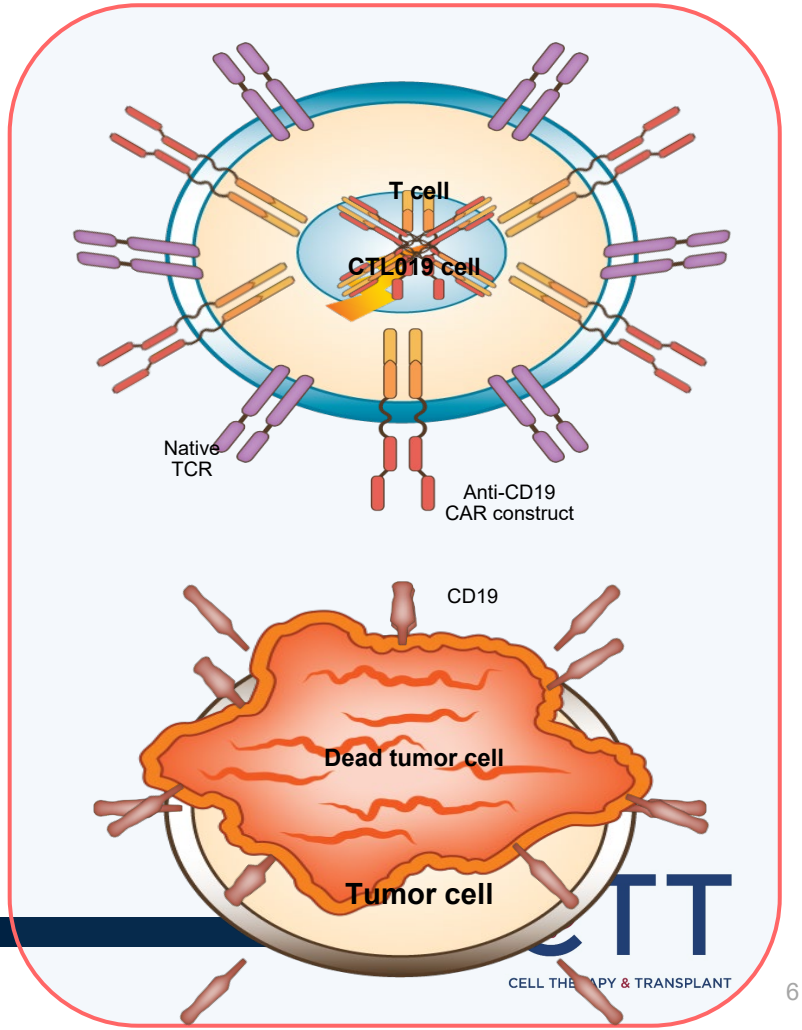


Targeting CD19 with CAR-Modified T cells

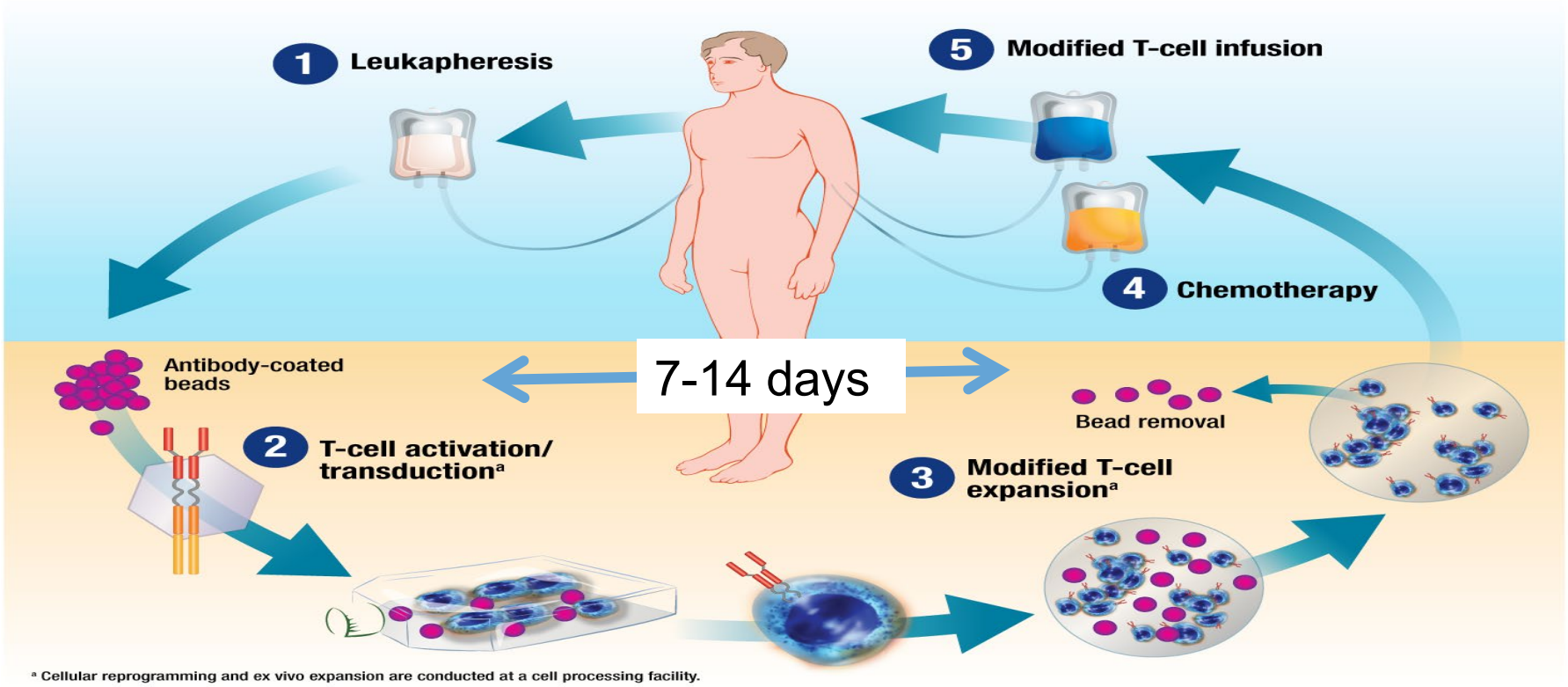
- Gene transfer (lentiviral (HIV-like) vector) bring new gene coding for CAR protein into T cell, conferring novel antigen specificity
- CAR modified T cells can now recognize and kill CD19+ cells



CAR T cells for B cell malignancies: Why all the excitement?

Disease	Standard therapy	CAR T cells
Relapsed, refractory ALL	Almost no probability of remission or cure	80-90% CR rates 50-60% LFS at 6-12 mo
Relapsed, refractory NHL	Almost no probability of remission or cure	50-70% CR 30-40% DFS
Relapsed, refractory CLL	Almost no probability of remission or cure	50-70% CR 30-40% DFS
Relapsed, refractory MM	Almost no probability of remission or cure	80%-100 ORR 33-74% DFS

Overview of CAR T Cell Therapy



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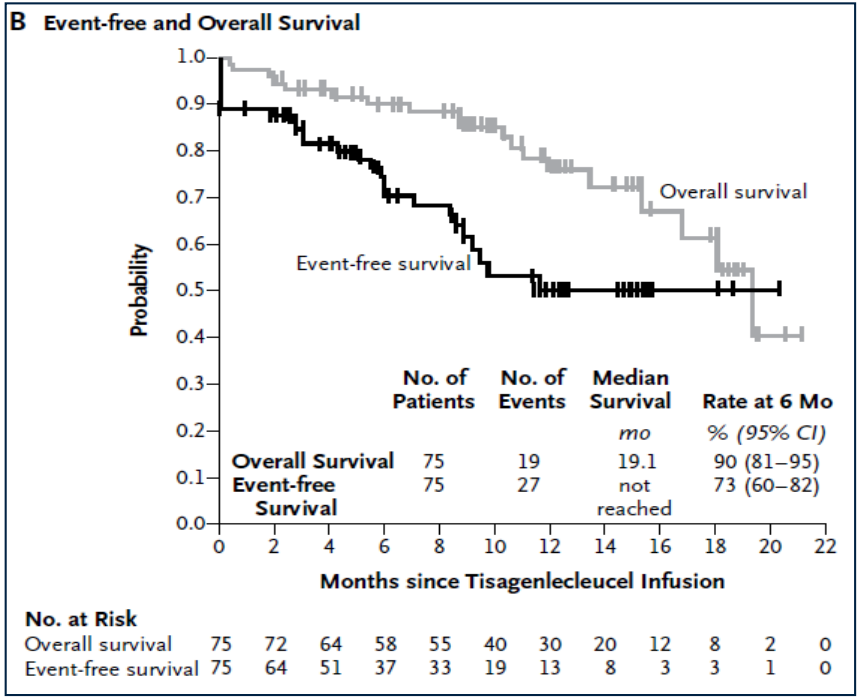
ALL: Rationale for Novel Therapies

- Prognosis for relapsed or refractory ALL poor
- Median survival < 1yr
- 3 yr survival <25%
- Allogeneic SCT for refractory ALL largely ineffective
- There is a desperate need for newer, more effective therapies for advanced and high risk ALL.

Eliana Study: Ped & AYA ALL: Outcomes Post CART19 (tisagenlecleucel)[1]

- EFS & OS for entire infused cohort



N=75 Ped&AYA ALL

↓

81%=MRD Neg CR

Only 8 Proceeded to HSCT in CR

Led to FDA approval of CTL019 (tisagenlecleucel, Kymriah) Aug 30, 2017.

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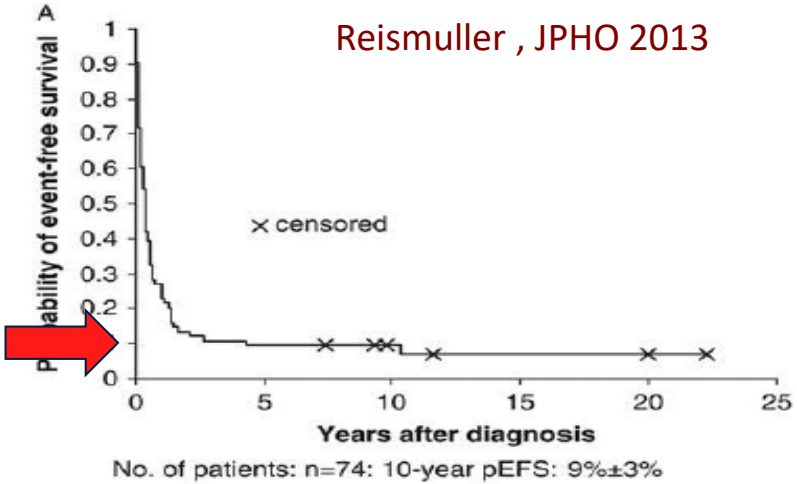
Maude et al, NEJM Feb 2018,378

Prognosis of 2nd or Greater Relapse of ALL: Impact of CAR T cell



Reismuller , JPHO 2013

10-30% remission rate

EFS 9%

FDA approved CAR T products

There are 5 FDA approved CAR T cell products for 5 indications

Indication	Product
ALL: Pediatric and young adults (up to age 25)	Tisagenlecleucel (tisa-cel)
Relapsed/refractory large B cell lymphoma (DLBCL, tFL, +/-PMBCL)	Tisa-cel Axicabtagene ciloleucel (axi-cel), Lisocabtagene maraleucel (liso-cel)
R/R Follicular lymphoma	Axi-cel
R/R Mantle cell lymphoma	Brexucabtagene autoleucel (brexu-cel)
R/R Multiple myeloma	Idecabtagene vicleucel (ide-cel)

Choosing a CAR-T product, location of care and managing patients

It's all about the toxicity….

CRS, Neurologic Toxicity, B Cell Aplasia

Toxicity: CAR T cells

- No significant acute infusional toxicity
- Tumor lysis syndrome
- Cytokine Release Syndrome (CRS)
- Neurologic toxicity
- Long-term B cell aplasia and hypogammaglobulinemia due to inability to make antibodies in some responding patients (toxicity or efficacy?) may increase risk infections
  - Supported with intravenous immunoglobulin (IVIG)

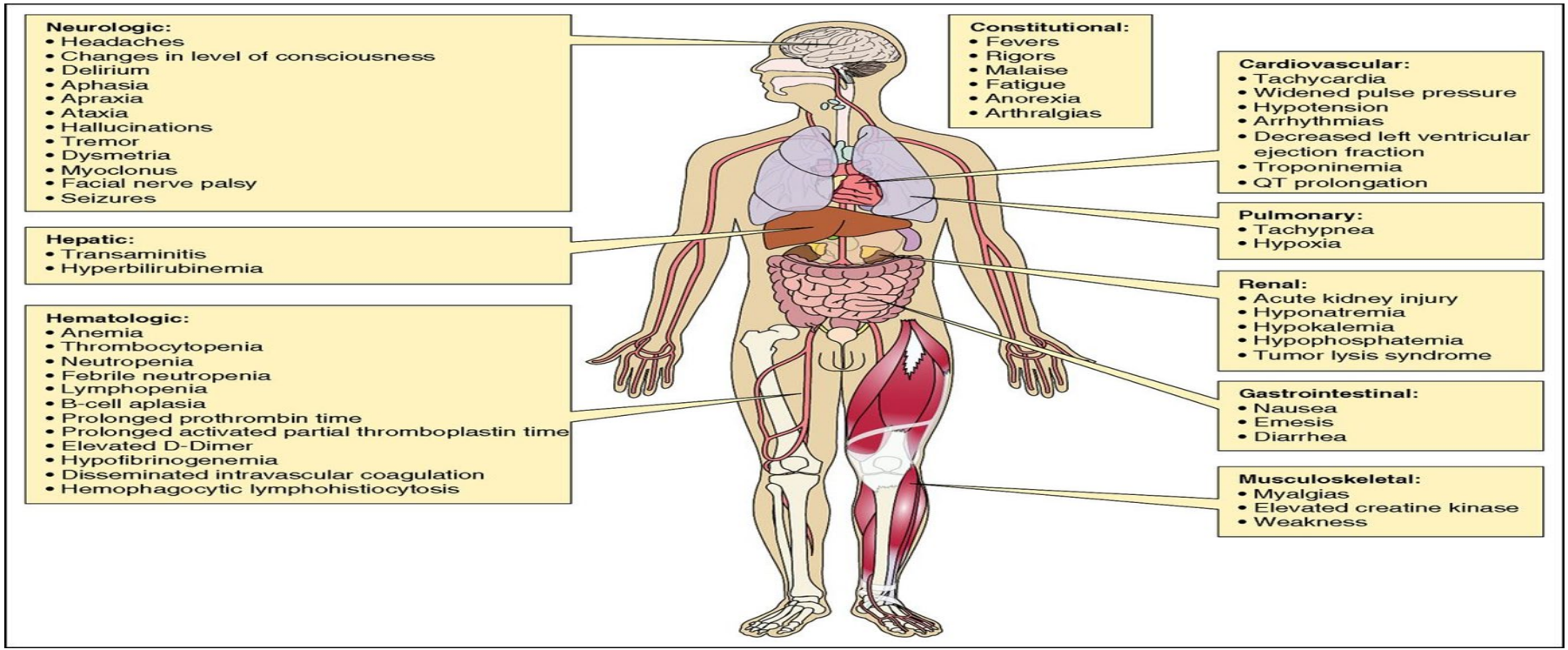
Cytokine Release Syndrome after CAR T Cell Therapy

- Correlates with CAR T activation and expansion resulting in intensive immune activation.
- Clinical syndrome: A mild to very severe “flu-like” syndrome
  - Onset 1-14 days after infusion, duration 1-10 days
  - Fevers in all patients (up to 105/41 deg)
  - Muscle and joint pain, anorexia, nausea, diarrhea
  - Capillary leak, leading to hypotension, hypoxia
  - May be self-limited or require anti-cytokine intervention
  - CRS-related mortality low but possible (<5%)
  - Biochemical changes
  - Marked increase in IL6
  - Dramatic elevations in ferritin (MAS/HLH), CRP

Neurologic Toxicity

- Less well understood; less defined management
- Symptoms:
  - Expressive aphasia (esp naming objects/people); perseveration, global aphasia
    - Often awake and alert
  - Encephalopathy
  - Tremor, myoclonus, seizures
  - Apraxia, dysgraphia
- Onset: within days to 2-3 weeks after CAR T
  - During or after resolution of systemic CRS
- Self limited; rare cases cerebral edema/death

CRS toxicities by organ system



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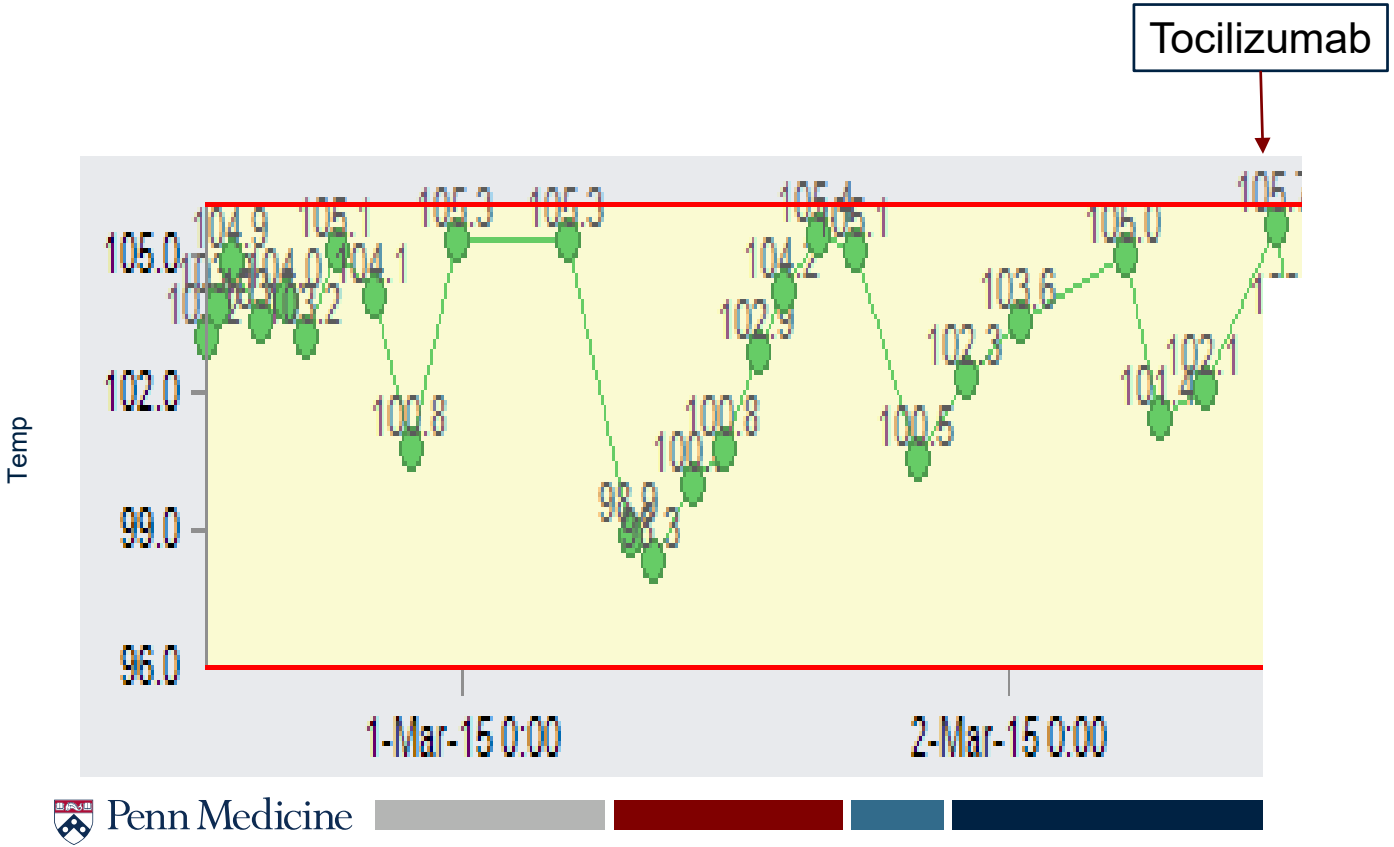
Brudno, Blood (2016) 127 (26): 3321–3330.

CRS After CAR T: Fever response to tocilizumab



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CAR T-cell Therapy and Toxicities- Key Points

- Major unique acute toxicities include CRS and neurologic toxicities
  - Neurologic toxicity managed with corticosteroids
- Almost all patients recover by day 30 (or day 90) after infusion with limited long term toxicities.
- Hypogammaglobulinemia (poor antibody production) is a long term toxicity
  - Possible increased risk of infection
  - Managed with IVIG infusions when appropriate.

Using CAR-T in the real world: Outpatient care

Select appropriate patient

- Physically ‘stable’
  - EF 40–45% or NYHA <gr3; CrCL >40, Cr <1.6–2.0, LFTs and pulmonary function ‘adequate’
- Reliable
- Within 1 hour of transplant center if outpatient treatment
- Caregiver available

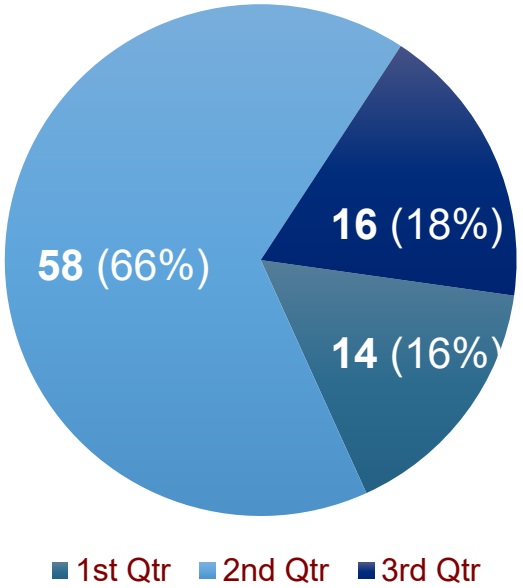
Select appropriate product

- Toxicity (CRS, NT) is predictable (tisa-cel > axi-cel)
- Gradual in onset

Available resources

- Outpatient expertise available around the clock
- Easily accessible
- Telemedicine or in-person evaluations frequently (2x/week minimum)
- Staff training

Toxicity profile conducive for outpatient management: Tisacel outpatients at University of Pennsylvania (2018–2020), N=88



- Not admitted within 30 days
- Admitted within 30 days
- Admitted within 3 days

Median time to admission = 4 days post infusion

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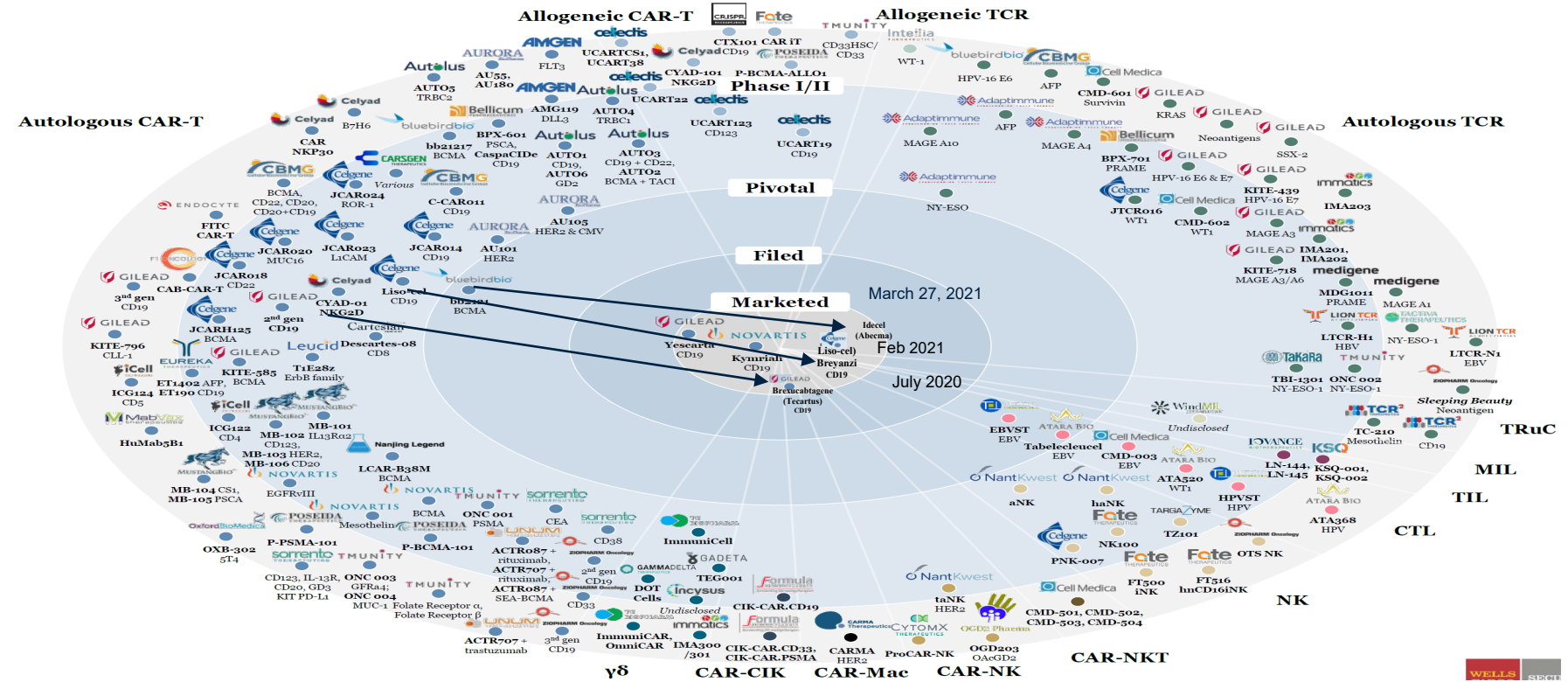
- EAP: expanded access program
- Unpublished experience, UPenn

Cell Therapy Landscape: 2018-2021 View



Can CAR T cells cure leukemia or lymphoma?

- MRD negative responses are frequent
- Majority of relapses in ALL, CLL, NHL happen within first 6-12 mo
- Many patients alive in CR well beyond 12mo
  - CLL - 10 yrs!
  - ALL - 8 yrs!
  - NHL - 7 yrs!
- Combination therapies are increasing the proportion of patients achieving “deep” CR
- CAR T cells may be curing some patients with ALL, CLL, NHL

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Discussion and Questions


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