CAR T-Cell Therapy for Your Patients: What You Need To Know

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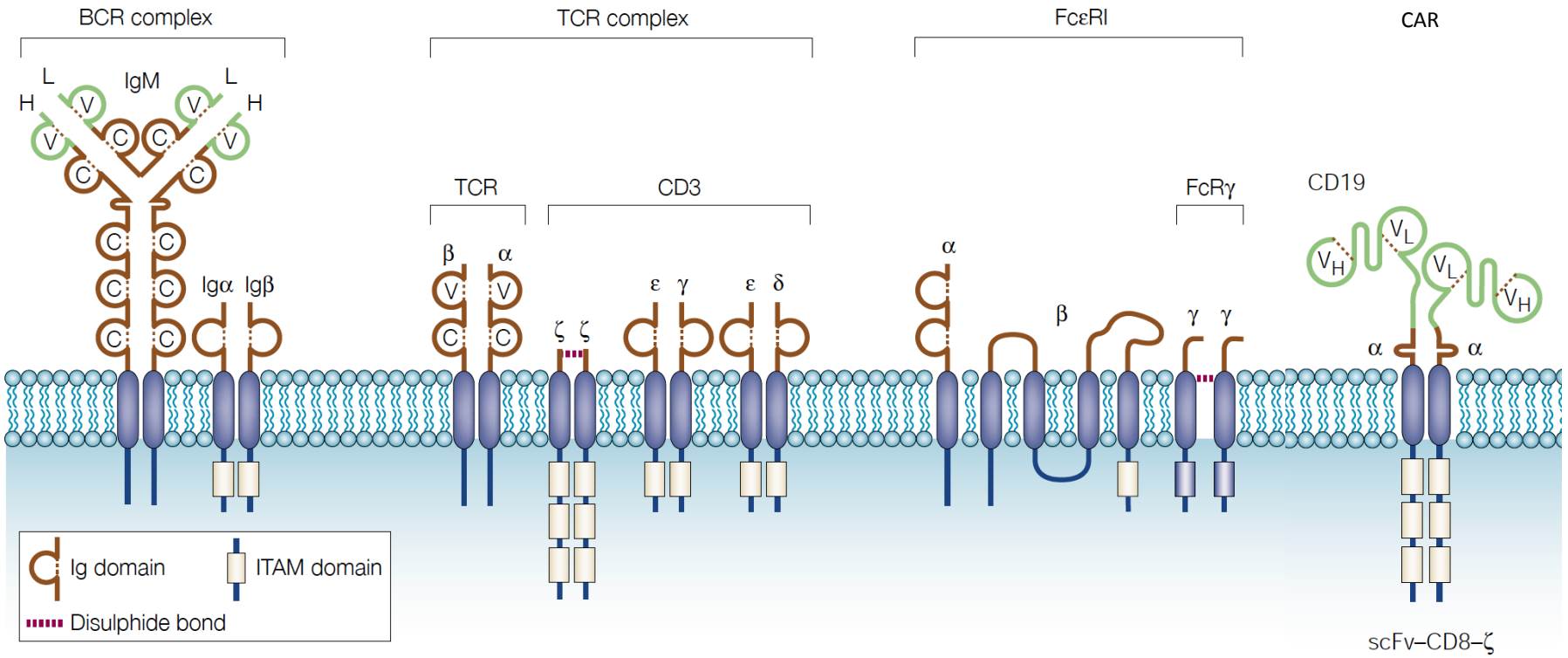
Learning Objectives

- Describe the MOA of Chimeric Antigen Receptor T-cell (CAR-T) therapy and approved-FDA indications
- Understand where CAR-T therapy might fit into the cancer care landscape and its future applications
- Recognize access and coordination of care issues and solutions associated with CAR-T therapies including availability, cost, administration, and operational considerations

CAR T-Cell Therapy Background

Antigen Receptors: Biologic and Synthetic

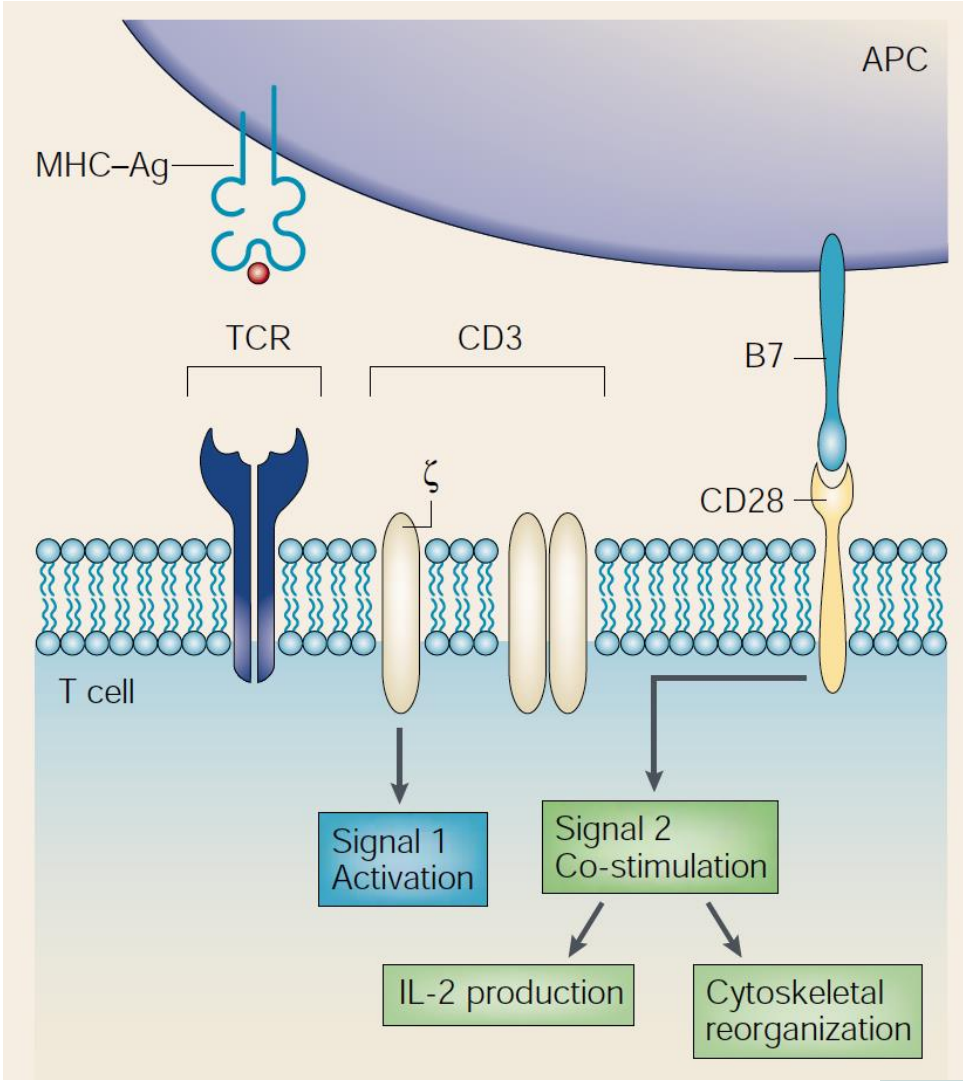


Sadelain et al. *Nat Rev Cancer 2003*

Advantages of the Chimeric Antigen Receptor

- HLA-independent antigen recognition
- Active in both $CD4^+$ and $CD8^+$ T cells
- Target antigens include proteins, carbohydrates, and glycolipids
- Rapid generation of tumor specific T cells
- Minimal risk of autoimmunity or GvHD
- A living drug, single infusion
- Universal application to all patients

T Cells Require 2 Signals for Complete Activation



2nd Generation CAR T-cells That Incorporate 2 Signals Function Better In Vivo

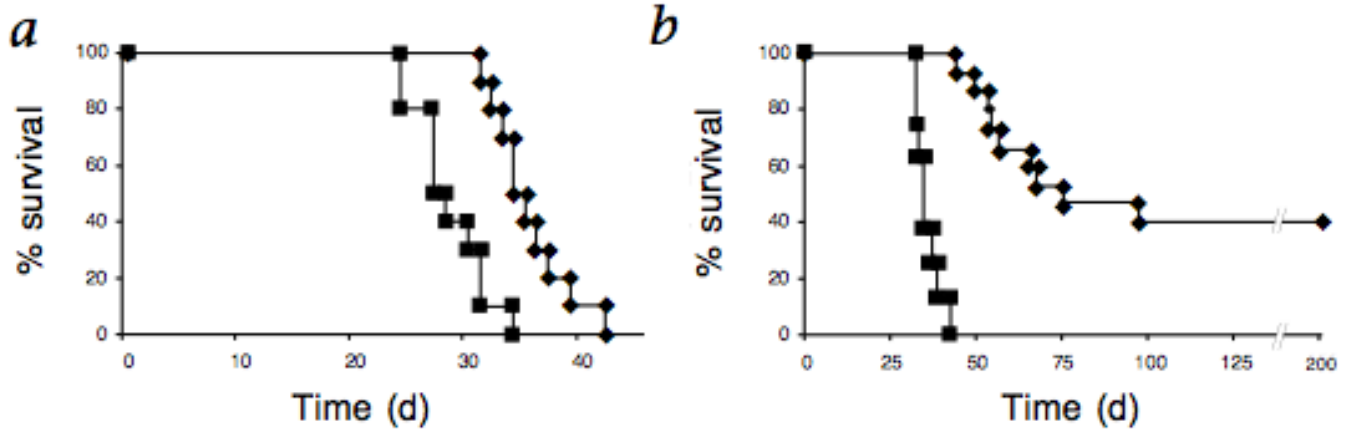
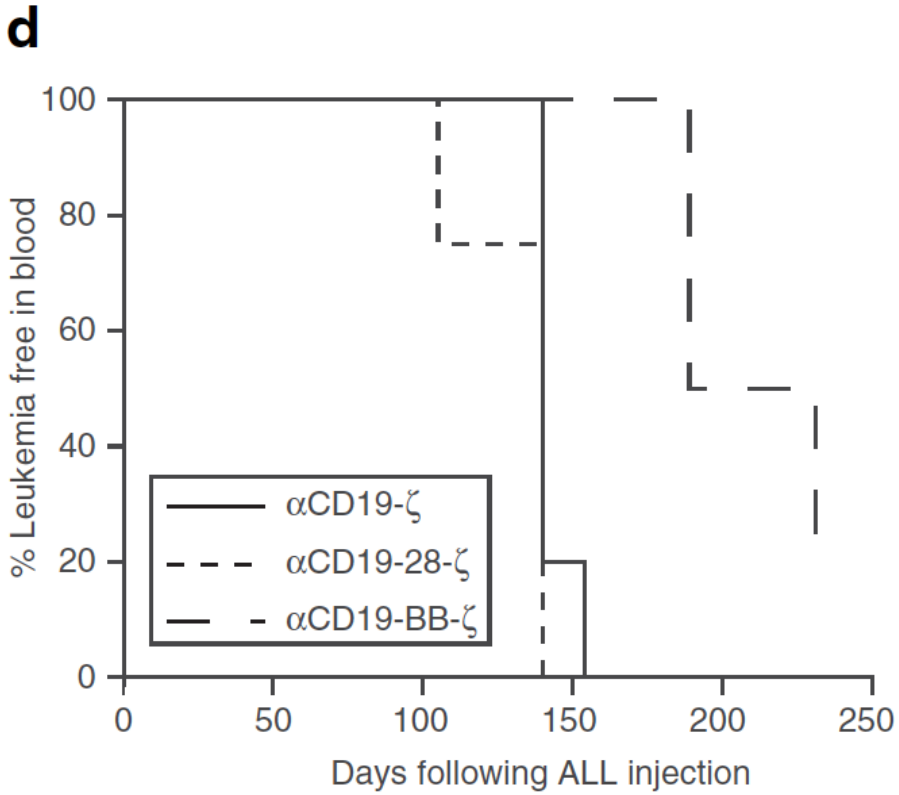


Fig. 4 Tumor cell eradication by 19z1$^+$ T cells is dependent on *in vivo* T-cell co-stimulation. ***a***, Kaplan-Meier survival curve of SCID-Beige mice treated with 1×10^7 19z1$^+$ (◆; $n = 10$) or Pz1$^+$ (■; $n = 10$) T cells 4 and 5 d after NALM-6 tumor cell injection. ***b***, Kaplan-Meier survival curve of SCID-Beige mice treated with 7.5×10^6 19z1$^+$ (◆; $n = 15$) or Pz1$^+$ (■; $n = 8$) transduced T cells 4, 5 and 6 d after NALM-6(CD80$^+$) tumor cell injection. Results represent data pooled from 2 independent experiments.

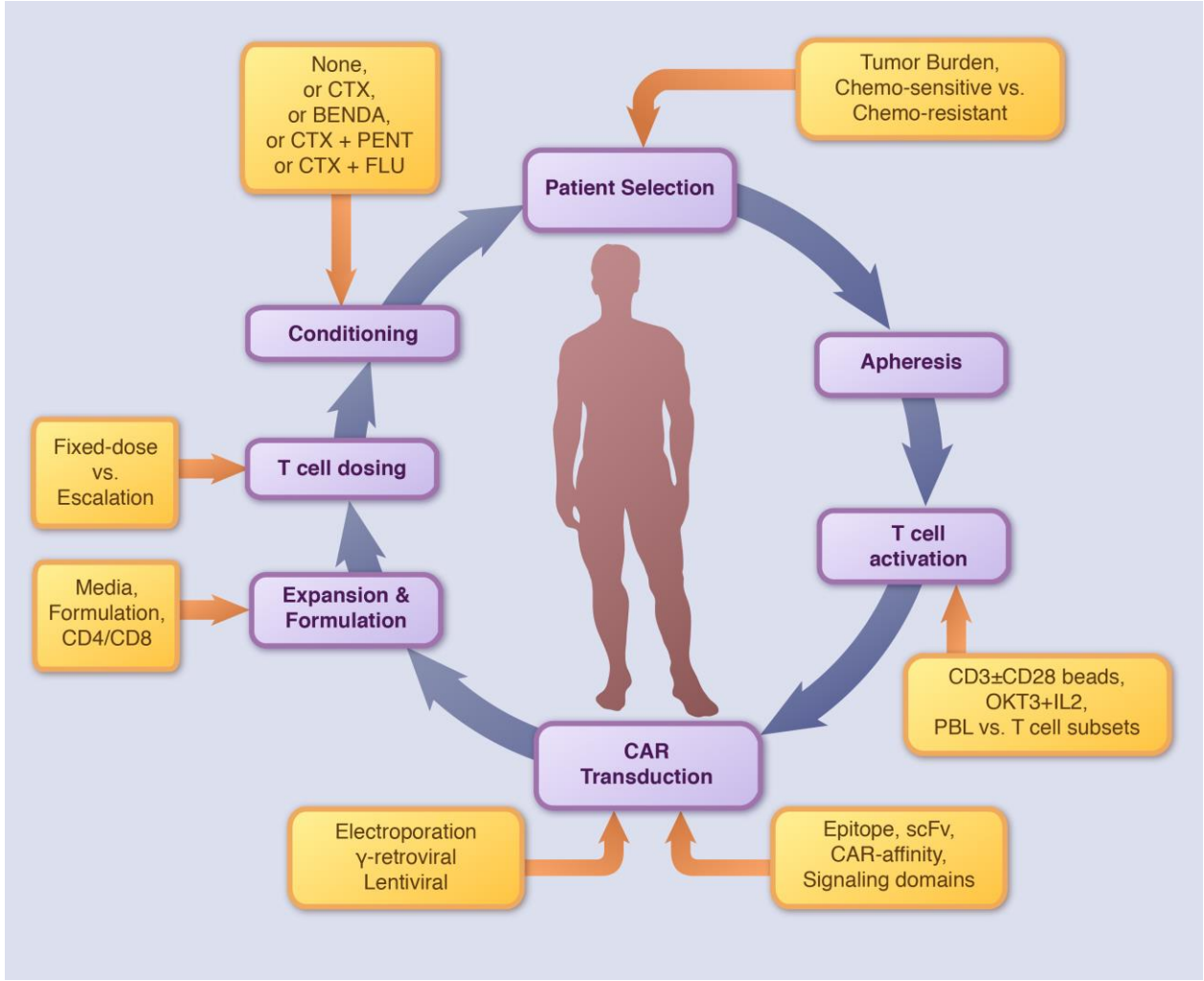
Brentejens et al. *Nat Med 2003*



Milone et al. *Molecular Therapy 2009*

New Approvals and Indications

Vast Differences Among Clinical Trials Evaluating CAR T-cells



Davila et al. *OncoImmunology* 2012

New Approvals and Indications

Agent	Breakthrough Therapy Designation	FDA Approval
CTL019 (tisagenlecleucel-T)	Relapsed/refractory ALL; July 2014 Relapsed/refractory DLBCL; April 2017	August 2017: for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse
KTE-C19 (axicabtagene ciloleucel)	Ref DLBCL, primary mediastinal B-cell lymphoma, and transformed FL; Dec 2015	Approved Oct 2017 for patients with relapsed/refractory DLBCL after 2 lines of therapy
JCAR017	NHL; Dec 2016	

Review of Published Results Targeting B-ALL

Center	N	scFv	CAR Design	Vector	Conditioning Chemo	Dose (CART/kg)
NCI	21 peds	FMC63	CD28-ζ	retro-virus	FLU/CY	$1\text{-}3x10^6$
UPENN[2]	25 peds 5 adults	FMC63	4-1BB-ζ	lenti-virus	varied	$8x10^5$ to $2x10^7$
MSKCC	16 adults	SJ25C1	CD28-ζ	retro-virus	CY	$3x10^6$
FHCRC	30 adults	FMC63	4-1BB-ζ	lenti-virus	FLU/CY vs CY	$2x10^5$ to $2x10^7$
Seattle Childrens	45 peds and AYA	FMC63	4-1BB-ζ	lenti-virus	FLU/CY vs CY	$0.5x10^6$ to $10x10^6$

Published Response Rates for B-ALL

- NCI: CR (70%), CRm (60%)
- UPENN: CR (90%), CRm (79%)
- MSKCC: CR (88%), CRm (75%)
- FHCRC: CR (93%), CRm (86%)
- Seattle Children's: CRm (89%)

CR, complete response; CRm, complete molecular response.

1. Lee et al. *Lancet.* 2015;385:517-528.
2. Maude et al. *N Engl J Med*. 2014;371:1507-1517.
3. Davila et al. *Sci Trans Med*. 2014;6:224ra25.
4. Turtle et al. *J Clin Invest*. 2016;126:2123-2138.

Survival After CD19-targeted CAR T-cells for B-ALL

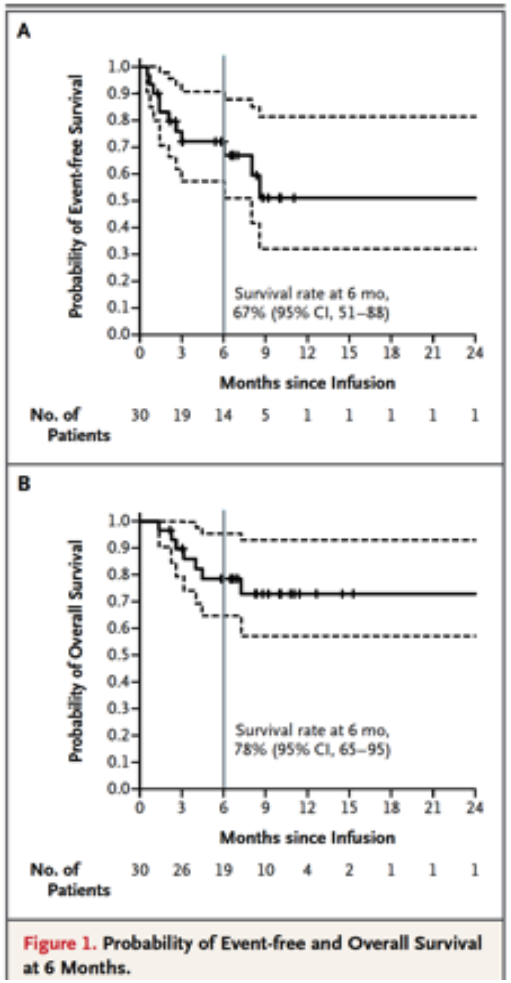
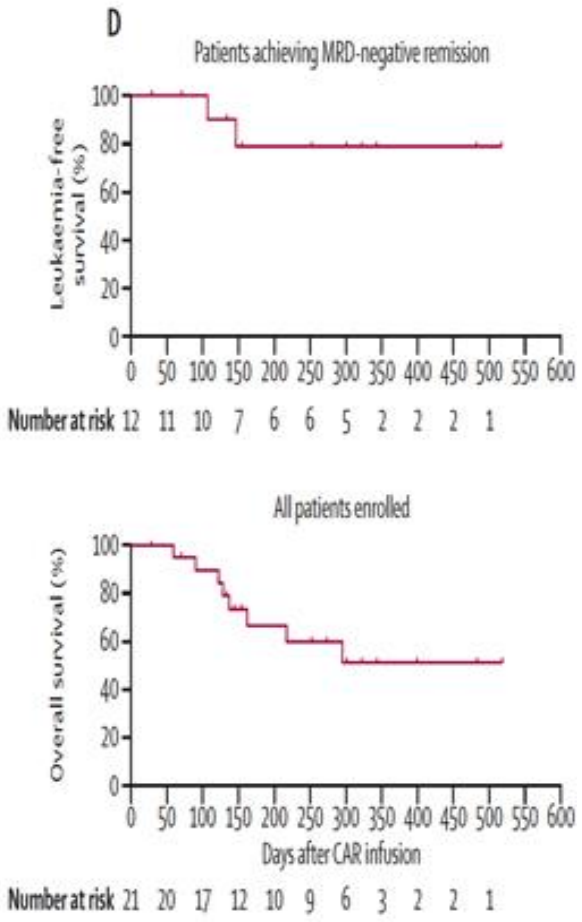
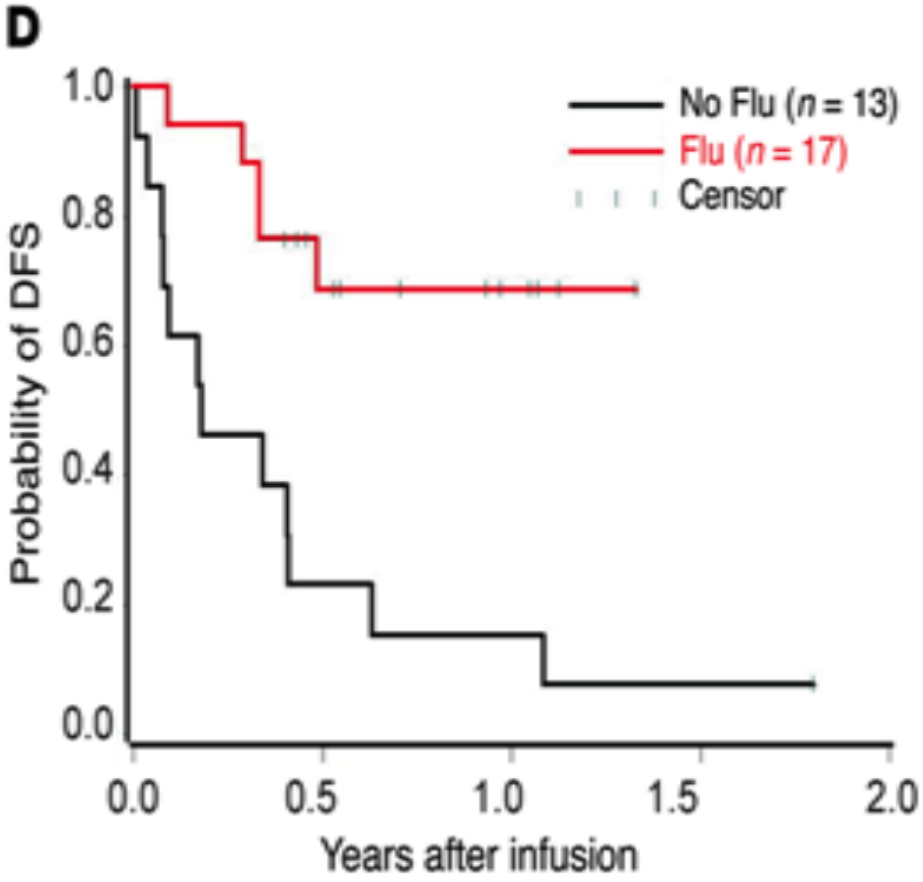


Figure 1. Probability of Event-free and Overall Survival at 6 Months.

Maude et al. *N Engl J Med*. 2014;371:1507-1517.



Lee et al. *Lancet.* 2015;385:517-528.



Turtle et al. *J Clin Invest*. 2016;126:2123-2138.

B-ALL, B-cell acute lymphoblastic leukemia; CAR, chimeric antigen receptors; DFS, disease-free survival; MRD, minimum residual disease.

Persistence Varies Among the Trials

- CAR with CD28 co-stimulatory domain not detected past 42 days for patients with B-ALL (Lee et al. *Lancet* 2015)
- CAR with CD28 co-stimulatory domain detected at 9 months in patients with NHL (Locke et al. *Mol Ther* 2017)
- CAR with 41BB co-stimulatory domain have been detected out to 11 months in patients with B-ALL (Maude et al. *NEJM* 2014)

Some Relapses are Related to Antigen Escape

- CD19-negative antigen escape has been identified by at least 2 mechanisms
  - Epitope is spliced out by alternative splicing[1]
  - Lineage switch from lymphoid to myeloid cell[2]

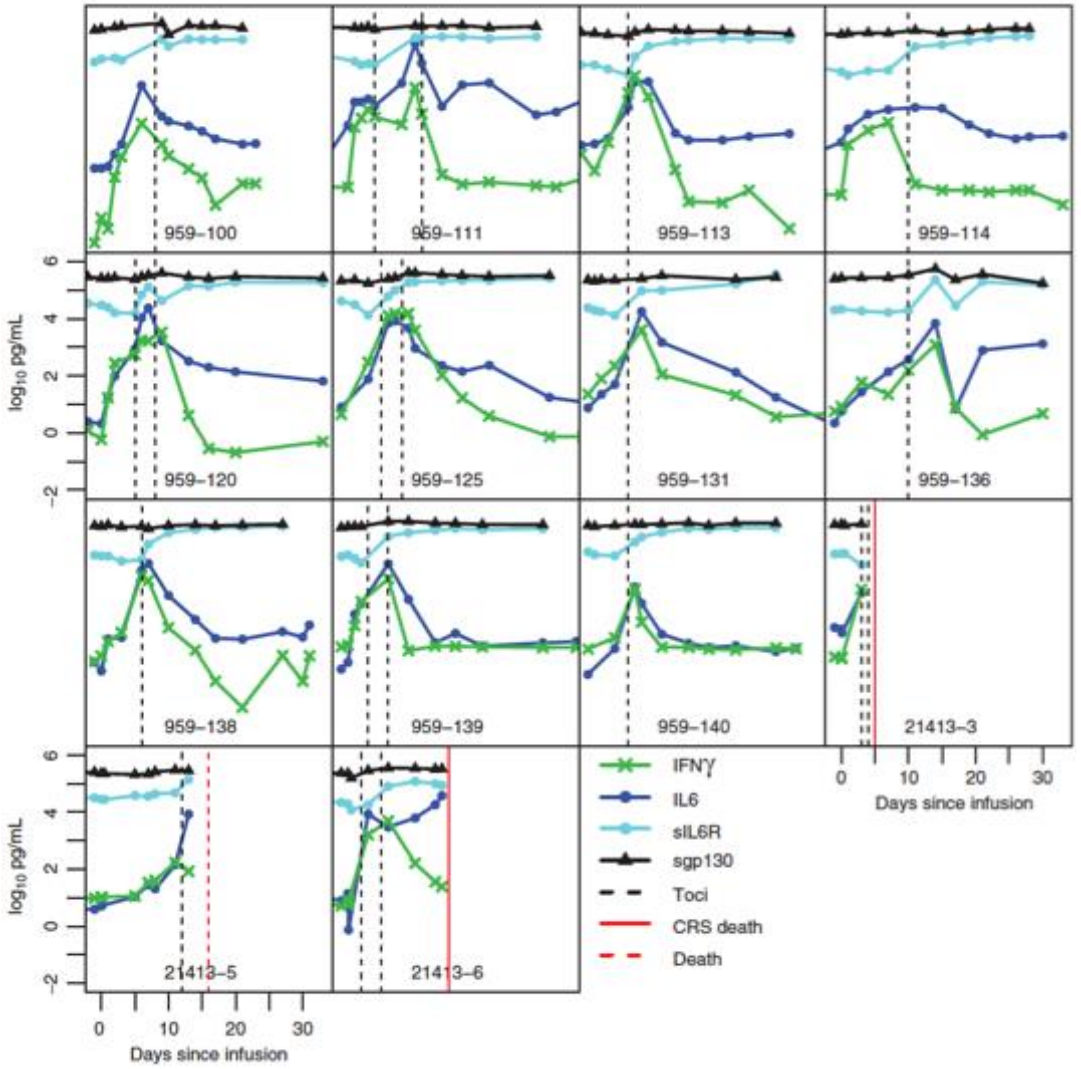
Toxicities

- Cytokine release syndrome (CRS)
- Neurologic toxicity
- B-cell aplasia

Cytokine Release Syndrome

- Fevers (usually the first sign of CRS)
- Cardiovascular disorder (tachycardia, hypotension)
- Respiratory disorder (tachypnea, hypoxia)
- Other organ toxicities can occur
- Toxicities correlate with tumor burden
- Some toxicities have resulted in death
- The toxicities correlate with a release of cytokines
- CRP and other biomarkers can be used as markers for CRS

Cytokine Blockade Ameliorates the CRS



CRS, cytokine release syndrome.
Teachey et al. *Cancer Discov*. 2016;6:664-679.

CRS Grading Schemes

	Grade 1	Grade 2	Grade 3	Grade 4
Penn Scale	*Mild reaction*	*Moderate reaction* Requires IV therapies; some signs of organ dysfunction (grade 2 Cr or grade 3 LFTs) Hospitalization for management of CRS symptoms including neutropenic fever	*More severe reaction* Hypoxia requiring supplemental O_2 Hypotension treated with IV fluids or low-dose pressor Hospitalization for management of organ dysfunction (grade 3 Cr or grade 4 LFTs)	*Life threatening* Hypotension requiring high-dose pressor, mechanical ventilation
Lee Criteria	*Require symptomatic treatment*	*Require & respond to moderate intervention* Hypoxia responds to < 40% O_2 Hypotension responsive to fluids or low-dose pressor Grade 2 organ toxicity	*Require and respond to aggressive intervention* O_2 requirement $\geq$ 40% Hypotension requires multiple or high-dose pressors Grade 3 organ toxicity or grade 4 transaminitis	*Life threatening symptoms* Ventilator support Grade 4 organ toxicity

CRS Management Scheme (Axicabtagene Ciloleucel)

CRS Severity (Lee criteria)	**Management**
Grade 1	Symptomatic treatment
Grade 2	Tocilizumab *Repeat tocilizumab every 8 hours (max 3 doses/24 hours) as needed if not responsive to IV fluids or increasing supplemental O_2*
Grade 3	Per Grade 2 Methylprednisolone 1 mg/kg IV BID or dexamethasone 10 mg IV every 6 hours. *Continue until the event is Grade 1 or less, then taper*
Grade 4	Per Grade 2 Administer methylprednisolone 1000 mg IV daily x 3 days; if improves then manage as above

Tisagenlecleucel Management Scheme

CRS Severity	Management
Prodromal syndrome: • Low-grade fever, fatigue, anorexia	Observe, exclude infection, provide symptomatic support
Overt CRS: • High fever, hypoxia, mild hypotension	Administer antipyretics, oxygen, IV fluids and/or low-dose vasopressors as needed
Severe or Life-Threatening CRS (one or more of the following): • Hemodynamic instability despite IV fluids and vasopressor support • Worsening respiratory distress, ↑ O_2 requirement (high flow O_2 and/or ventilation) • Rapid clinical deterioration	Administer high dose/multiple vasopressors, O_2, mechanical ventilation and/or supportive care as needed Administer tocilizumab
Resistant CRS: • No clinical improvement in 12-18 hours or worsening at any time, despite prior management	Methylprednisolone 2 mg/kg, then 2mg/kg per day until vasopressors and high-flow O_2 are no longer needed, then taper quickly. If no response to steroids within 24 hours, repeat tocilizumab. If no response to 2nd dose within 24 hours, consider a 3rd dose or alternative measures.

Toxicity Management

- August 2017: FDA approved tocilizumab for the treatment of patients 2 years of age or older with CRS that occurs with CAR T-cell therapy.

- In an analysis of data from clinical trials of CAR T-cells, 69% of patients with severe or life-threatening CRS had resolution of CRS within 2 weeks following one or two doses of tocilizumab.

Neurologic Toxicities

- Include signs such as aphasia, tremors, seizures, obtundation.
- Range from mild to severe, including deaths (some due to cerebral edema).
- Common in B-ALL patients: severe (> grade 3) toxicities noted in 15 of 30 patients treated at FHCRC and 6 of 17 at MSKCC.
- Believed to be separate of the cytokine release syndrome but mechanism is unknown.
- At least appears to be related to CAR T-cell activation.
  - CAR T-cells found in the CSF
  - Worsening neurologic toxicities correlate with increased serum cytokines

Neurologic Toxicities

- Prophylaxis is common but efficacy is unknown.
- Workup generally includes neurology consult, blood and cerebrospinal fluid analyses, neuro-imaging, and electroencephalography.
- Gold standard of treatment is steroids.
- Cytokine blockade can be given but it's unknown if these are effective since they do not cross the blood-brain barrier.
- Intervention is based on neurologic toxicity severity.

B-cell Aplasia

- Detected by flow cytometry of blood and/or bone marrow.
- Also detected by measuring serum immunoglobulins.
- An on-target, off-tumor toxicity since CD19 is expressed on developing and mature B cells
- Toxicities from prolonged B-cell aplasia have not been described but as more patients are treated, infections complications should be anticipated.
- Infections would be managed by antibiotics and/or gamma globulin

CAR T-Cells in Development

B-ALL Future Indications

- Ultimately will be evaluated as first-line therapy considering the high-relapse rate and long duration (>3 yr) of chemotherapy.
  - This could be potentially evaluated in a MRD+ cohort that would be at high-risk for relapse if concerned about toxicities in patients cured with chemo alone.
- Toxicities (CRS and neurologic) are severe for B-ALL so most patients will require inpatient treatment and management.
- May have to avoid blinatumomab to preclude selection of CD19-antigen loss.

DLBCL Future Indications

- Toxicities (CRS and neurologic) are less severe and less frequent for NHL so treatment may incorporated as outpatient therapy (at select, high-volume CAR T-cell therapy sites) with hospitalization reserved for patients with severe toxicities.
- Inpatient CAR T-cell therapy may be required for patients with co-morbidities.
- May not be valid as frontline for newly diagnosed patients considering the toxicities, cost, and low-relapse rates associated with CHOP-R.
- However, may ultimately supplant Auto-SCT as first-line salvage therapy for this patient population.

CD19-targeted CAR T-Cell Therapies in Clinical Development

CD19:

Bi-specifics to address antigen escape

Combination therapies:

- ibrutinib
- checkpoint inhibitors
- PI3K inhibitors

New indications:

- MCL
- CLL
- FL

Other CAR T-Cell Therapies in Development

Other targets:

- Multiple Myeloma
- Prostate Cancer
- Lung Cancer
- Ovarian Cancer
- Others

Other CAR-T Cell Therapies in Development

Next-gen CARs:

- Off-the-Shelf CAR T cells
- Molecular Switches
- iCAR
- Third-generation CARs
- Cytokines secreting CAR T cells
- Armored CAR T cells

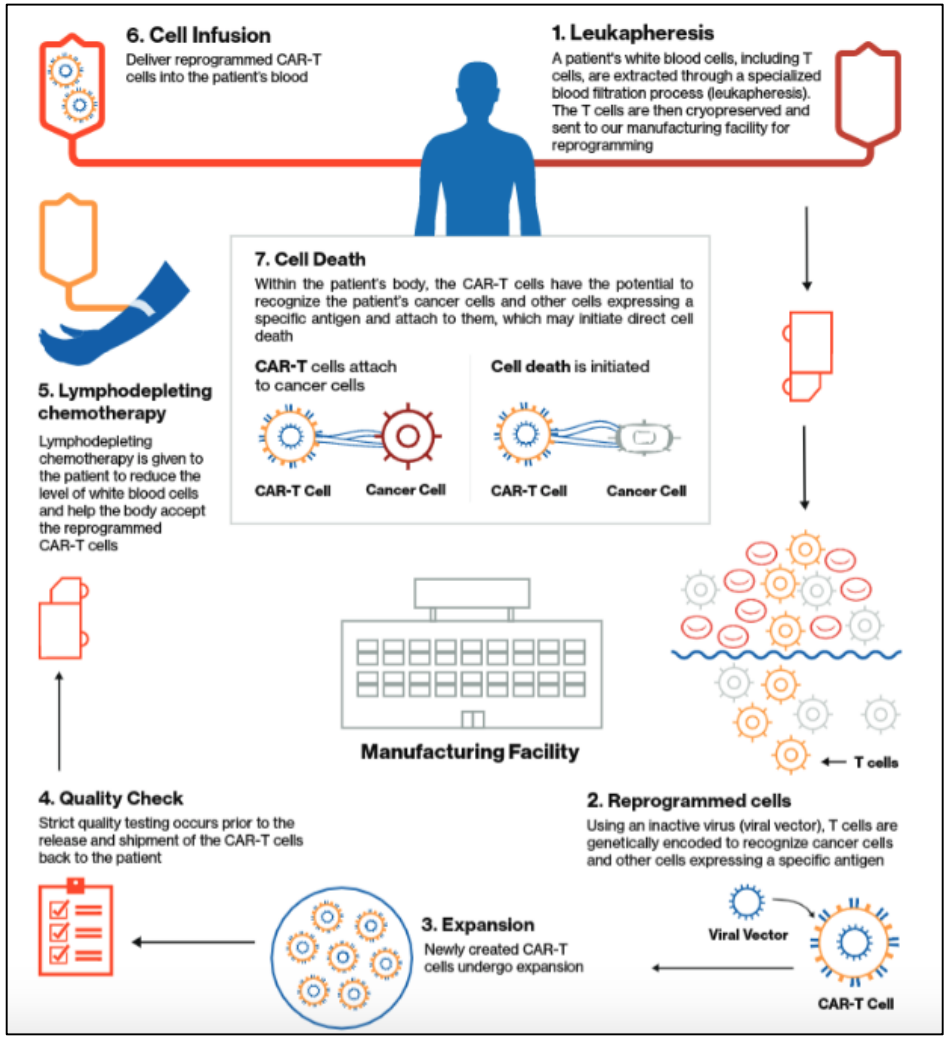
Access and Coordination of Care

Currently Approved CAR-T Products are Restricted to Certified Healthcare Facilities

- Both currently approved CAR-T products are available under a Risk Evaluation and Mitigation Strategy (REMS)
- Certified facilities must ensure that healthcare providers who prescribe, dispense or administer are trained regarding the management of CRS and neurological toxicities.
- Requires immediate access to tocilizumab including 2 doses for each patient within 2 hours of the infusion if needed

Kymriah® [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2017. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=368

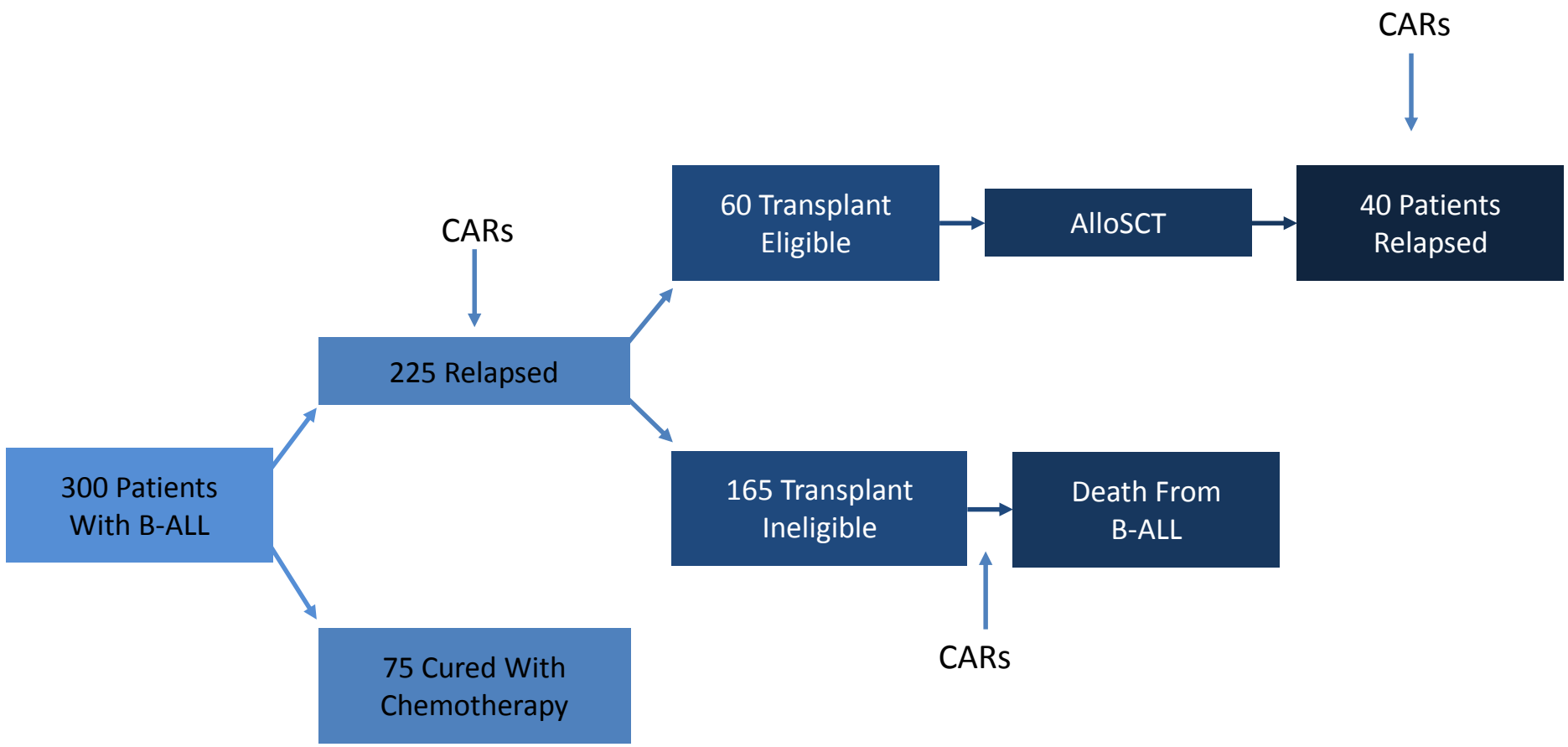
The Collection, Production, and Infusion Cycle



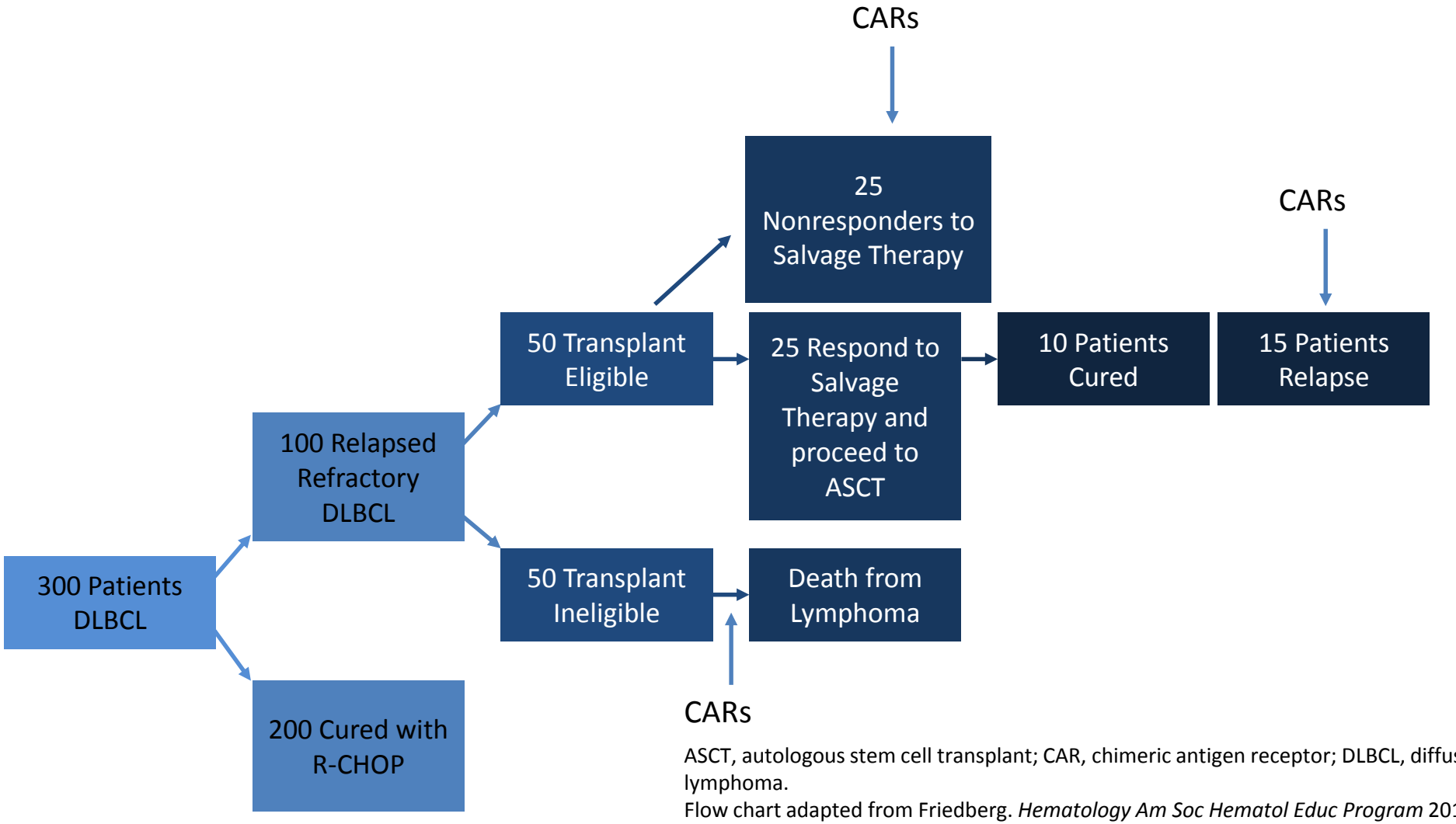
Who to Treat

- Ideally, patients appropriate for CAR T-cell therapy will display the following characteristics:
  - Good performance status
  - Adequate organ function and physiological reserve to tolerate pronounced fevers and accompanying symptoms
  - Lack of other suitable low-risk treatment options.
- Patients with cancers that express a target surface antigen such as CD19 to sustain potential benefit.
- Adequate venous access for initial apheresis procedure.
- Advanced relapse/refractory disease.
- Patients with a history of significant autoimmune disease might not be good candidates.

Who Gets Treated with B-ALL?



Who Gets Treated with DLBCL?



ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma.

Flow chart adapted from Friedberg. *Hematology Am Soc Hematol Educ Program* 2011;2011:498-505.

Cost and Reimbursement

- Outside estimates prior to approval ranged as high as $700,000
- Price tag understates the total per-patient cost
  - Does not include costs for: pre-infusion treatment, drug administration, hospitalization, or costs associated with adverse events, follow-up, etc.
  - Tocilizumab 800 mg is ~$4800/dose
- The manufacturer of Tisagenlecleucel has announced:
  - Price tag of $475,000
  - A plan to enter into outcomes-based contracts where it would not charge for the product if the patient does not respond within 30 days
- The manufacturer of Axicabtagene has announced a Price tag of $373,000
- No Patient Assistance programs as of yet

Case Report

- 56 year-old gentleman with a h/o relapsed DLBCL s/p CD19-targeted CAR T cells 8 months prior.
- In a durable CR
- Has been traveling last few months and reports intermittent fevers, cough, 1 episode of bronchitis and 2 episodes of pneumonia.
  - Recurrent infections could be a sign of B cell aplasia
- Has been treated with 3 courses of antibiotics and the most recent pneumonia required inpatient hospitalization and IV antibiotics.
- IgG levels are low and B cells are not be detected by flow cytometry
  - This is an expected on-target, off-tumor toxicity
- His IV antibiotic course was lengthened and he was treated with IVIG, and advised for monthly monitoring of CBC and intermittent monitoring of IgG levels and B cell levels by flow cytometry
  - These patients should be followed closely for infections and treated with antibiotics and/or IVIG if developing recurrent infections

Questions?