CAR T CELL IMMUNOTHERAPY FOR ALL

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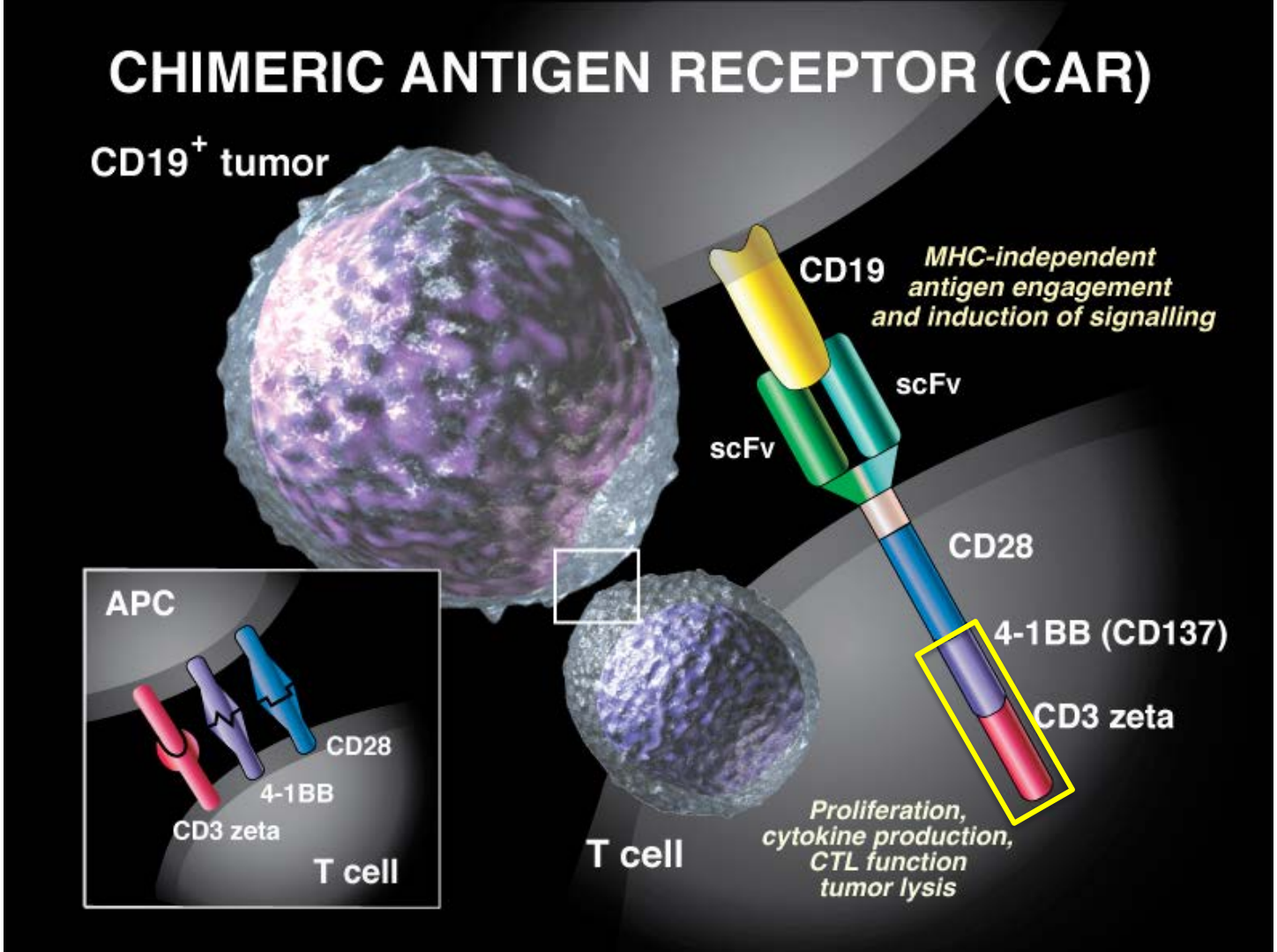
Disclosures

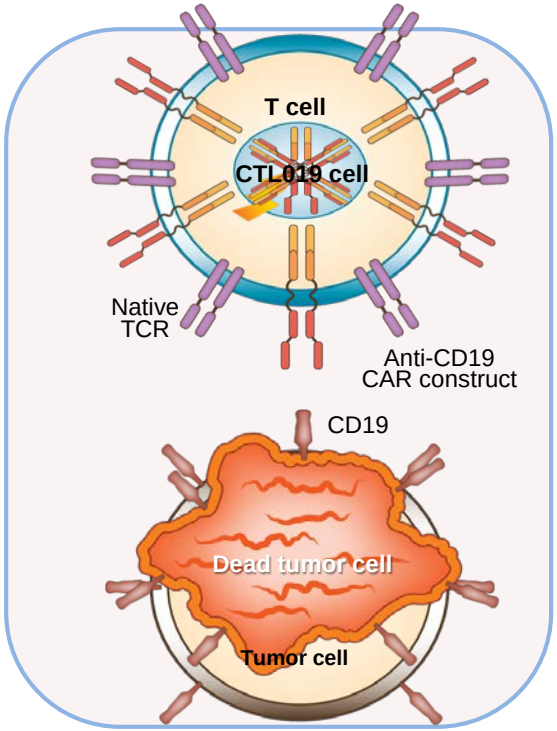
- Research and/or clinical trial support from Novartis, Servier, Vertex and Kite
- Study steering committees, consulting, or scientific advisory boards: Novartis, Adaptimmune, Eureka, TCR2, Juno, CRC Oncology, Cure Genetics, GlaxoSmithKline, Cellectis, Janssen, Vertex, Roche
- Toxicity management patent managed by U Penn policies


CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent
antigen engagement
and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation,
cytokine production,
CTL function
tumor lysis

Making CAR T cells work

Goals for modern, highly active cell therapy

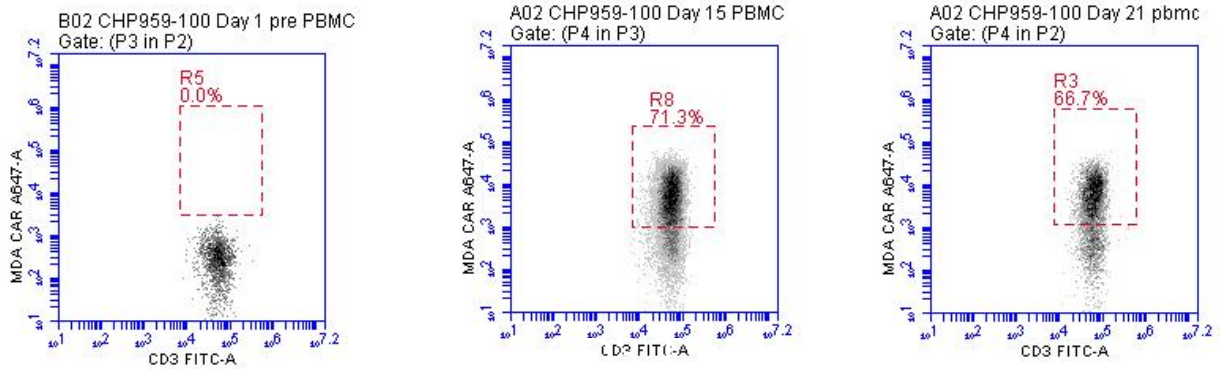
- Proliferation: leads to 90%+ complete responses (CHOP/Penn studies)
- Persistence: longer term persistence leads to 50-60% long term disease free, and no need for BMT in most
- Length of persistence required is unknown
  ?? 6mo??



Proliferation is key to highly active CAR therapy

D+1 **D+15** **D+21**

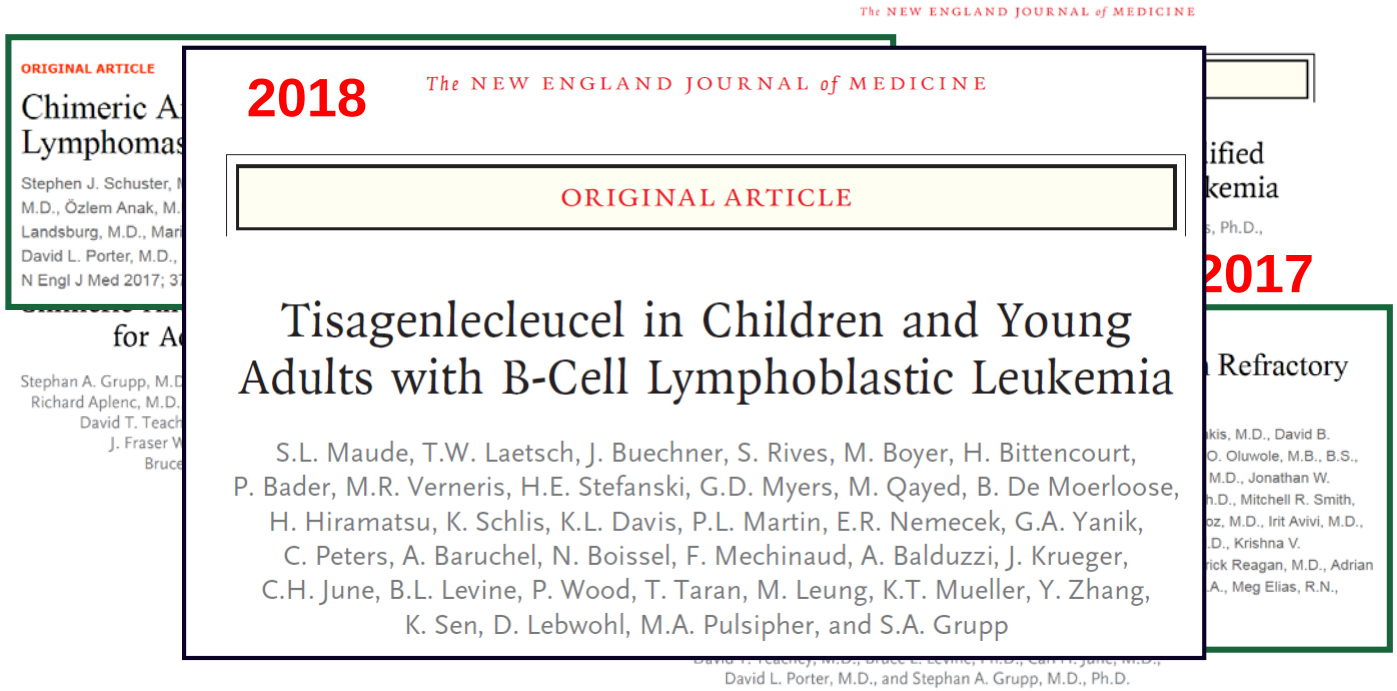
CTL019



CD3 T cells

<u>Persistence of CTL019 and B cell aplasia out to 8 years in responding patients</u>

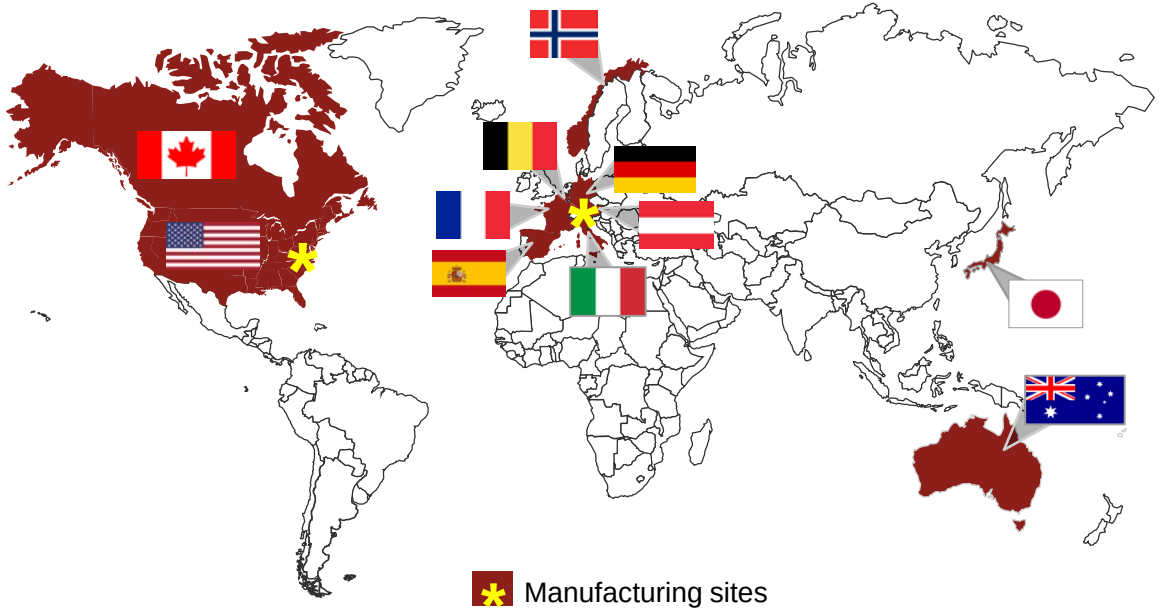
History of CTL019 development



ELIANA: Pivotal Phase 2 Study

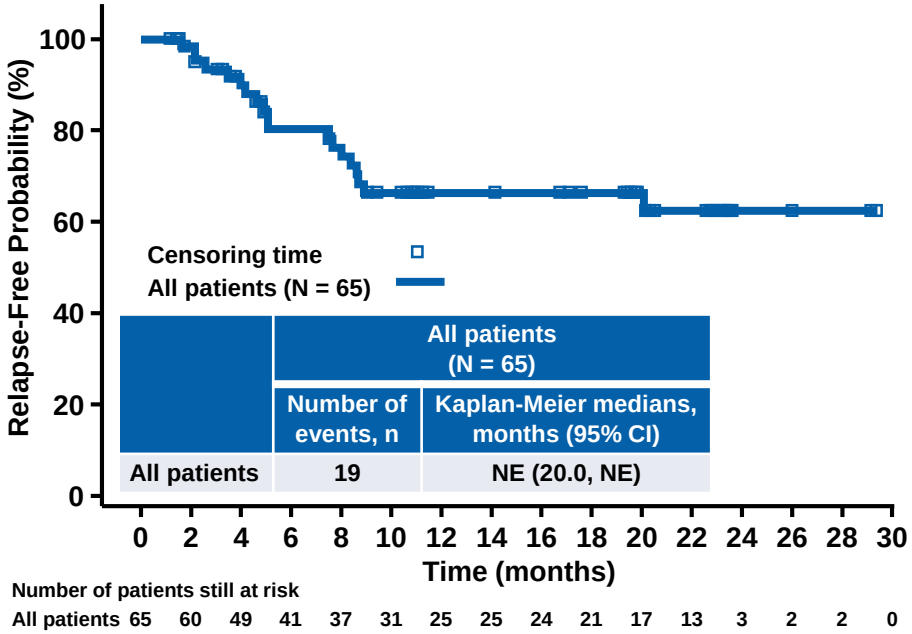
ELIANA is the first global, multicenter trial of CAR T cell therapy

- Tisagenlecleucel (CTL019) produced at a central manufacturing site with global distribution
- 25 sites across 11 countries in North America, Europe, and Asia-Pacific



Maude et al. NEJM 2018
Updated ASH 2018

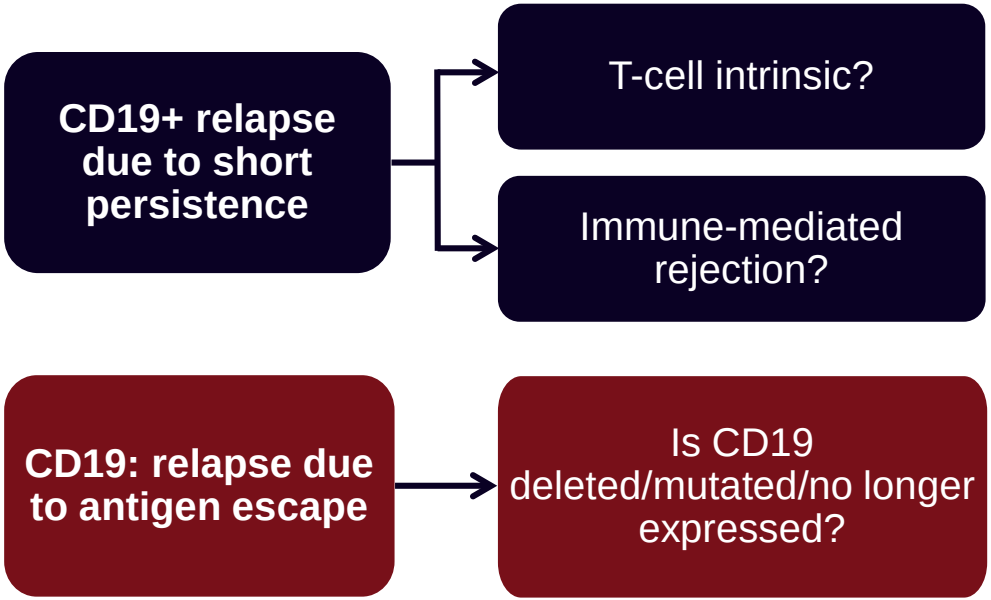
High Response Rate; Median Duration of Remission Not Reached



- CR + CRi (within 3 months) 82% (65/79 infused; 95% CI, 72-90)[a,b]
- 98% (64/65) MRD(–)
- RFS among responders
  - 12-month: 66% (95% CI, 52-77)
  - 18-month: 66% (95% CI, 52-77)
  - 24-month: 62% (95% CI, 47-75)
- OS among all infused patients
  - 12-month: 76% (95% CI, 65-85)
  - 18-month: 70% (95% CI, 58-79)
  - 24-month: 66% (95% CI, 54-76)

Note: Only patients who achieved CR or CRi were included. Time is relative to onset of remission.
[a] The response was unknown in 6 patients.
[b] While in remission, 8 patients went on to stem-cell transplantation.
[c] MRD negative = MRD < 0.01%, as assessed by flow cytometry.
CR, complete remission; CRi, complete remission with incomplete blood count recovery

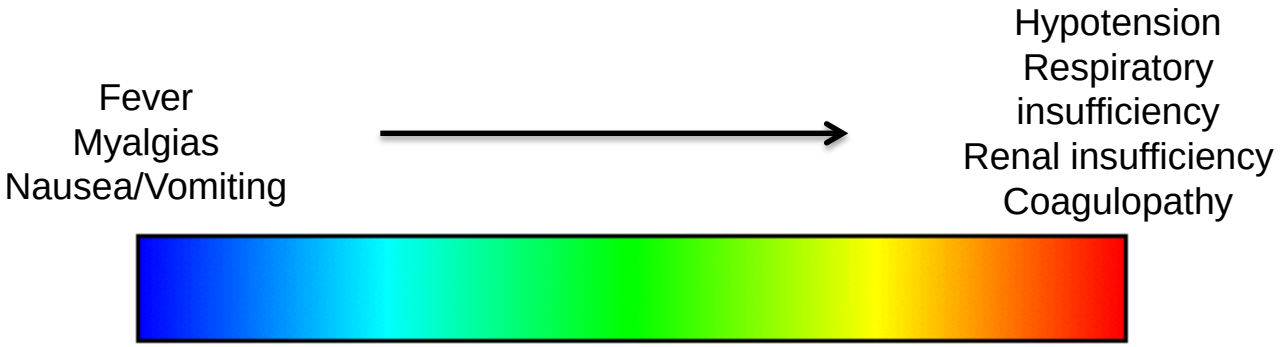
Mechanisms of Relapse



Cytokine Release Syndrome (CRS)

CRS is related to T cell expansion and may be necessary for efficacy

- Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL



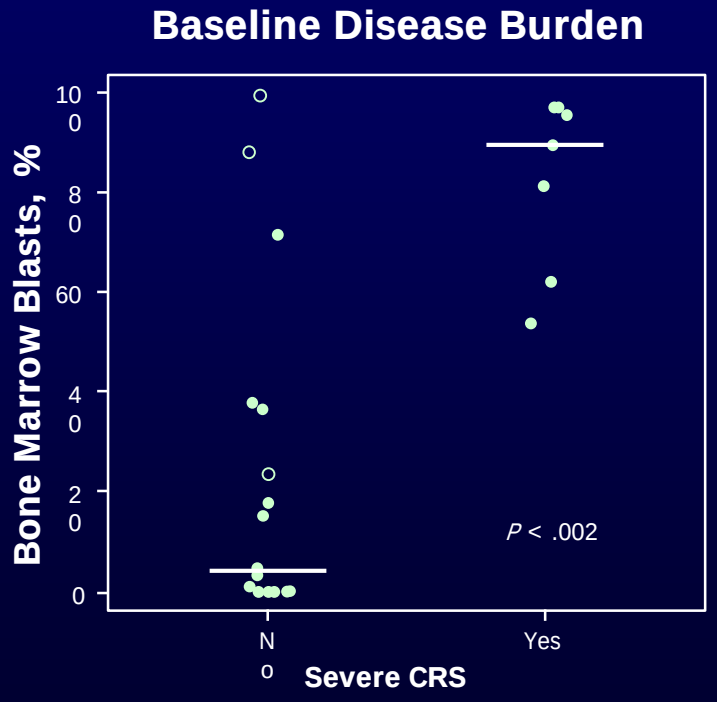
- Severity scales with disease burden

Tocilizumab (Actemra) aka “toci”

- **IL-6 receptor antagonist**
- **Blocks IL-6 mediated effects**
- **Indicated in:**
  - **juvenile idiopathic arthritis (JIA)**
  - **Rheumatoid arthritis (RA)**
  - **In Japan, indication for Castleman’s Disease**
- **Given once or twice**
- **Rare side effects of transaminitis and neutropenia**
- **Now indicated for CRS treatment**

Grupp et al, NEJM 2013

Disease Burden Highly Predictive of Severe CRS



Maude et al. NEJM 2014

Neurotoxicity (ICANS)

- Seen across CD19 immunotherapy trials with CAR T cells (NCI, CHOP/UPENN, MSKCC, Seattle) as well as blinatumomab
- Delirium, confusion, encephalopathy, rare seizures
- In our experience: generally untreated, fully resolves
- No cerebral edema seen in our studies
- Cerebral edema was a major toxicity seen in one study (Juno ROCKET trial)

Overall Safety and AEs of Special Interest Within 8 Weeks After Infusion

AESI[a]	Patients (N = 79)		
	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	77	22	27
Infections	43	20	4
Cytopenias not resolved by day 28	42	18	18
Neurological events	39	13	0
Tumor lysis syndrome	5	5	0

- Majority of AEs occurred in the first 8 weeks after tisagenlecleucel infusion
- No cases of cerebral edema reported

[a] Occurring within 8 weeks of tisagenlecleucel infusion.
[b] Cytokine release syndrome was graded using the Penn scale.
AESI, adverse events of special interest.

ASBMT Consensus Grading for CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one 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, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

ASBMT Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading (Adults)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score (Immune effector Cell-associated Encephalopathy)	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 Non-convulsive 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
Raised 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

Global access:
approved in the EU, UK, Canada in addition to US

- Kymriah (Novartis) for pediatric/young adult ALL
- Kymriah (Novartis) for DLBCL
- Yescarta (Kite/Gilead) for DLBCL

What is are the current labeled indications for Kymriah?

- ALL up to age 25 (CHOP treats to 29)
- Refractory or second relapse

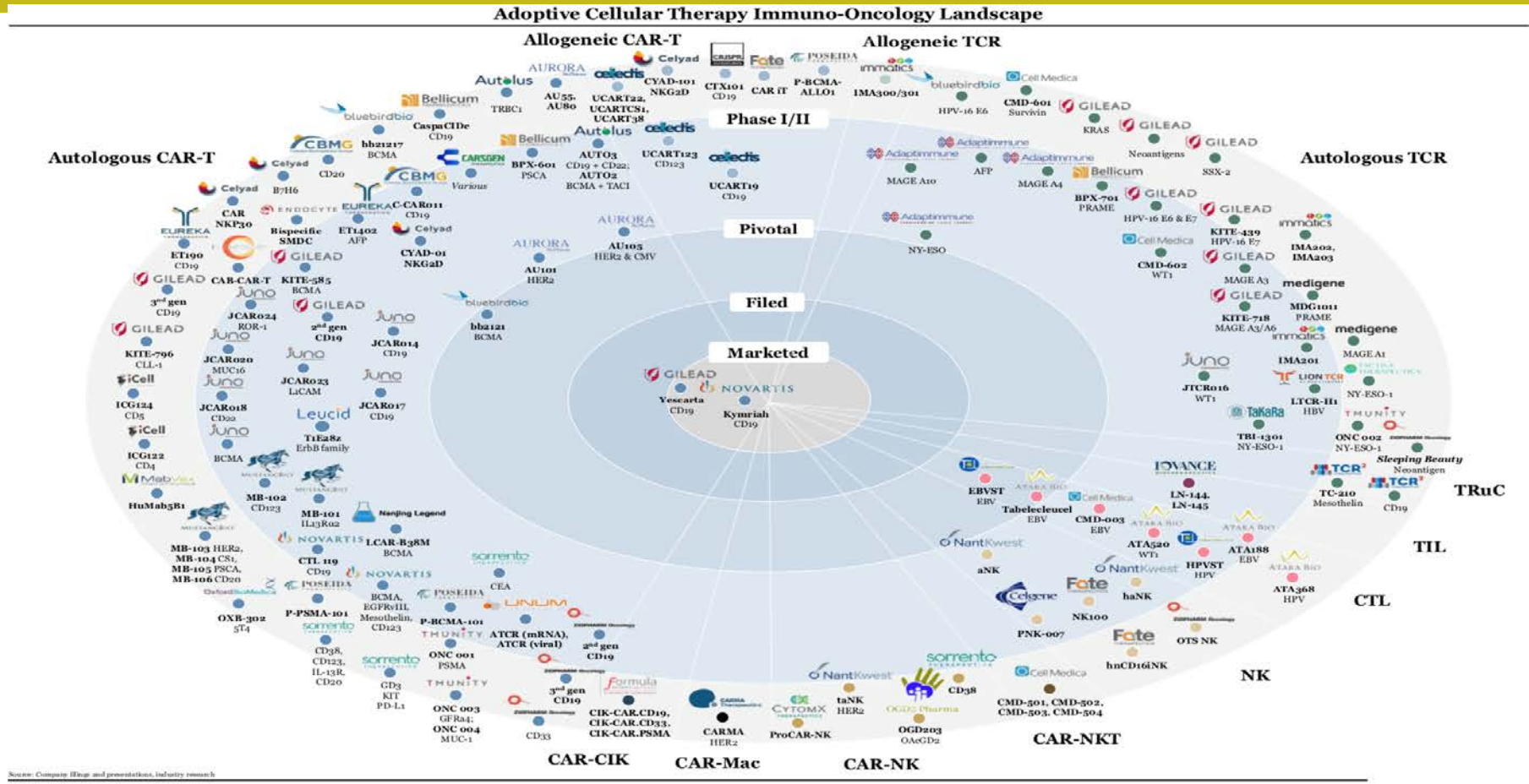
Other key points:

- Patients do not need to be in complete remission to receive treatment
- No donor is required
- Contraindications:
  - Rapidly progressing refractory disease
  - Active infection
  - Inadequate organ function suggesting inability to tolerate CRS (risk adjusted)

What about adult ALL?

- Higher CRS toxicity burden
- Related to comorbidities??
- Upcoming adult ALL trials – Kite, Novartis, Juno, others
- Opportunities – VHR CR1, MRD +
  - These would be very low toxicity

Rapidly Evolving CAR-T Landscape



Indications for BMT

Is CAR T a bridge to transplant in ALL?
When to consider BMT

- Plan for BMT all along
- MRD+ at D28 (rare)
- Early B cell recovery (<6 mo):
  BMT vs. CAR T reinfusion
- 2nd post-CAR remission
- ??? MLL rearranged ???

Cytokine Release Syndrome

	Patients Infused (N = 79)
Patients developed CRS, n (%)	**61 (77)**
Time to onset, median (range), days	3.0 (1-22)
Duration of CRS, median (range), days	8.0 (1-36)
ICU admission, n (%)	38 (48)
Anticytokine therapy, %	31 (39)
Tocilizumab, %	31 (39)
1 dose	18 (23)
2 doses	10 (13)
3 doses	3 (4)
Corticosteroids, %	16 (20)
Hypotension that required intervention, %	42 (53)
High-dose vasopressors, %	19 (24)
Intubation, %	12 (15)
Dialysis, %	8 (10)

CRS was graded using the Penn scale and managed by a protocol-specific algorithm[1]

CRS, cytokine release syndrome; ICU, intensive care unit.

1. Porter DL, et al. *Sci Transl Med*. 2015;7(303):303ra139.