CAR T-Cell Therapy and the Pharmacology of Managing Cytokine Release Syndrome

Jae Park, MD
Assistant Attending Physician
Leukemia Service & Cellular Therapeutics Center
Memorial Sloan Kettering Cancer Center

Amber C. King, PharmD, BCOP
Clinical Pharmacy Specialist, Leukemia
Memorial Sloan Kettering Cancer Center

2018 JADPRO Live
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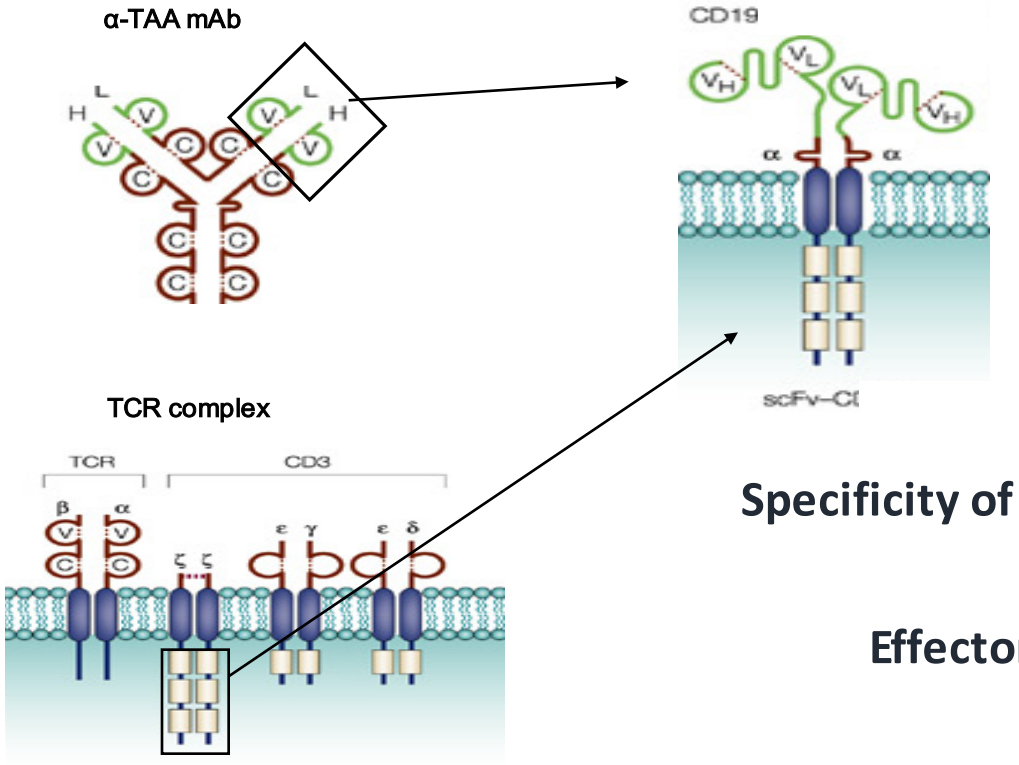
Learning Objectives

1. Identify patients who meet criteria as candidates for CAR-T therapy
2. Devise strategies to mitigate cytokine release syndrome and other serious side effects with CAR T-cell therapy in concordance with Risk Evaluation Mitigation Strategy (REMS) requirements

Financial Disclosure

- Dr. Park has nothing to disclose.
- Dr. King has served on advisory boards for Genentech.

Design of a Tumor Targeted Chimeric Antigen Receptor (CAR)



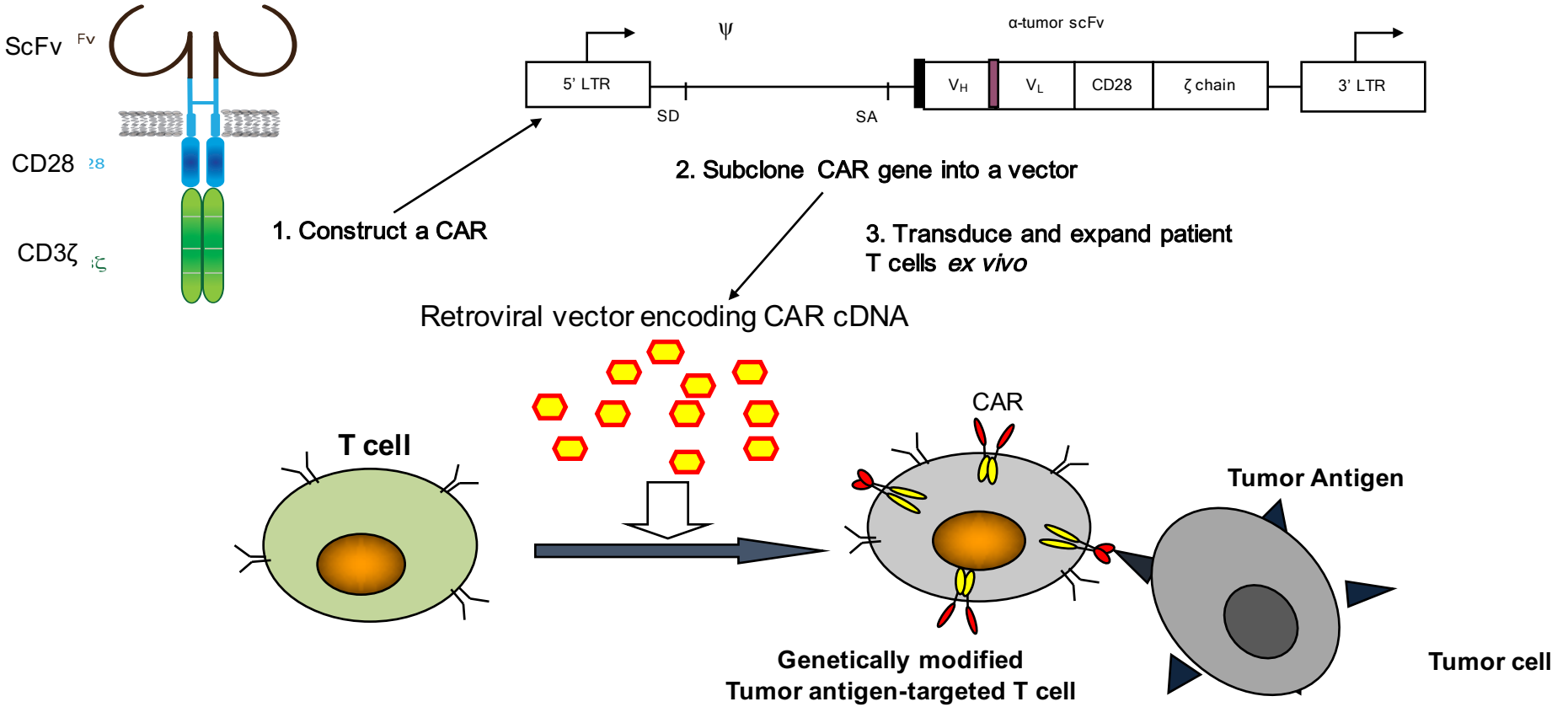
Specificity of antibody target recognition

+

Effector mechanisms of T cell

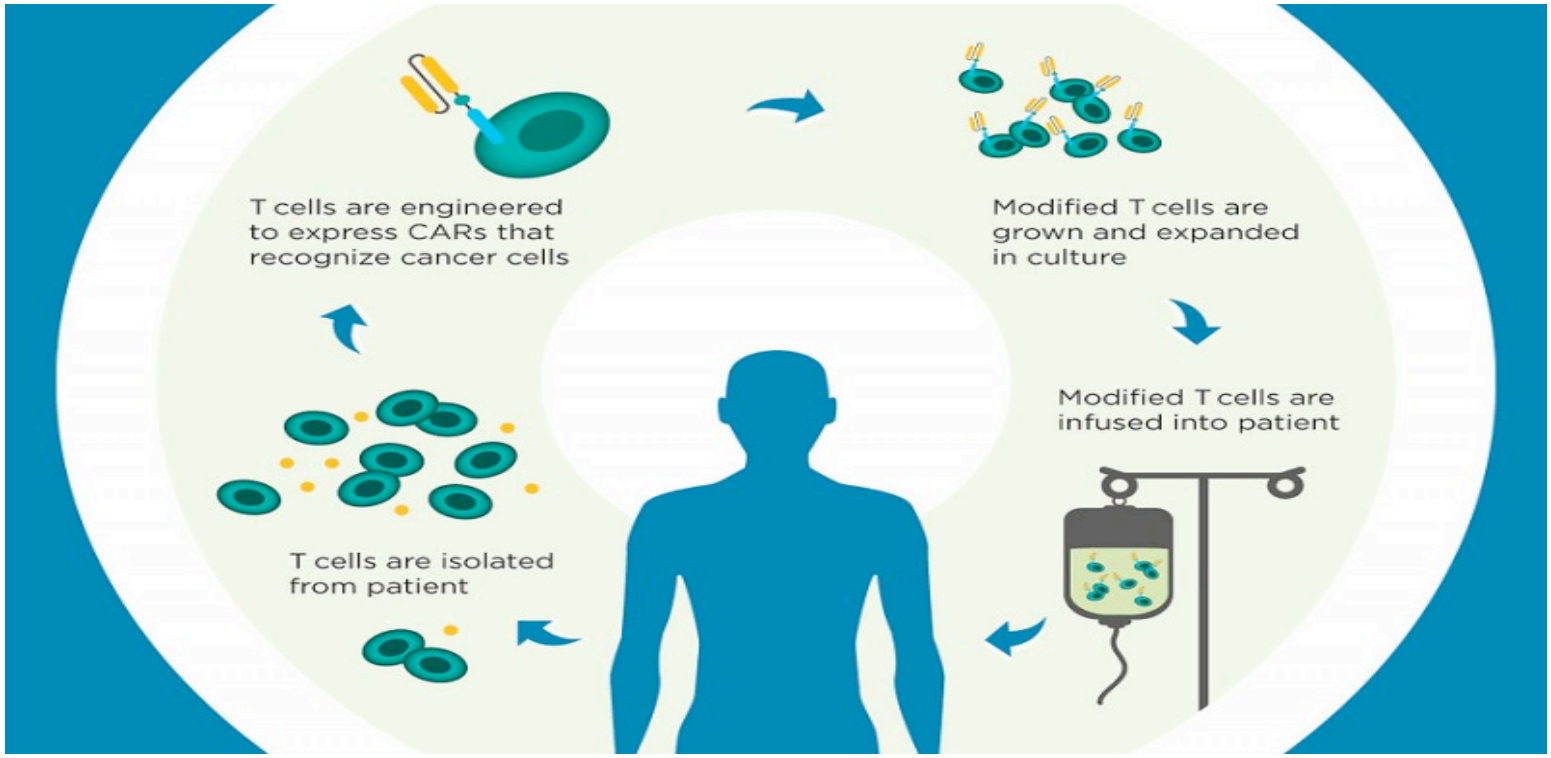
Graphic courtesy of Memorial Sloan Kettering Cancer Center

Generation of CAR T Cells



Graphic courtesy of Memorial Sloan Kettering Cancer Center

CAR T Cells as Cancer Therapy



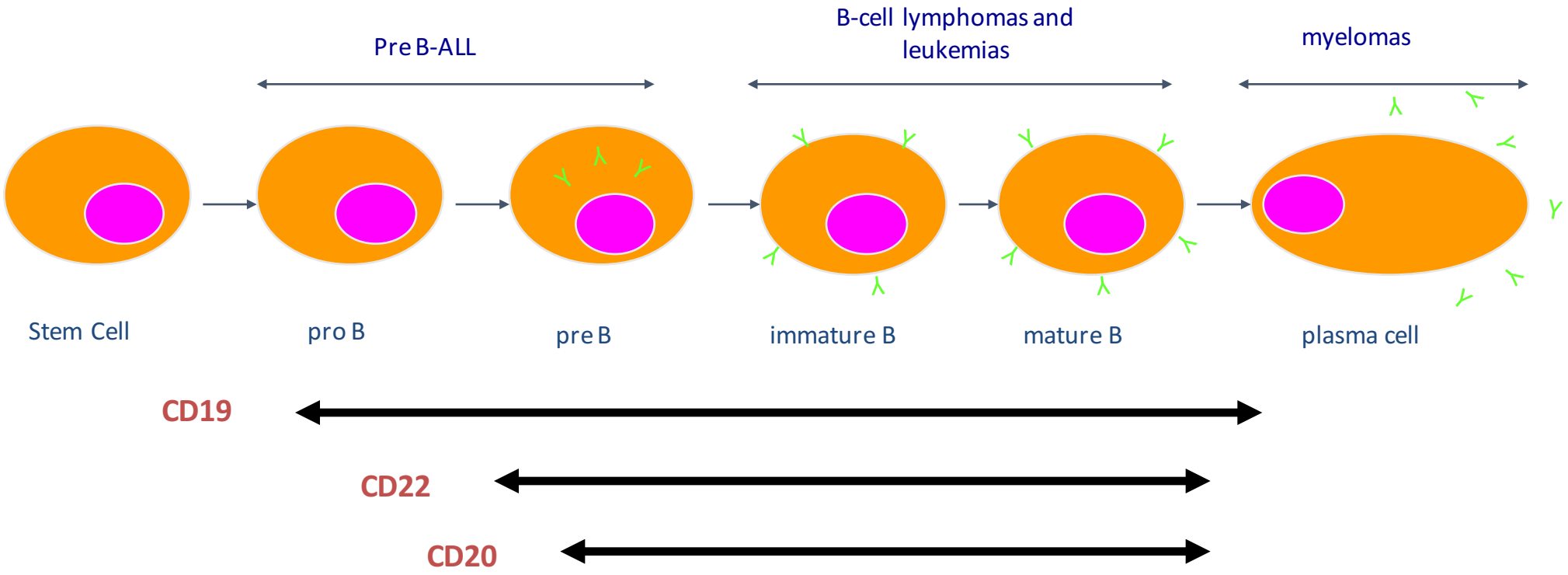
Graphic courtesy of Memorial Sloan Kettering Cancer Center

Advantages of CAR T-Cell Therapy

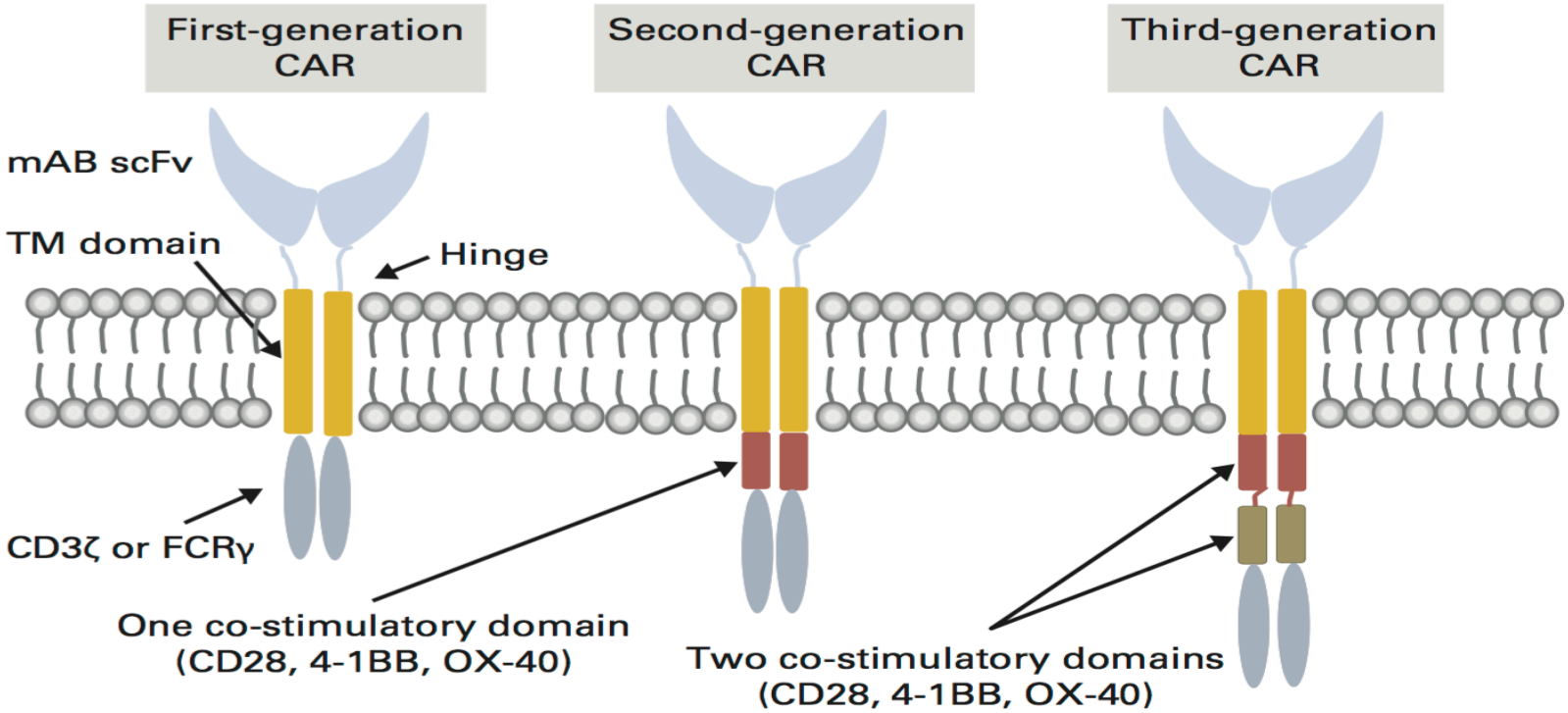
- HLA-independent antigen recognition, therefore universal application
- Target antigens include proteins, carbohydrates and glycolipids
- Rapid generation of tumor-specific T cells
- Minimal risk of GvHD
- A living drug: potential for lasting immunity
- Selective modification of specific T-cell subtypes
- Additional modification capability of CAR construct

GvHD = graft-versus-host disease; HLA = human leukocyte antigen.

CD19 as a Target of B-Cell Malignancies

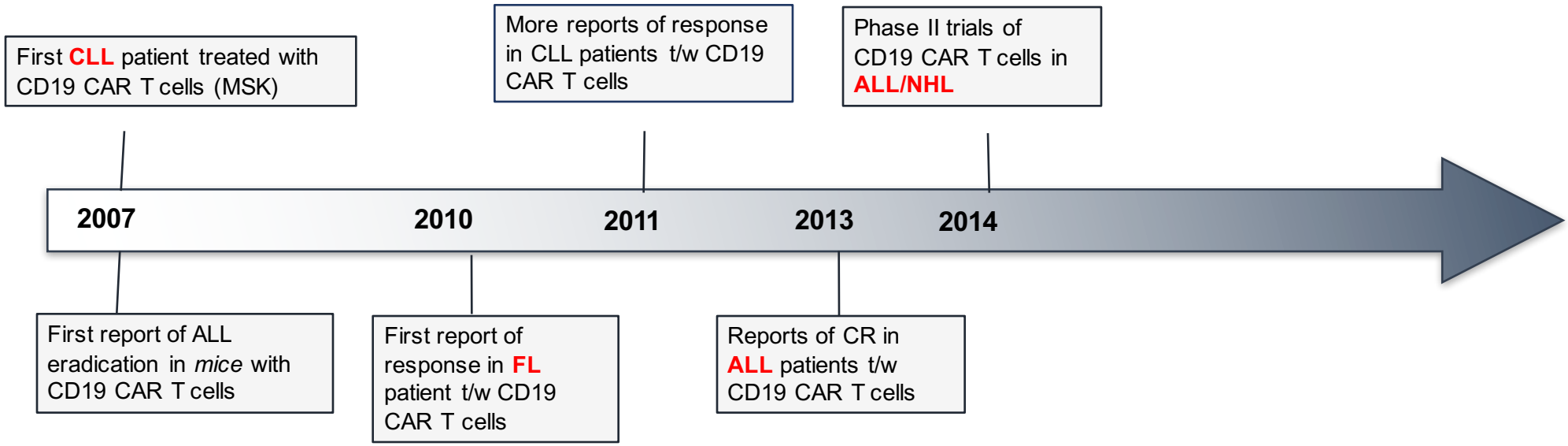


Evolution in CAR Design



Park J et al. *J Clin Oncol*. 2015;33(6):651-653.

Timeline of Clinical Development of CD19 CAR-T Cells in Hematologic Malignancies

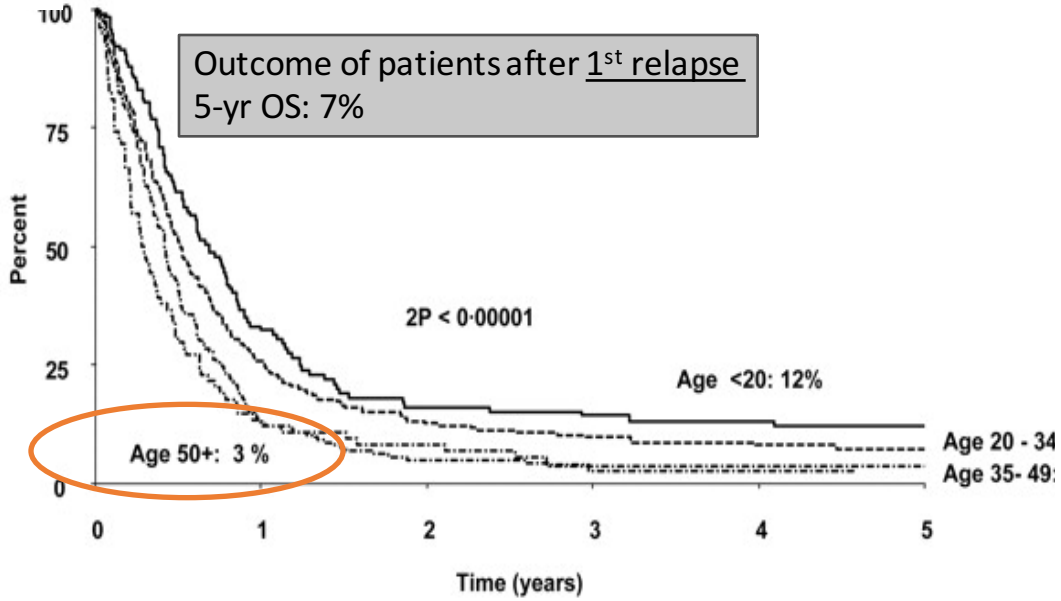


ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; CR = complete response; FL = follicular lymphoma; NHL = non-Hodgkin lymphoma.

Graphic courtesy of Memorial Sloan Kettering Cancer Center

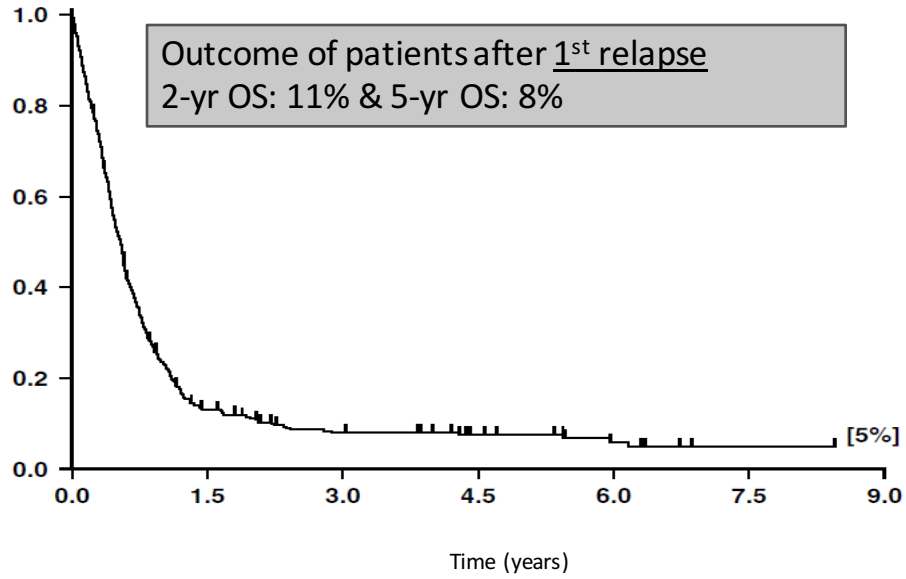
Poor Prognosis of Relapsed ALL in Adults With Chemotherapy

MRC UKALL2/ ECOG2993 Study (n=609)



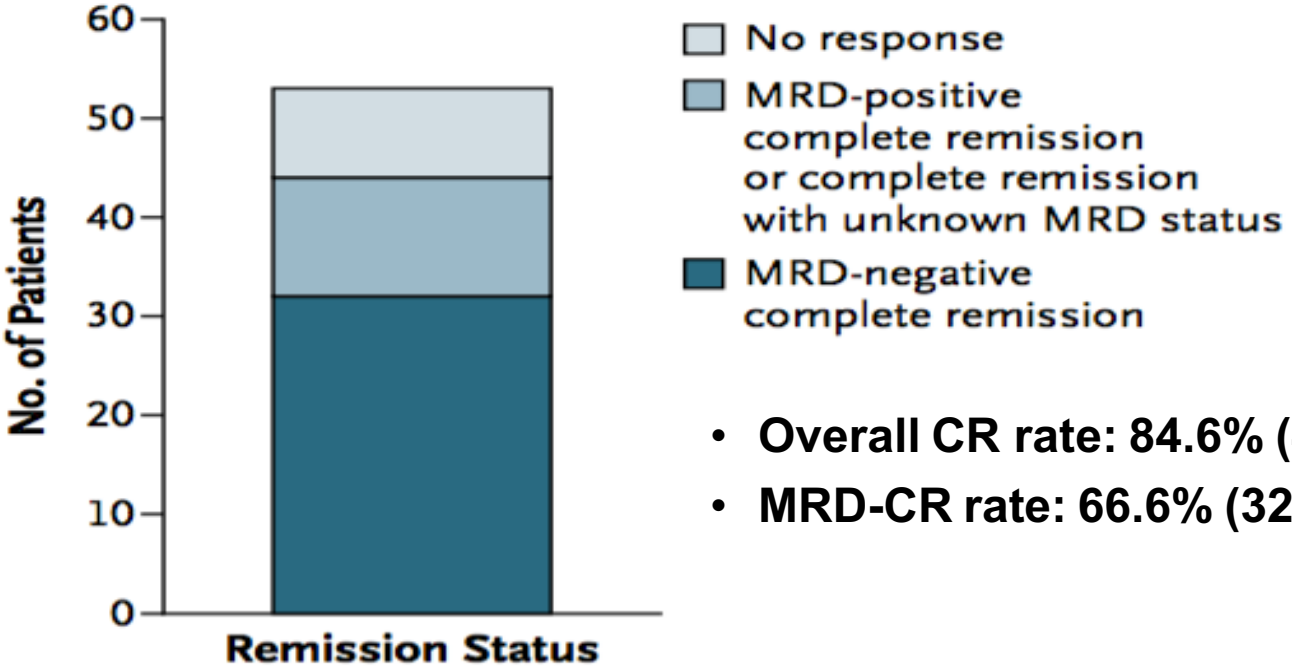
Fielding A, et al. *Blood* 2007;109(3):944-950.

LALA-94 Study (n=421)



Tavernier E, et al. *Leukemia* 2007;21:1907-1914.

A Phase I Trial of 19-28z CAR T Cells in R/R ALL at MSKCC: Study Outcome



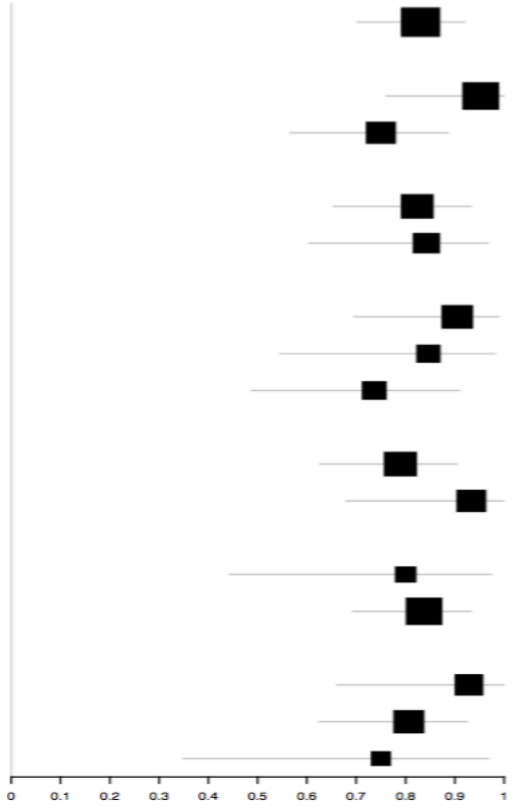
- **Overall CR rate: 84.6% (44 of 52 pts)**
- **MRD-CR rate: 66.6% (32 of 48 evaluable pts)**

MRD = minimal residual disease.

Park J et al. *N Engl J Med* 2018;378(5):449-459

CR Rates by Subgroups

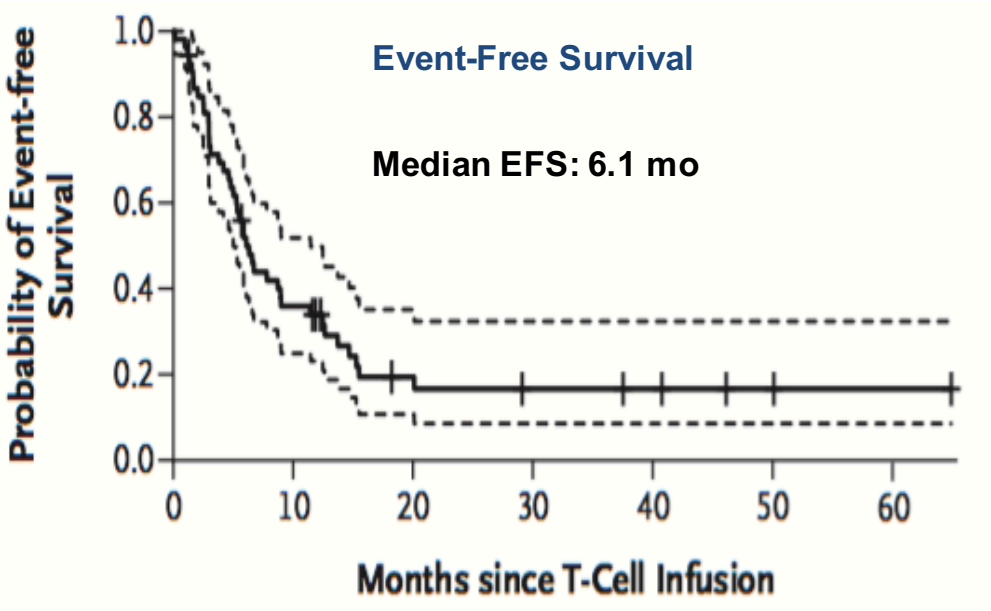
Subgroups	N	CR Rate (%)
Overall	53	83.0
Disease Burden		
Minimal	21	95.2
Morphological	32	75.0
Pre–CAR HSCT		
No	34	82.4
Yes	19	84.2
# of Prior Therapies		
2	21	90.5
3	13	84.6
>=4	19	73.7
Ph Status		
Ph–	38	78.9
Ph+	15	93.3
Conditioning Chemo		
Cy/Flu	10	80.0
Cy	43	83.7
Age Group		
18–30	14	92.9
30–60	31	80.6
>60	8	75.0

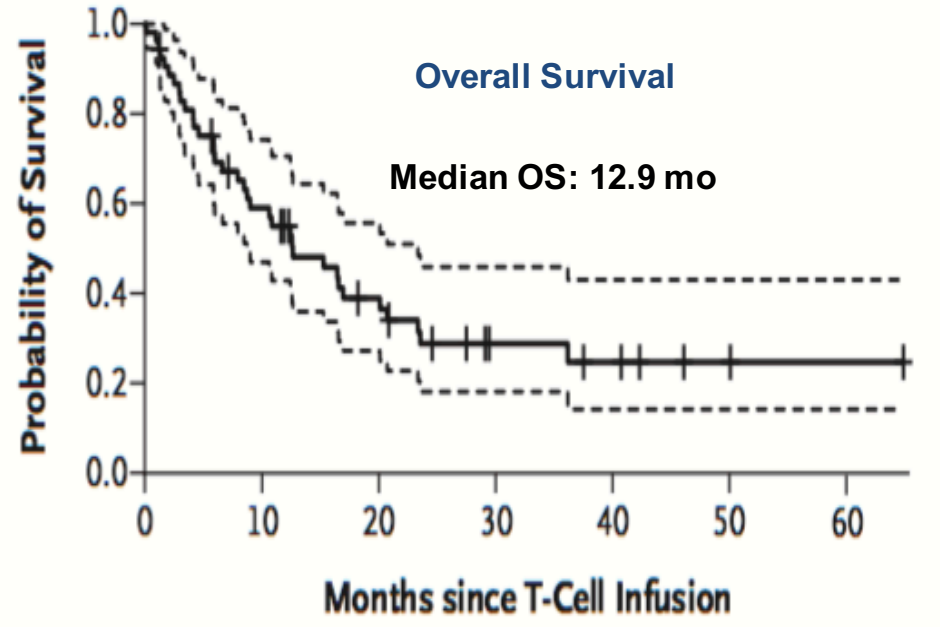


Park J et al. *N Engl J Med* 2018;378(5):449-459

Long-Term Outcome: All Patients

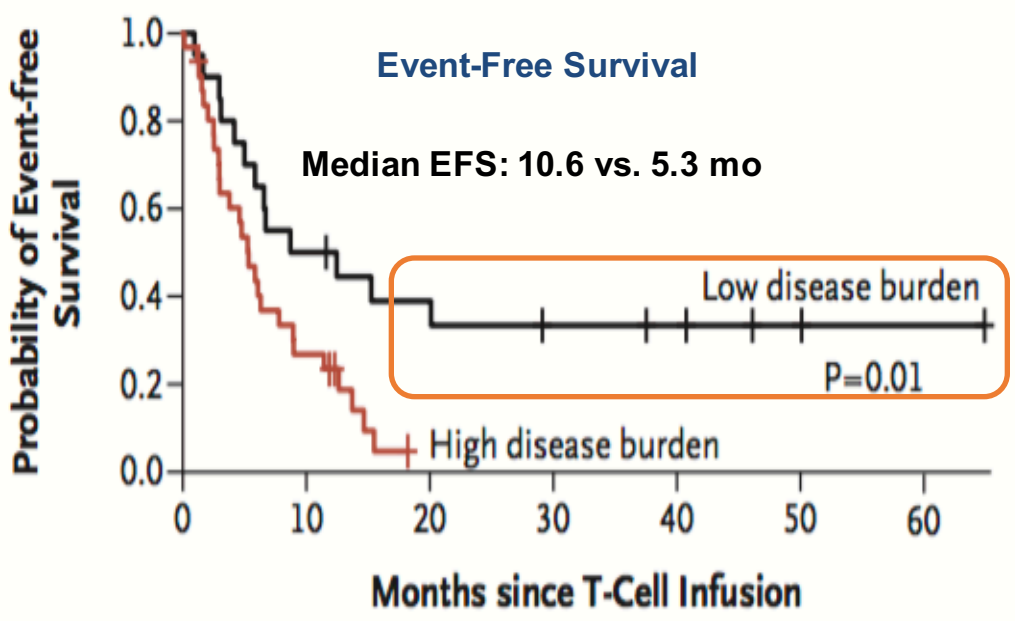
Median follow up:
29 months (range, 1 – 65)

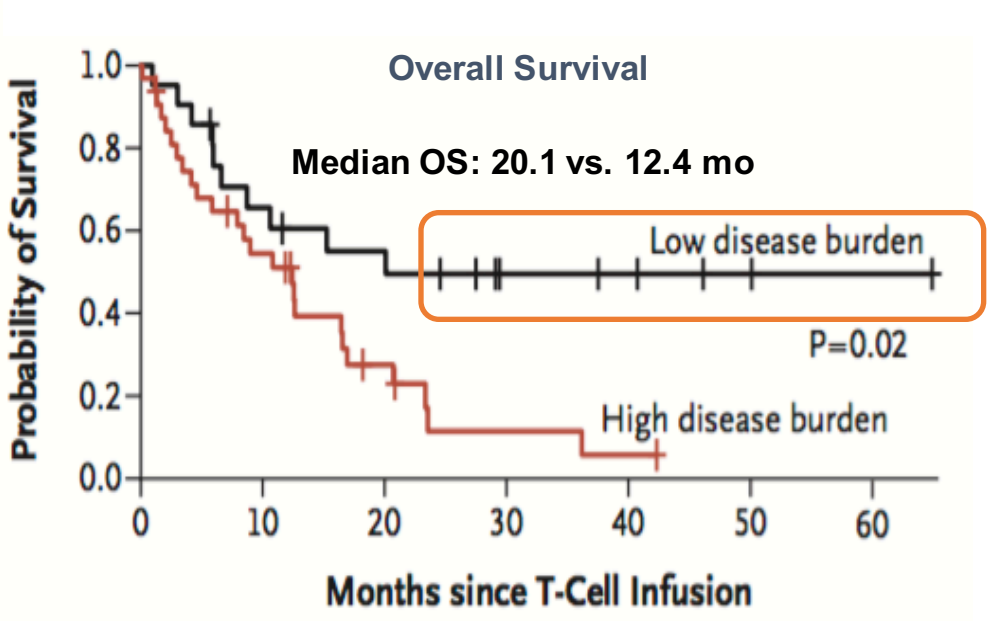




Park J et al. *N Engl J Med* 2018;378(5):449-459

Long-Term Outcome: By Pretreatment Disease Burden





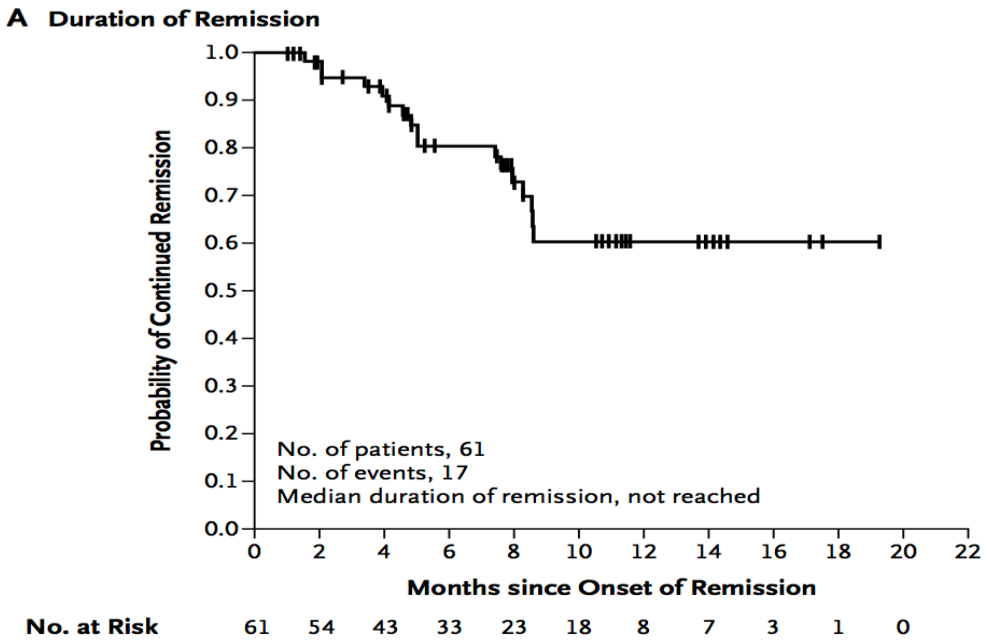
Park J et al. *N Engl J Med* 2018;378(5):449-459

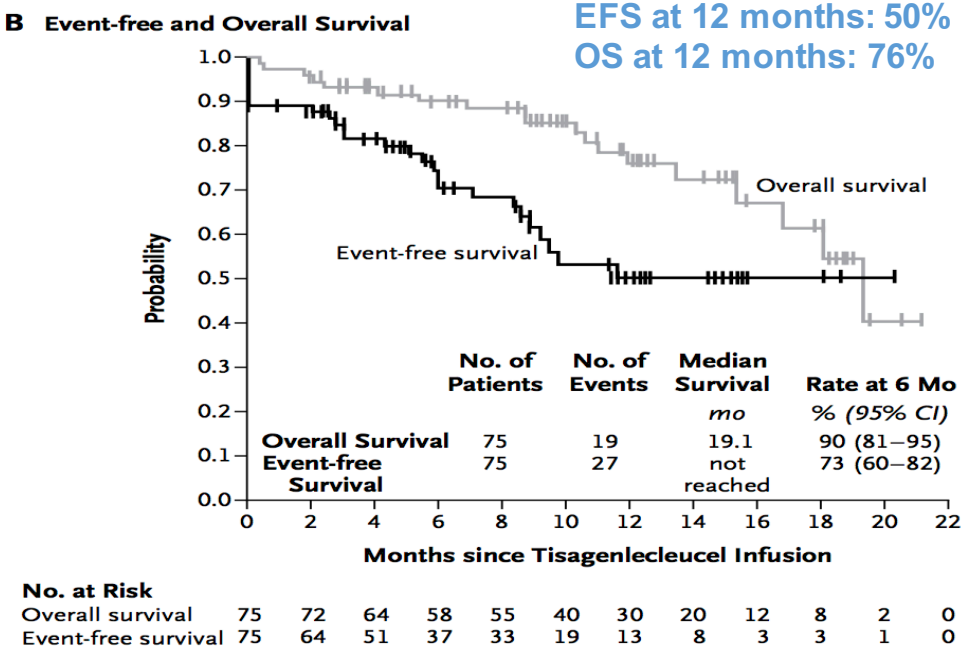
Tisagenlecleucel in Children and Young Adults With R/R B-ALL

- Phase II, global, 25-center study
  - Primary endpoint: Overall response in 3 months
- 92 pts enrolled → 75 pts (82%) treated
  - Median age: 11 (range, 3 to 23)
  - Median prior # of tx: 3 (range, 1 to 8)
  - Prior alloHSCT: 61%
- Conditioning regimen: Cy and Flu
- T-cell dose (median): 3.1 x 10^6 CAR T cells/kg

Cy = cyclophosphamide; Flu = fludarabine; HSCT = hematopoietic stem cell transplantation; R/R = relapsed/refractory.

Tisagenlecleucel in R/R B-ALL: Remission Duration and Survival





EFS at 12 months: 50%
OS at 12 months: 76%

- **Overall Response Rate: 81% (60% CR + 21% CRi)**

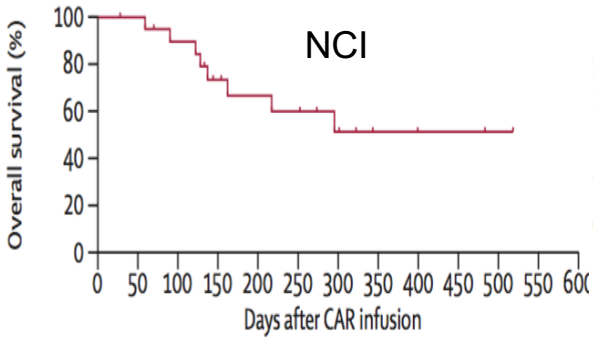
Tisagenlecleucel for B-Cell ALL

- FDA approved August 2017 for treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse
  - First chimeric antigen receptor T-cell immunotherapy approved by FDA
- FDA approved with a Risk Evaluation and Mitigation Strategy

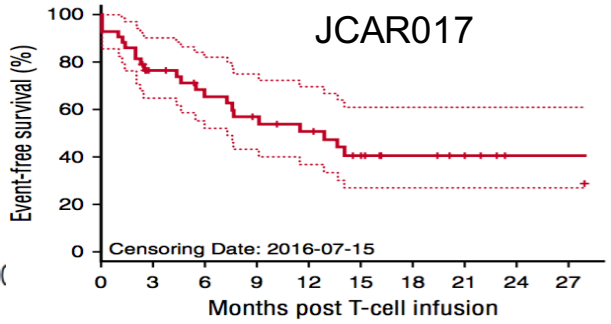
Clinical Course After CD19 CAR

Pediatric ALL

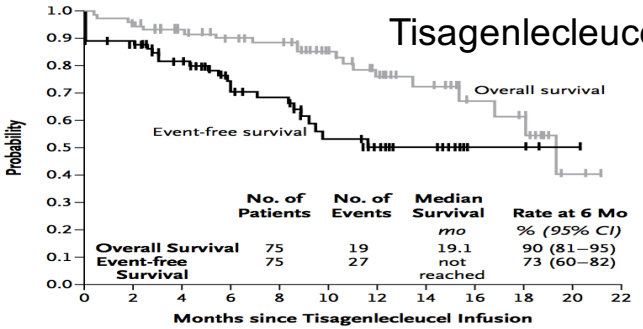
NCI



JCAR017

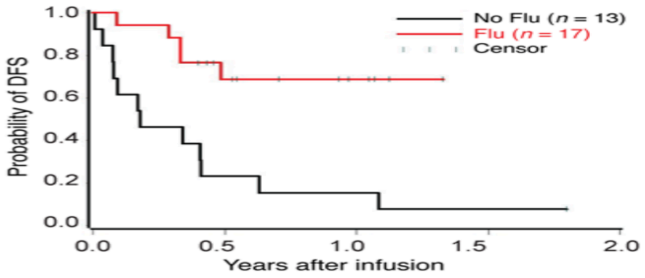


Tisagenlecleucel

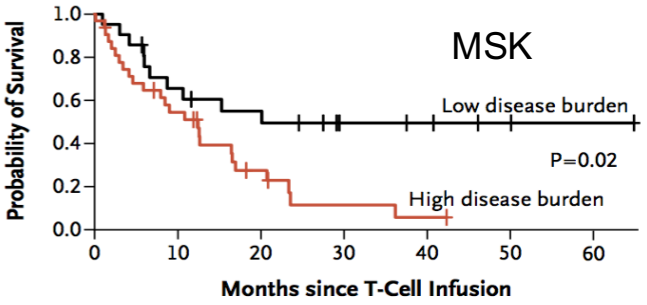


Adult ALL

JCAR017



MSK



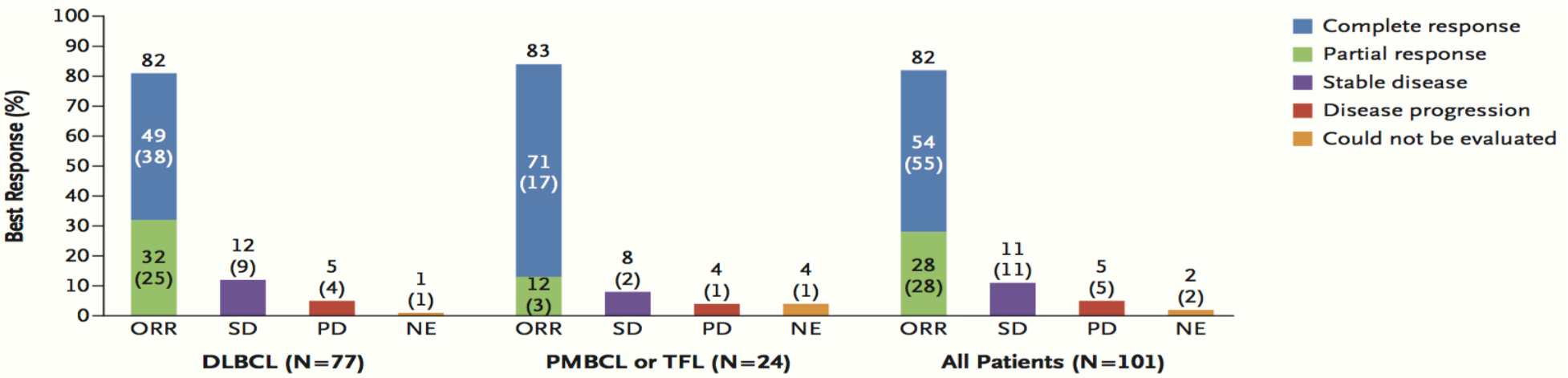
Park J at al. *N Engl J Med* 2018; Turtle C et al. *J Clin Invest* 2016; Maude S et al. N Engl J Med 2014; Maude S et al. *N Engl J Med* 2018; Gardner R et al. *Blood* 2017; Lee D et al. *Lancet 2015.*

Clinical Efficacy of CD19 CAR T Cells in R/R ALL

	T-Cell Product	Age, med (range)	No. of Pts.	Prior HSCT	T-Cell Dose	CR	Survival
Adults	**19-28z (MSKCC)**	44 (23-74)	53	36%	1-3x10^6 CAR T cells/kg	85%	Med OS: 13 mo Med EFS: 6.1 mo Post-CAR HSCT: 39%
	19-41BBz (UPenn)	N/A	12	N/A	4x10^7–1x10^9 CAR T cells	89%	N/A
	19-41BBz (FHRC)	40 (20-73)	30	37%	2x10^5–10^7 CAR T cells/kg	100%	**31% relapse** (17% died in CR) Post-CAR HSCT: 48%
Peds	**19-41BBz (CTL019)****	12 (3-23)	68	61%	0.2–5x10^6 CAR T cells/kg	83%	Med OS: 19 mo 6 mo EFS: 73% Post-CAR HSCT: 12%
	19-28z (NCI)	14 (5-27)	20	38%	1-3x10^6 CAR T cells/kg	70%	6 mo OS: **~65%** Post-CAR HSCT: 71%
	19-41BBz (SCRI)	12 (1-25)	45	62%	0.5–10x10^6 CAR T cells/kg	89%	12 mo EFS: 51% (**45% relapse**) 12 mo OS: 70%

Park J at al. *N Engl J Med 2018*; Frey N et al. *ASH* 2014; Turtle CJ et al. *J Clin Invest* 2016; Buechner J et al. *EHA* 2017 Abstract S476; Lee D et al. *Lancet Oncology 2014*; Gardner R et al. *Blood* 2017

Axicabtagene Ciloleucel in R/R DLBCL [ZUMA-1]: Overall Response

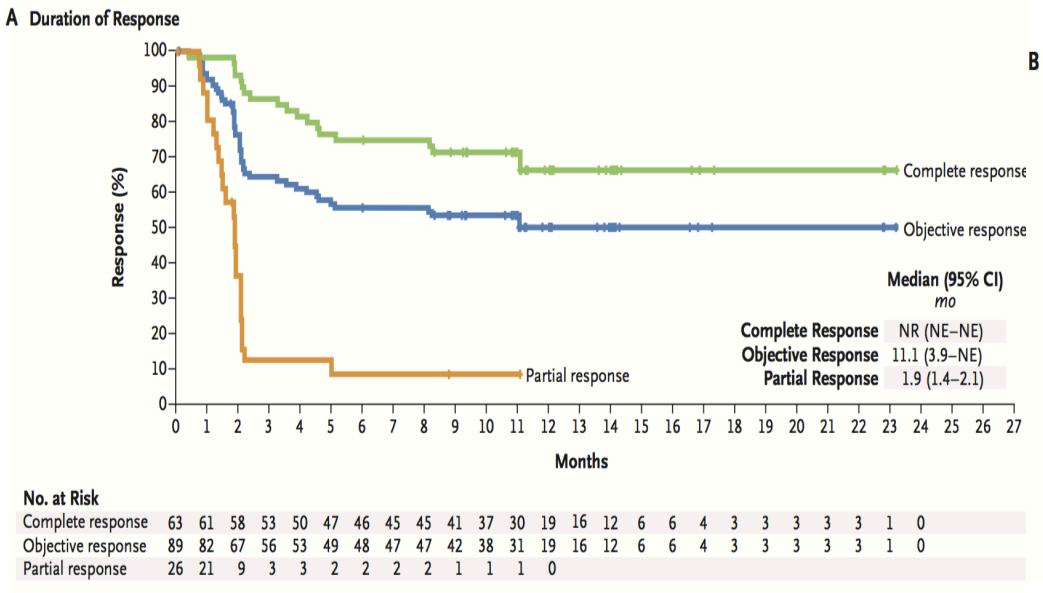


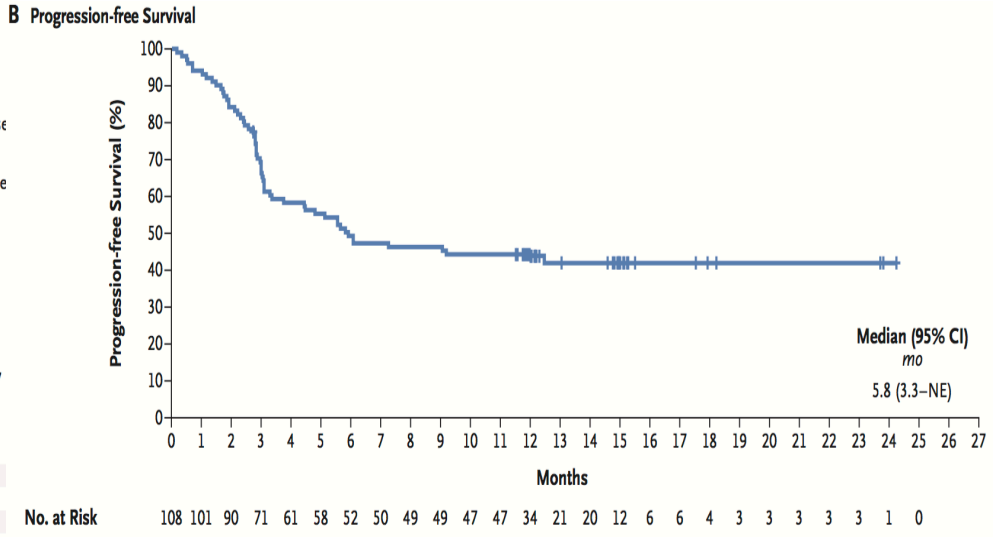
- **Overall response rate: 82% (54% CR + 28% PR)**

DLBCL = diffuse large B-cell lymphoma; PR = partial response.

Axicabtagene in R/R DLBCL: Remission Duration and Survival

Median F/u: 15.4 months
OS at 18 months: 52%





Neelapu S et al. *N Engl J Med* 2017;377:2531-44

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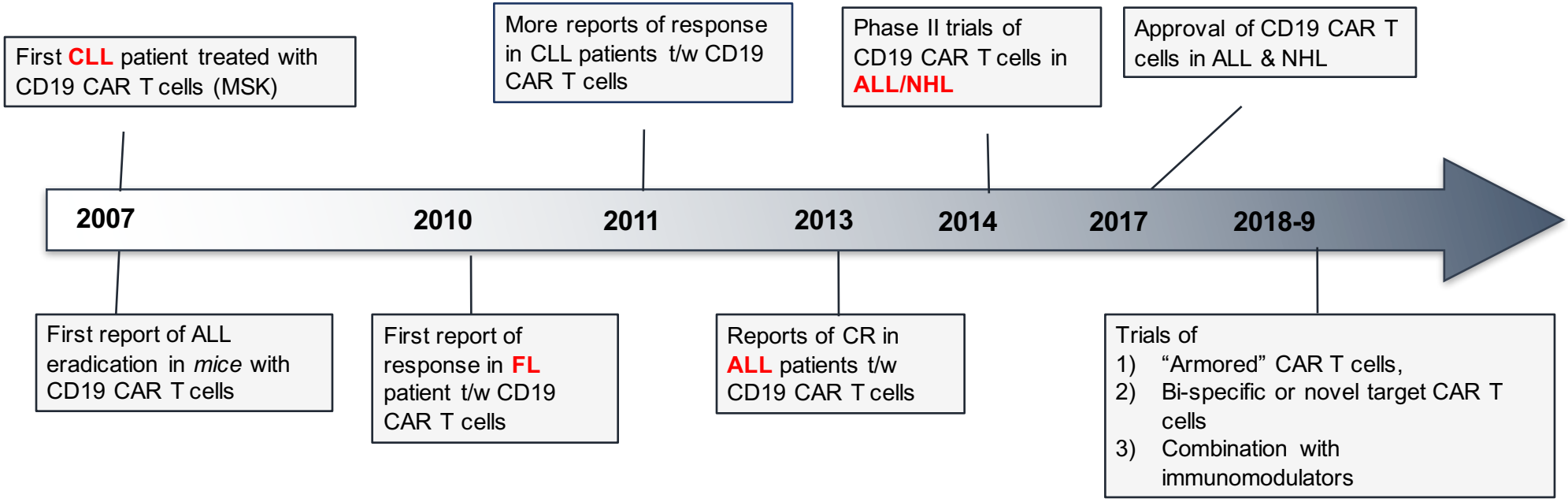
CD19 CARs Approved for Large B-Cell Lymphoma

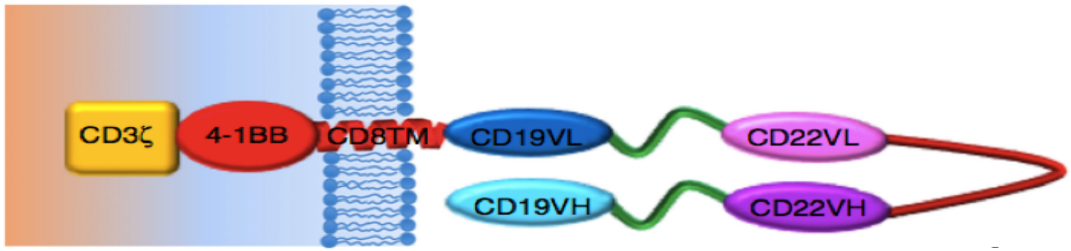
- FDA approved axicabtagene October 2017 for treatment of adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma
- FDA approved tisagenlecleucel May 2018 for treatment of adult patients with relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
- FDA approved with a Risk Evaluation and Mitigation Strategy

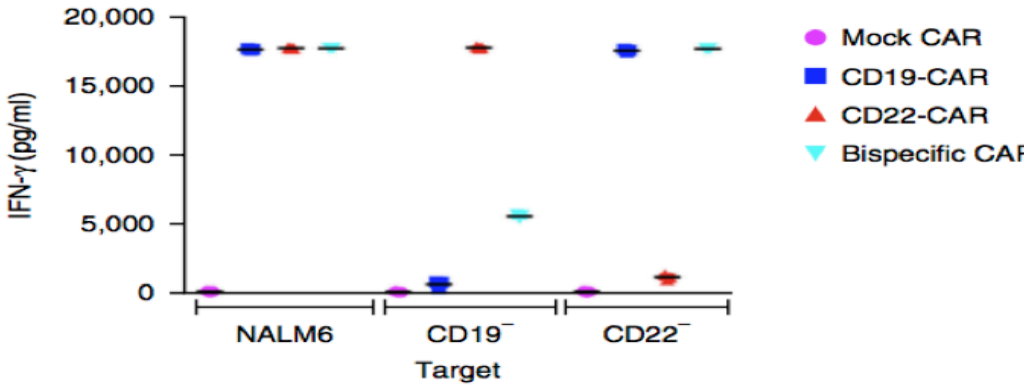
Timeline of Clinical Development of CD19 CAR T Cells in Hematologic Malignancies

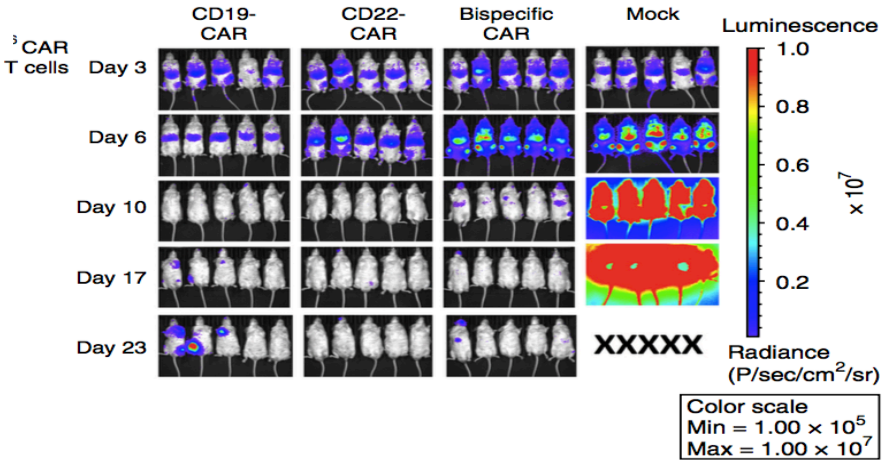


Graphic courtesy of Memorial Sloan Kettering Cancer Center

CD19 and CD22-Bispecific CAR T Cells





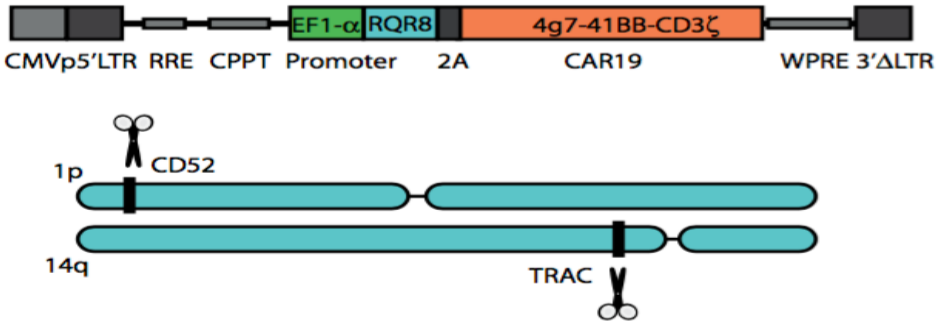


Fry T et al. *Nat Med* 2018; 24(1):20-28

Universal or "off-the-shelf" CAR T Cells

Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells

Waseem Qasim,[1,2]* Hong Zhan,[1] Sujith Samarasinghe,[2] Stuart Adams,[2] Persis Amrolia,[1,2] Sian Stafford,[1] Katie Butler,[1] Christine Rivat,[1] Gary Wright,[2] Kathy Somana,[2] Sara Ghorashian,[1] Danielle Pinner,[2] Gul Ahsan,[2] Kimberly Gilmour,[2] Giovanna Lucchini,[2] Sarah Inglott,[2] William Mifsud,[2] Robert Chiesa,[2] Karl S. Peggs,[3] Lucas Chan,[4] Farzin Farzaneh,[4] Adrian J. Thrasher,[1] Ajay Vora,[5] Martin Pule,[3] Paul Veys[1]



Disruption of CD52 gene & TRAC (loss of TCRαβ)

Qasim et al. *Sci Transl Med* 2017

Study Updates

PALL study of pediatric ALL:

- 5 children treated
- CRS: 1 Gr1, 3 Gr2 and 1 Gr3
- 4/5 pts w/ viral complications
- Response: 5/5 CRi → alloHSCT → 2 relapse, 1 death in CR and 2 alive in CR

CALM study of adult ALL:

- 6 adults treated (4 MRD+ pts)
- CRS: 1 Gr1, 4 Gr2, 1 Gr4 → 1 death on D15
- Response: 4/6 Cri → alloHSCT → 1 relapse, 1 death in CR and 2 alive in CR

Qasim W et al. *ASH 2017,* Abstract *1271;* Graham C et al. *ASH 2017,* Abstract 887

Common Toxicities of CD19 CAR T cells

Cytokine Release Syndrome (CRS) Clinical Spectrum

Fever
Hypotension
Capillary leak
Respiratory insufficiency
Hyperferritinemia/MAS
Coagulopathy/DIC
Multi-organ failure

Symptoms rapidly resolve with IL-6R blockade

Neurotoxicity

Delirium
Global encephalopathy
Aphasia
Seizure, seizure-like activity
Tremor/myoclonus
Hallucinations
"CAR T cell related encephalopathy syndrome (CRES)"

Rapid onset cerebral edema

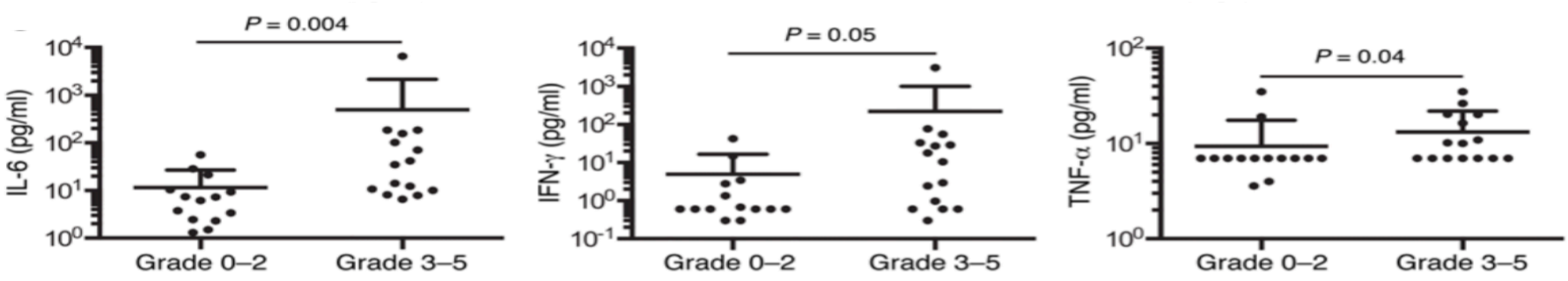
Severe symptoms do not resolve with IL-6R blockade

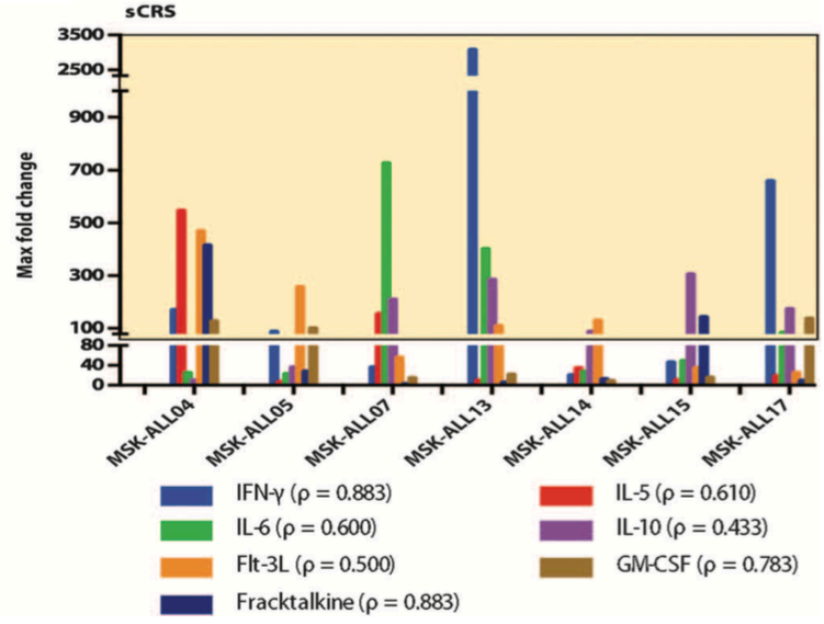
CD19 CAR Associated CRS and NTX Incidences

	T Cell Product	Disease	No. of Patients	CRS, All grades (%)	≥Gr3 CRS (%)	≥Gr3 NTX (%)
Adults	**19-28z (MSK)**	ALL	53	85	26	41
	KTE-C19 (ZUMA-3)	ALL	29	93	28	52
	KTE-C19 (ZUMA-1)	DLBCL	101	93	13	28
	CTL019 (JULIET)	DLBCL	99	58	23	12
	JCAR017 (TRANSCEND)	DLBCL	55	35	2	16
Peds	**CTL019 (ELIANA)**	ALL	75	77	47	13
	JCAR017 (PLAT-02)	ALL	43	93	23	21
	19-28z (NCI)	ALL	21	76	29	5

Park J at al. *N Engl J Med* 2018; Shah B et al. *ASH 2017* abstract 888; Neelapu S et al. *N Engl J Med* 2017; Schuster S et al. ICML 2017; Abramson J et al. ICML 2017; Maude S et al. *N Engl J Med* 2018; Gardner R et al. *Blood* 2017; Lee D et al. *Lancet 2015*.

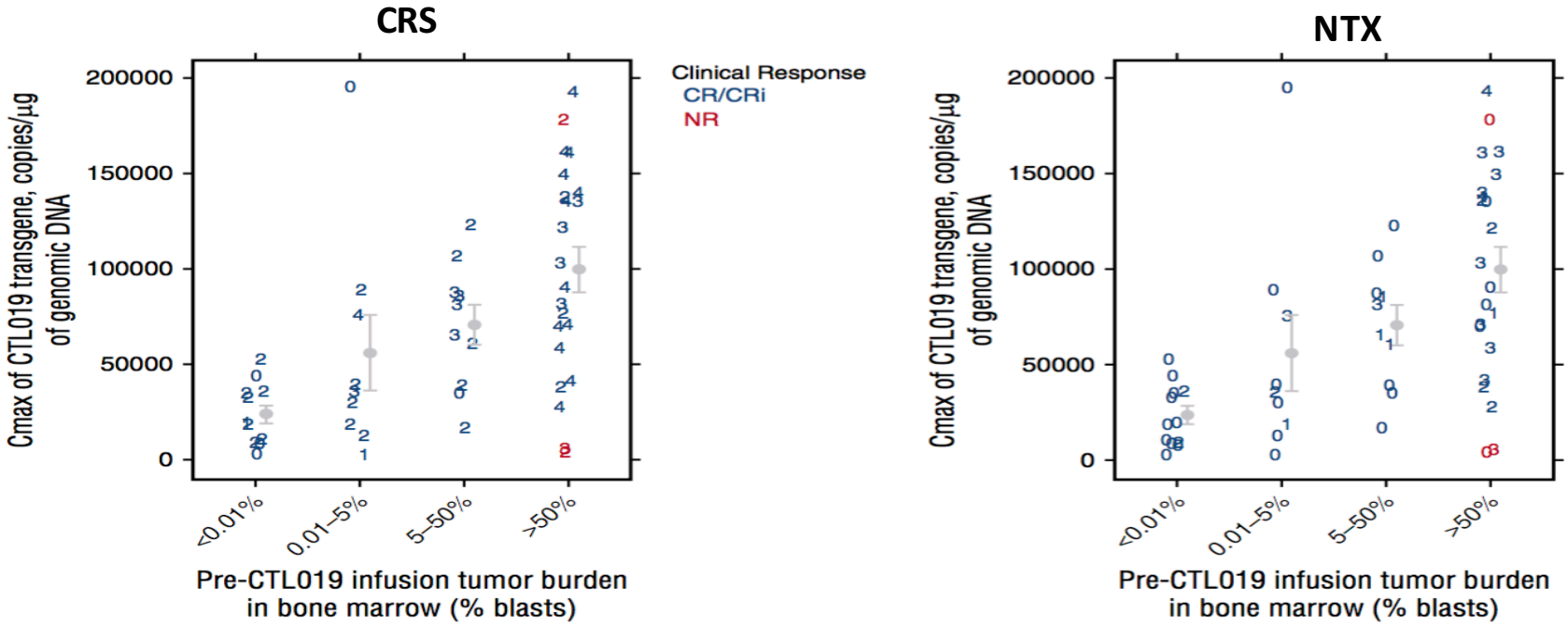
CRS Is Associated With Elevated Proinflammatory Cytokines





Turtle C et al. *J Clin Invest* 2016; 126(6):2123-2138. Davila M et al. *Sci Transl Med* 2014; 6(2224):224ra25

High Tumor Burden and Greater in vivo T-Cell Expansion Correlate With CAR-Associated Toxicity



Muller K et al. *Blood* 2017;130(21):2317-2325

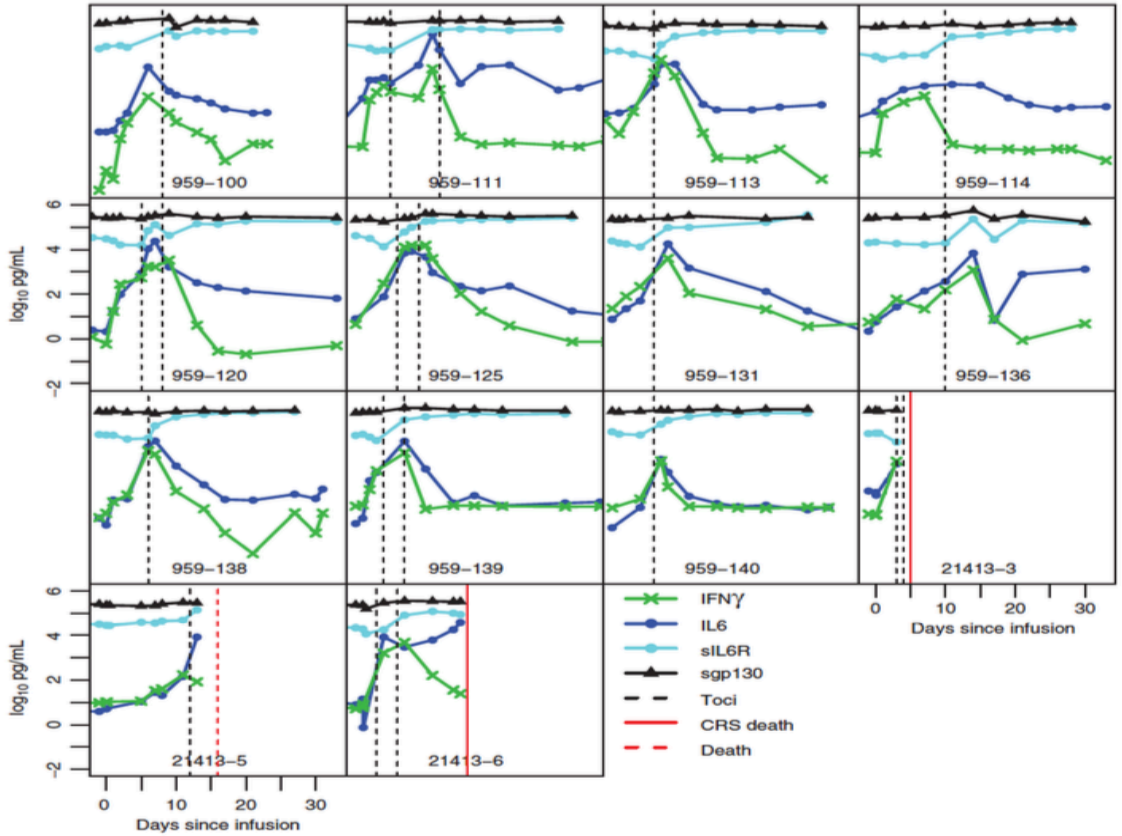
Severity of CRS Correlates With CAR T-Cell Dose in ALL

CTL019 in Adult Patients with R/R B-ALL

Cohort	Dose	Schedule	N	CRS ≥ Gr 3, %	Response, %
1	High dose (5×10^8)	Split	15	66	86 (0 TRM)
2	High dose (5×10^8)	Single	6	100	100 (3 TRM)
3	Low dose (5×10^7)	Split	6	66	33
4	Low dose (5×10^7)	Single	3		
Overall	---	---	30	75	72 (3 TRM)

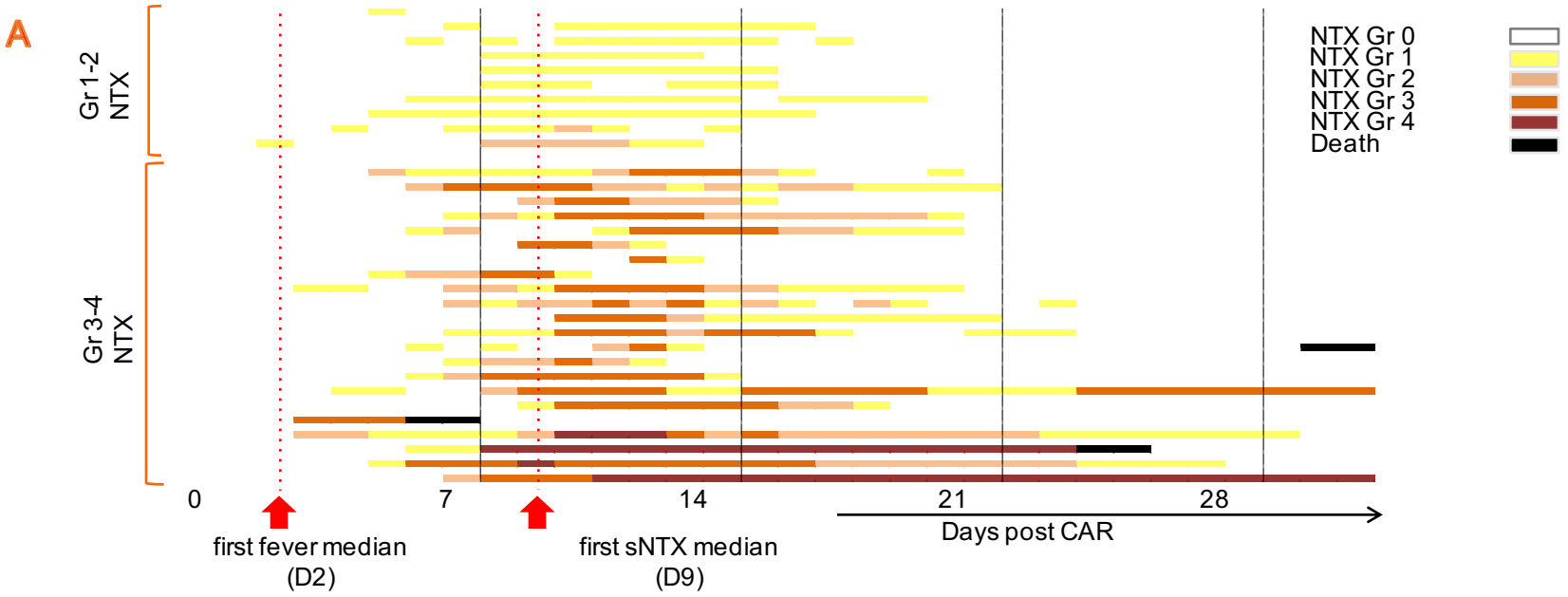
Frey N et al. *ASCO 2016 Annual Meeting.* Abstract 7002

CRS Is Abrogated by IL-6 Blockade

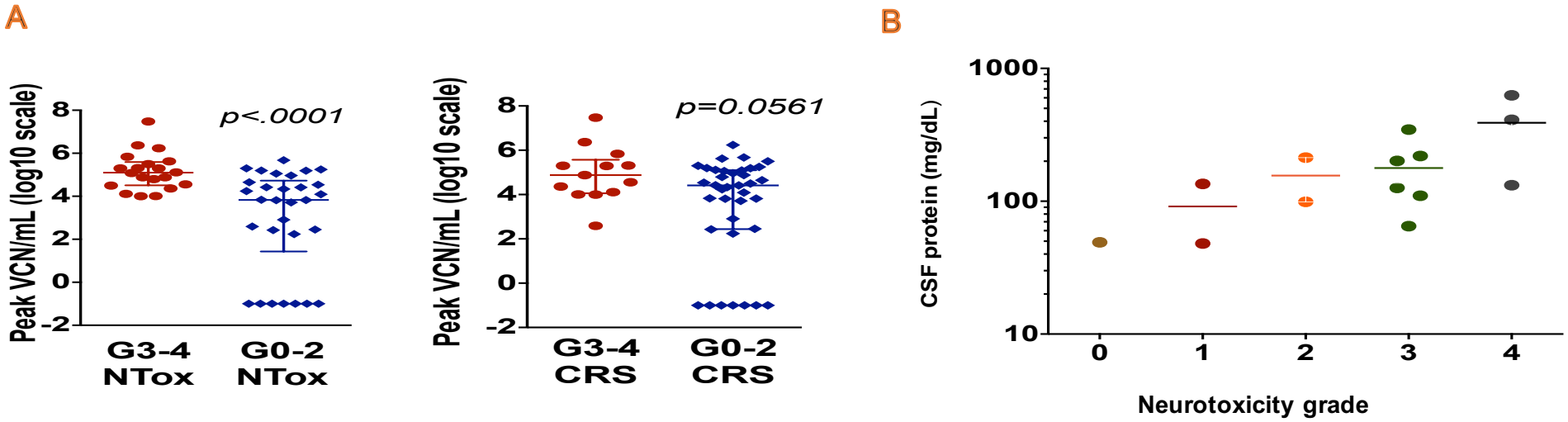


Teachey D et al. *Cancer Discovery* 2016; 6:664-679

Neurotoxicity in Relation to CRS



NTX Correlates With T-Cell Expansion and CSF Protein



Pharmacotherapy in Cytokine Release Syndrome

Supportive Care Modalities:

Fever
Hypotension

Supportive Care Pharmacotherapy: Fever

- Antipyretics (e.g., acetaminophen)
- Broad-spectrum antibiotics
  - Blood cultures, radiographic studies, frequent vital sign checks
- Consideration of G-CSF (e.g., filgrastim) if neutropenic

Lee DW, et al. Blood 2014;124:188-95; Brudno, et al. Blood 2016;127(26):3321-330

Supportive Care Pharmacotherapy: Hypotension

- Fluid boluses
  - 0.9% normal saline recommended
  - 500–1000 mL
  - Escalate to vasopressors, tocilizumab, and/or glucocorticoids after failure of response
- Vasopressors
  - Escalation to high dose or multiple pressors → tocilizumab and/or glucocorticoids

Vasopressor	High Dose Equivalents (must be on ≥3 hours)
Norepinephrine	≥ 20 µg/kg/min
Dopamine	≥ 10 µg/kg/min
Phenylephrine	≥ 200 µg/kg/min
Epinephrine	≥ 10 µg/kg/min
Norepinephrine + vasopressin	≥ 10 µg/kg/min
Combo vasopressin (non-vasopressin)	≥ 20 µg/kg/min of norepinephrine equiv.

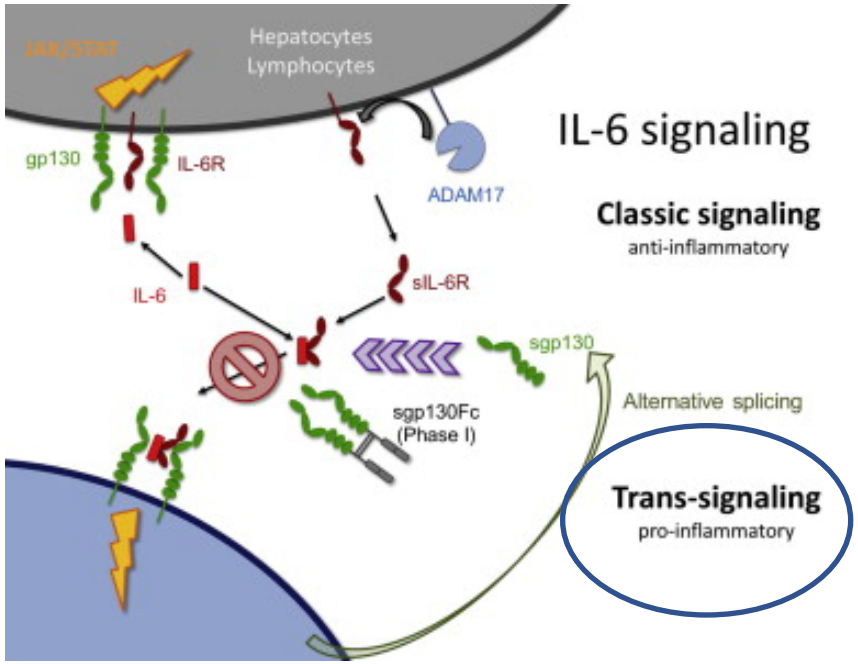
Teachey, et al. *Clinical Oncology* **volume 15**, page 218 (2018); Lee DW, et al. Blood 2014;124:188-95; Brudno, et al. Blood 2016;127(26):3321-330

Pharmacotherapy in Cytokine Release Syndrome

Tocilizumab

IL-6 (Interleukin-6)

- Correlation between severity of CRS and serum IL-6 levels
- IL-6 can signal multiple ways:
  - Direct binding to membrane bound IL-6R and gp130 complex (classic signaling)
  - Direct binding to soluble IL-6R → interaction with membrane bound gp130 (trans-signaling)



*Gp130 – glycoprotein 130

Wolf J, et al. Cytokine (70);1:13; Lee DW, et al. Blood 2014;124:188-95

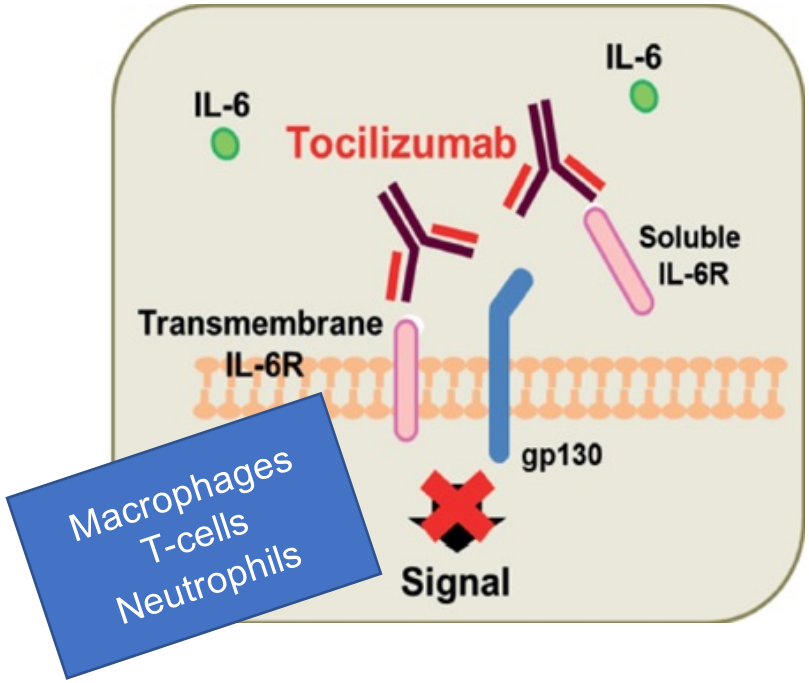
Tocilizumab

- Interleukin-6 receptor antagonist (IL-6R Antagonist)
- Available as subcutaneous (SC) or intravenous (IV) injection
  - Intravenous recommended for cytokine release syndrome (CRS)
- FDA approved
  - CRS:
    - Patients ≥ 2 years of age after CAR-T cell induced CRS (severe or life-threatening)

Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017

Tocilizumab: IL-6

- Tocilizumab binds to both soluble and membrane-bound IL-6 receptors
- Mitigates downstream activation of JAK/STAT pathway/pro-inflammatory effects
- Serum IL-6 levels have been shown to increase after doses
  - IL-6 displaced by tocilizumab at receptor
  - Concern for increased risk of neurotoxicity
    - Potential increased uptake of IL-6 into CNS



Santomasso, et al. *Neurology*. April 10, 2018; 90 (15 Supplement); Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017

Tocilizumab: Administration

- Dosing based on weight (*cap at 800 mg per infusion)*:
  - >30 kilograms: 8 mg/kg intravenously
  - <30 kilograms: 12 mg/kg intravenously
- Infusion over 60 minutes
  - Prepared in 0.45% or 0.9% normal saline
- If no clinical improvement tocilizumab may be re-dosed
  - Minimum 8-hour interval between doses
  - Limit to a maximum of 4 total doses
- Commercial CAR T cell products (REMS requirement):
  - At least two doses of tocilizumab required on site per CAR T-cell patient

Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017; Novartis. Kymriah (tisagenlecleucel) package insert. East Hanover, NJ 2017; Kite Pharma. Yescarta (axicabtagene ciloleucel) package insert. Santa Monica, CA 2017

Tocilizumab: Pharmacokinetics

- Onset (CRS): Median time to defervescence = 4 hours
- Renal: No adjustment required for mild or moderate dysfunction
  - Minimal clinical data for creatinine clearance (CrCl) <50 mL/min
- Hepatic: Caution if baseline AST/ALT >1.5 x ULN
  - The decision to administer in CRS should take into account risk vs. benefit profile
- Drug-Drug Interactions:
  - IL-6 elevation may lead transient inhibition of various CYP enzymes
    - Function restored in vitro with tocilizumab administration
  - Recommended therapeutic monitoring with high-risk medications
  - Sensitive drug substrate concentrations may increase or decrease

Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017

Tocilizumab: Adverse Effects

Non-CRS Population

Organ System	Manifestations
Central nervous system	Dizziness, headache
Gastrointestinal	Nausea/vomiting, diarrhea
Hematologic	Neutropenia, thrombocytopenia
Hepatic	Hepatitis, increased ALT/AST/bilirubin
Dermatologic	Local irritation/rash (2%)
Renal	Nephrolithiasis (<2%)
Infection	Upper respiratory tract infection, herpes simplex

CRS Population

- Retrospective analysis
  - Adult and pediatric patients
- No adverse effects independently attributable to tocilizumab (intravenous)
  - No differences in adults vs. pediatrics

Le, et al. The Oncologist. Aug 2018;23(8)
Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017

Tocilizumab: Clinical Evidence

Pooled retrospective analysis from CTL019 and KTC-C19 trials

- Open-label; multicenter phase II trial
- N= 60
- Received tocilizumab for life threatening or severe CRS
- Primary objective:
  - Characterize CRS resolution

Intervention
Tocilizumab 8 mg/kg (adults)
Tocilizumab 12 mg/kg (peds)

CRS resolution:
Absence of fever and off vasopressors for at least 24 hours

Responders:
CRS resolved within 14 days of first dose

≤2 doses of tocilizumab

Assessments at 2, 7, and 21 days post first dose

Le, et al. The Oncologist. Aug 2018;23(8) Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017

Tocilizumab: Clinical Evidence (Demographics)

Demographics	CTI019 CAR-T	KTC-C19 CAR-T
Years of age (range)	12 (3-23)	60 (9-75)
Gender M F	 24 (53.3%) 21 (46.7%)	 10 (66.7%) 5 (33.3%)
Underlying Malignancy ALL DLBCL PMBCL	 45 (100%) 0 0	 2 (13.3%) 12 (80%) 1 (6.7%)

PMBCL = primary mediastinal B-cell lymphoma.

Le, et al. The Oncologist. Aug 2018;23(8)

Tocilizumab: Clinical Evidence (Demographics)

Characteristics and treatment	CTL019 CAR-T	KTC-C19 CAR-T
Baseline CRS grade Grade 3 Grade 4	 10 (22.2%) 35 (77.8%)	 14 (93.3%) 1 (6.7%)
Baseline CRS duration 0-4 days 4+ days	 23 (51.5%) 22 (48.9%)	 12 (80%) 3 (20%)
Doses of tocilizumab 1 2 3+	 25 (55.5%) 13 (28.9%) 7 (15.6%)	 6 (40%) 5 (33.3%) 4 (26.7%)
Initial dose of tocilizumab 8 mg/kg 12 mg/kg	 38 (84.4%) 7 (15.6%)	 15 (100%) 0

Le, et al. The Oncologist. Aug 2018;23(8)

Tocilizumab: Clinical Evidence (Results)

Primary Outcome	CTL019 CAR-T n (%, 95% CI)	KTC-C19 CAR-T n (%, 95% CI)
Response by D14	31 (68.9%, 53.4 – 81.8)	8 (53.3%, 26.6 – 78.7)

Additional Outcomes	CTL019 CAR-T n (%, 95% CI)	KTC-C19 CAR-T n (%, 95% CI)
Response by D2 Response by D7 Response by D21	9 (20%, 9.6-34.6) 26 (57.8%, 42.2 – 72.3) 31 (68.9, 53.4 – 81.8)	3 (20%, 4.3-48.1) 8 (53.3%, 26.6 – 78.7) 8 (53.3%, 26.6-78.7)

Le, et al. The Oncologist. Aug 2018;23(8)

Tocilizumab: Clinical Evidence (Safety)

- No reports of adverse drug reactions attributable to tocilizumab
- Even number of deaths in both CTL019 and KTC-C19
  - 5 deaths in each group within 30 days of first tocilizumab
- Pharmacokinetic data supports safety of dosing range of up to 4 doses given 8 hours apart

Le, et al. The Oncologist. Aug 2018;23(8); Genentech Inc. Actema (tocilizumab) package insert. San Francisco, CA 2017.

Tocilizumab: Concerns With Efficacy?

- Tocilizumab has NOT been demonstrated to blunt efficacy of CAR T-cell therapy
- Axicabtagene ciloleucel trial
  - Rates of overall response did not differ (subgroup analysis) among tocilizumab users

Tocilizumab Use	Patient Events	Objective Response Rate (95% CI)
Yes	36 events out of 43 evaluable pts	0.84 (26.6–78.7)
No	47 events of out 58 evaluable pts	0.81 (0.69–0.90)

Tocilizumab: Clinical Evidence (Summary)

- Only FDA-approved agent for CRS management
- Strongly recommend for patients if progression despite supportive care modalities (e.g., grade 2 and beyond)
- FDA approval based on pooled retrospective series
  - Appropriate based on population/severity of illness
  - Studies not powered to specifically assess for tocilizumab toxicity or efficacy
- Unlikely to diminish efficacy of CAR-T cells based on currently available data
- More studies/real world experience needed to elucidate best practices for use of tocilizumab

Pharmacotherapy in Cytokine Release Syndrome (CRS)

Siltuximab

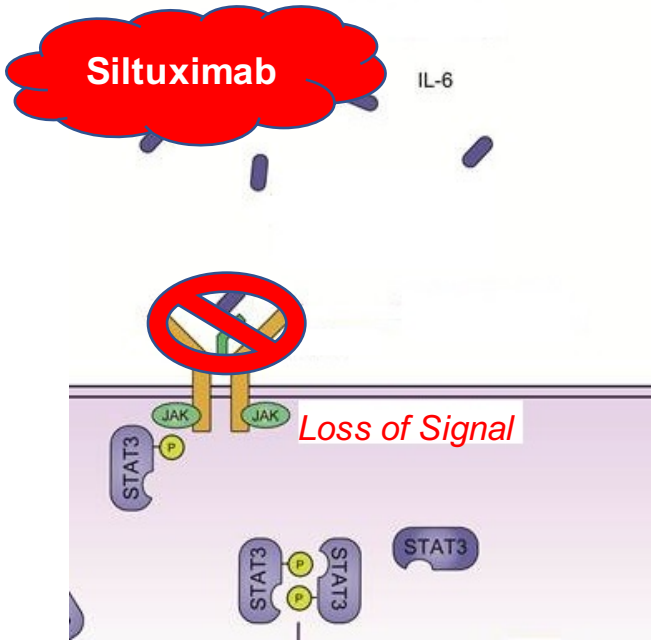
Siltuximab

- Interleukin-6 antagonist (IL-6 antagonist)
  - Chimeric monoclonal antibody
- Available as intravenous (IV) injection only
- *Expert opinion*:
  - Consider for salvage treatment of CRS refractory to tocilizumab/corticosteroid

Sylvant (siltuximab) for injection package insert. Janssen Biotech, Inc.: Horsham, PA; 2018 May
Teachey, et al. *Clinical Oncology* **volume 15**, page 218 (2018)

Siltuximab: Mechanism

- Siltuximab binds directly to IL-6
- Prevents binding of IL-6 to both soluble and membrane-bound IL-6 receptors
- Lowers serum IL-6 levels



Chen, F. et al. *J. Immunol. Methods* **434**, 1–8 (2016); Sylvant (siltuximab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; May 2018

Siltuximab: Administration

- Dosing based on weight (*no known dose cap)*:
  - 11 mg/kg
  - Dosing extrapolated from use in Castleman's disease
- Infusion over 60 minutes
  - Prepared in 250 mL of D5W
  - Must be administered within 4 hours of reconstitution
- No data available re: dosing intervals

Sylvant (siltuximab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; May 2018

Siltuximab

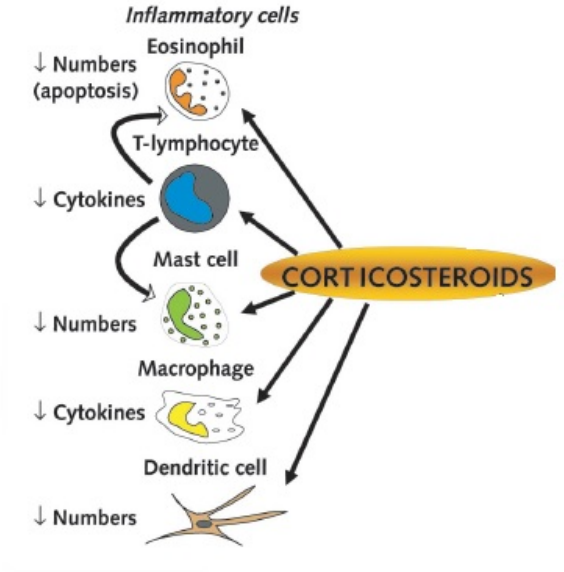
- Routine first line use is NOT generally recommended
  - Absence of published data
- Mechanism of action suggests less risk of “IL-6 flare” seen with tocilizumab
- Strongly consider for refractory CRS when:
  - Suboptimal response after tocilizumab + glucocorticoid
  - Concern for overlapping neurotoxicity
- Studies ongoing to establish role of siltuximab in CRS management

Pharmacotherapy in Cytokine Release Syndrome (CRS)

Glucocorticoids

Glucocorticoids: Mechanism

- Decreases inflammation by suppression of neutrophil migration
- Decreased transcription of:
  - IL-1, IL-2, IL-6
  - TNF-a
  - Bradykinin
- Increases transcription of
  - IL-1 receptor antagonist
  - Secretory leukocyte inhibitory protein



Ausiello DA, et al. Ann of Intern Med. 2003;139:359-370

Glucocorticoids: Selected Agents

Dexamethasone

- Long-acting (t(1/2) = 36-72h)
- Five times the potency of methylprednisolone
- Partial metabolism in choroid plexus
  - CNS Penetration
- Proposed dosing
  - Dexamethasone 0.5 mg/kg (max 10 mg/dose) followed by taper

Methylprednisolone

- Intermediate-acting (t(1/2)= 8-12h)
- Poor CNS penetration
- Proposed dosing
  - 2 mg/kg/day followed by taper

Koszdin KK, et al. Anesthesiology 1 2000, Vol.92, 156; Meikle AW, et al. Am J of Med 1977;63:200; Lee DW, et al. Blood 2014;124:188-95.

Glucocorticoids: Adverse Effects

Organ System	Manifestations
Cardiovascular	Hypertension, tachycardia, thromboembolism, fluid retention
Central nervous system	Depression, emotional lability, euphoria
Endocrine/metabolic	Hyperglycemia, adrenal suppression, hypokalemia
Gastrointestinal	Peptic ulcers, GI hemorrhage, increased appetite, esophagitis
Hematologic	Lymphopenia
Dermatologic	Acne vulgaris, hyperpigmentation, skin atrophy, cataracts
Infectious disease	Opportunistic, fungal, and viral infection

Meikle AW, et al. Am J of Med 1977;63:200

Glucocorticoids: Concerns With Efficacy?

- Diminish the expansion and persistence of T cells → concern of limiting of effectiveness of CAR-T cells
  - Attempt to reserve use only when CRS is refractory to tocilizumab/other intervention
- Axicabtagene ciloleucel trial
  - Rates of overall response did not differ (subgroup analysis) among glucocorticoid users

Glucocorticoid Use	Patient events	Objective Response Rate (95% CI)
Yes	27 events out of 21 evaluable pts	0.78 (26.6 – 78.7)
No	74 events of out 62 evaluable pts	0.84 (0.69-0.90)

Teachey, et al. *Clinical Oncology* **volume 15**, page 218 (2018); Neelapu, et al. N Engl J Med 2017; 377:2531-2544

Glucocorticoids: Clinical Evidence (Summary)

- Suppress inflammatory response
  - Strongly consider for CRS that is refractory to tocilizumab
- Dexamethasone and methylprednisolone are drugs of choice
  - Dosing range varies based on grade of CRS and concern for overlapping neurotoxicity
- Some data suggest steroids may not mitigate response to CAR-T cells
  - More prospective/controlled data needed to assess true steroid effect
- Concerns for decreased T-cell expansion/decreased efficacy require caution with routine glucocorticoid use

Lee DW, et al. Blood 2014;124:188-95; Neelapu, et al. Nat Rev Clin Onc 2018;15:47-62

Case Study

AK is a 24-year-old female with R/R B-cell ALL who is day +2 of anti-CD19 CAR-T therapy. The RN pages you to report a fever (T_{max} 101.3F) and hypotension (BP: 89/70). Patient is A&O x4 after exam. Which of the following the most appropriate intervention for AK at this current time?

A. NS fluid bolus of 1L, antipyretics, broad spectrum antibiotics, blood cultures, chest x-ray

B. NS fluid bolus of 1L, dexamethasone, norepinephrine, blood cultures, chest x-ray,

C. Tocilizumab, blood cultures, chest x-ray, broad spectrum antibiotics

D. NS fluid bolus of 1L, dexamethasone, broad spectrum antibiotics

Case Study (continued)

You are called to bedside about 1 hour after your previous intervention. AK is now persistently febrile with a SBP of 80/60. The ICU is consulted, and she is started on low-dose vasopressors. Patient remains alert and oriented upon exam but is visibly diaphoretic and is still febrile; blood cultures return negative. What agent is most appropriate to consider at this time?

A. Vancomycin

B. Tocilizumab

C. Dexamethasone

D. Siltuximab

Case Study (continued)

AK's symptoms resolve within 3 hours after receipt of tocilizumab. Unfortunately, AK experiences a resurgence of febrile episodes and hypotension. She is transferred to the ICU for further management. After 3 doses of tocilizumab and high-dose vasopressors, she remains hypotensive, febrile, and is now only minimally responsive. What agent is most appropriate to consider at this time?

A. Additional dose of tocilizumab (patient has not reached max dose recommendation)

B. Siltuximab

C. Dexamethasone

D. Methylprednisolone

Future Directions

- Role of prophylactic tocilizumab for at risk patients
- Role of siltuximab in the treatment or prevention of CRS
- Other anti-inflammatory therapies
  - Anakinra
- Formal consensus guidelines for CRS management
  - Which agents?
  - When to use?
  - When to combine?

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Thank You for Your Attention!

Please email with any questions:
parkj6@mskcc.org or kinga@mskcc.org