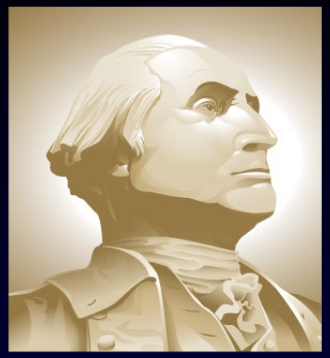

THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC

CAR T-cells in Oncology

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Director, George Washington Cancer Center

Professor, Department of Medicine

George Washington University School of Medicine and Health Sciences

GW Cancer Center

Chimera

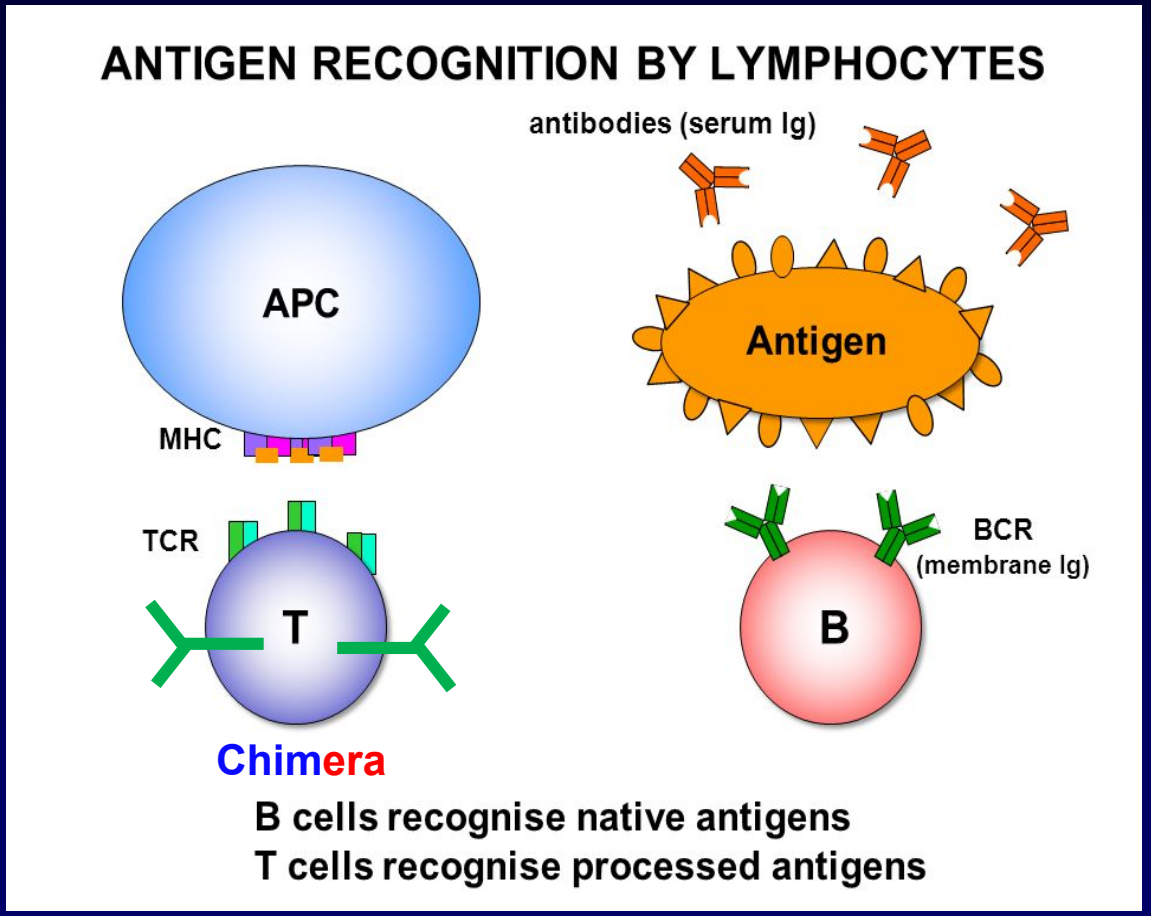
chi·me·ra
/kīˈmirə, kəˈmirə/ : in Greek mythology: a fire-breathing female monster with a lion's head, a goat's body, and a serpent's tail.

(i) any mythical animal with parts taken from various animals.
(ii) Any cell with parts/molecules taken from another cell

Chimeric Antigen Receptor (CAR) T-cells

(ii) A T-cell with parts/molecules taken from another cell

….T cells that have been genetically engineered to produce an artificial receptor that recognize an specific antigen. This receptor is naturally present in B-cells, but not in T-cells



CAR T-cells targeting CD19

Chimeric Antigen Receptor (CAR) T-cells

- Emerged from the groundwork set by the clinical successes of monoclonal antibody technology…

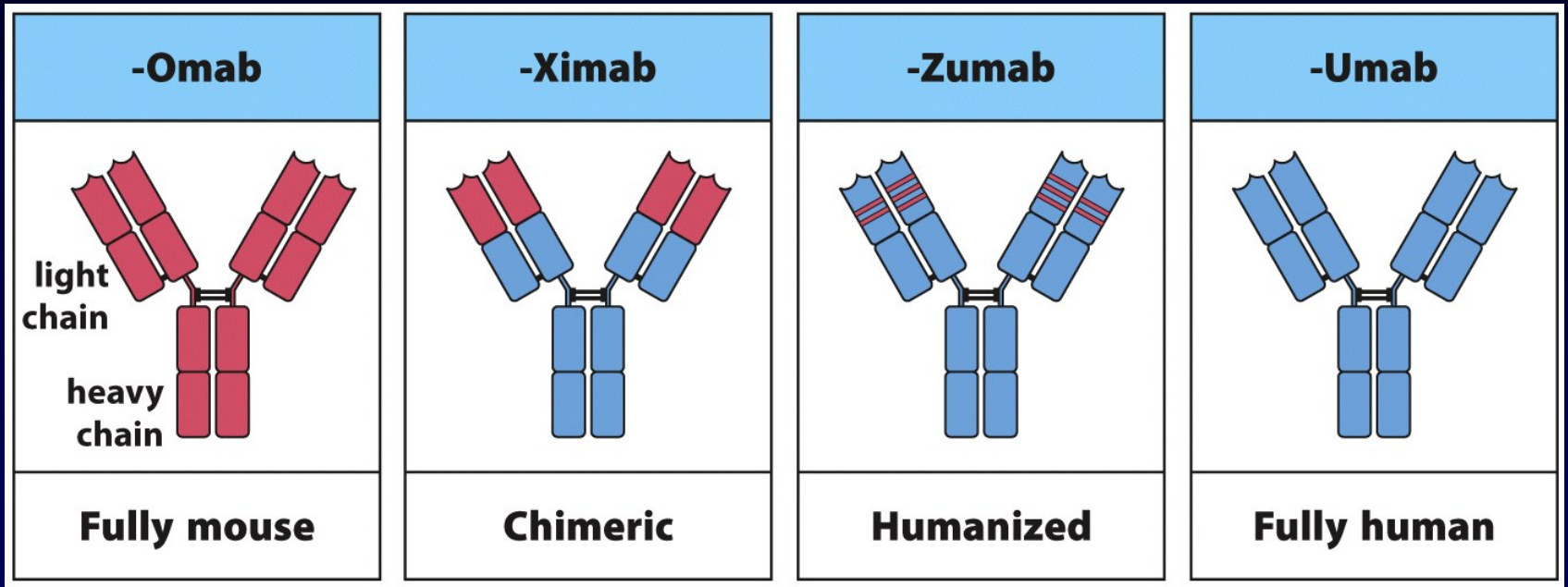
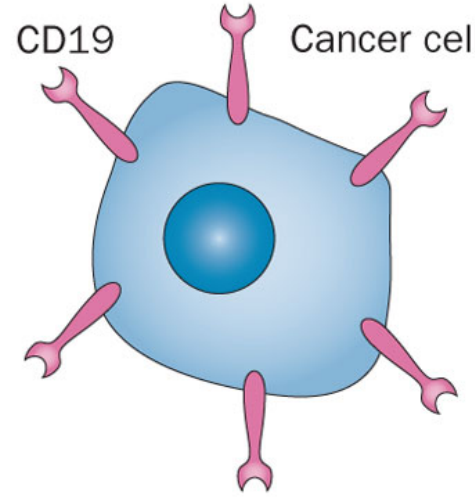


Figure 16.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

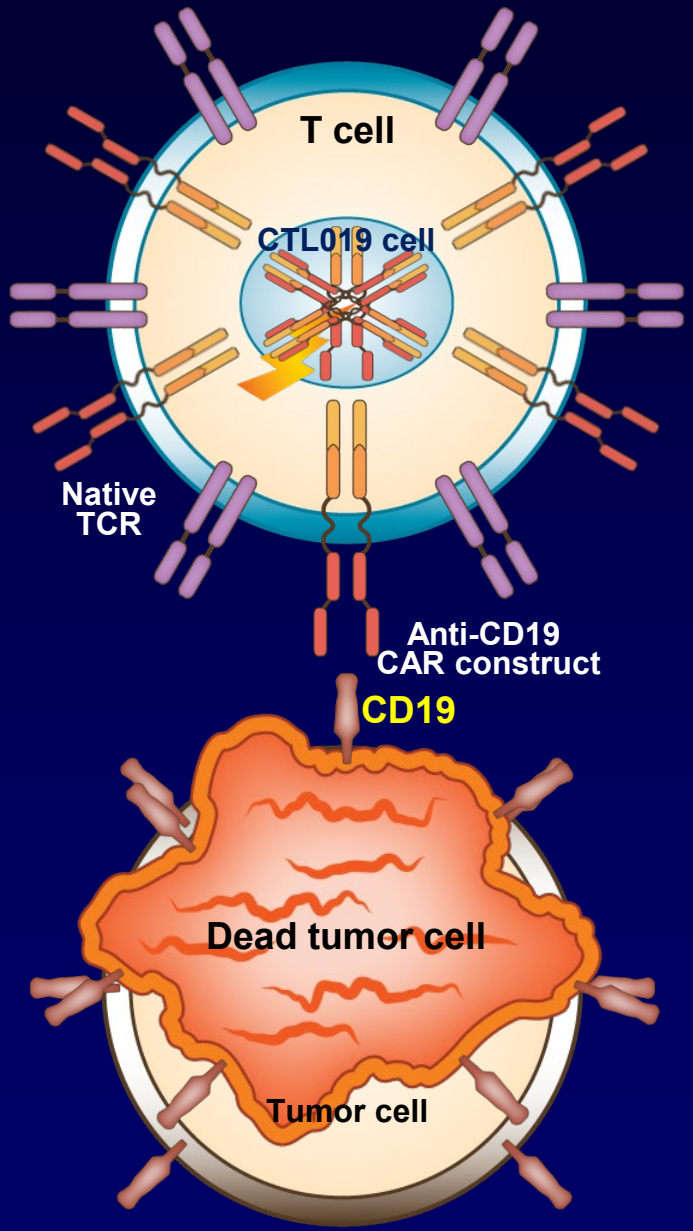
- Antibodies against CD19 have been generated and are highly specific…. Can this specificity be "given" to T-cells? How?

- CD19-CARs are antibody-derived receptors (anti-CD19) genetically "introduced" into T cells to allowed them to better recognize and destroy tumor cells expressing CD19……

Chimeric Antigen Receptor (CAR) T-cells

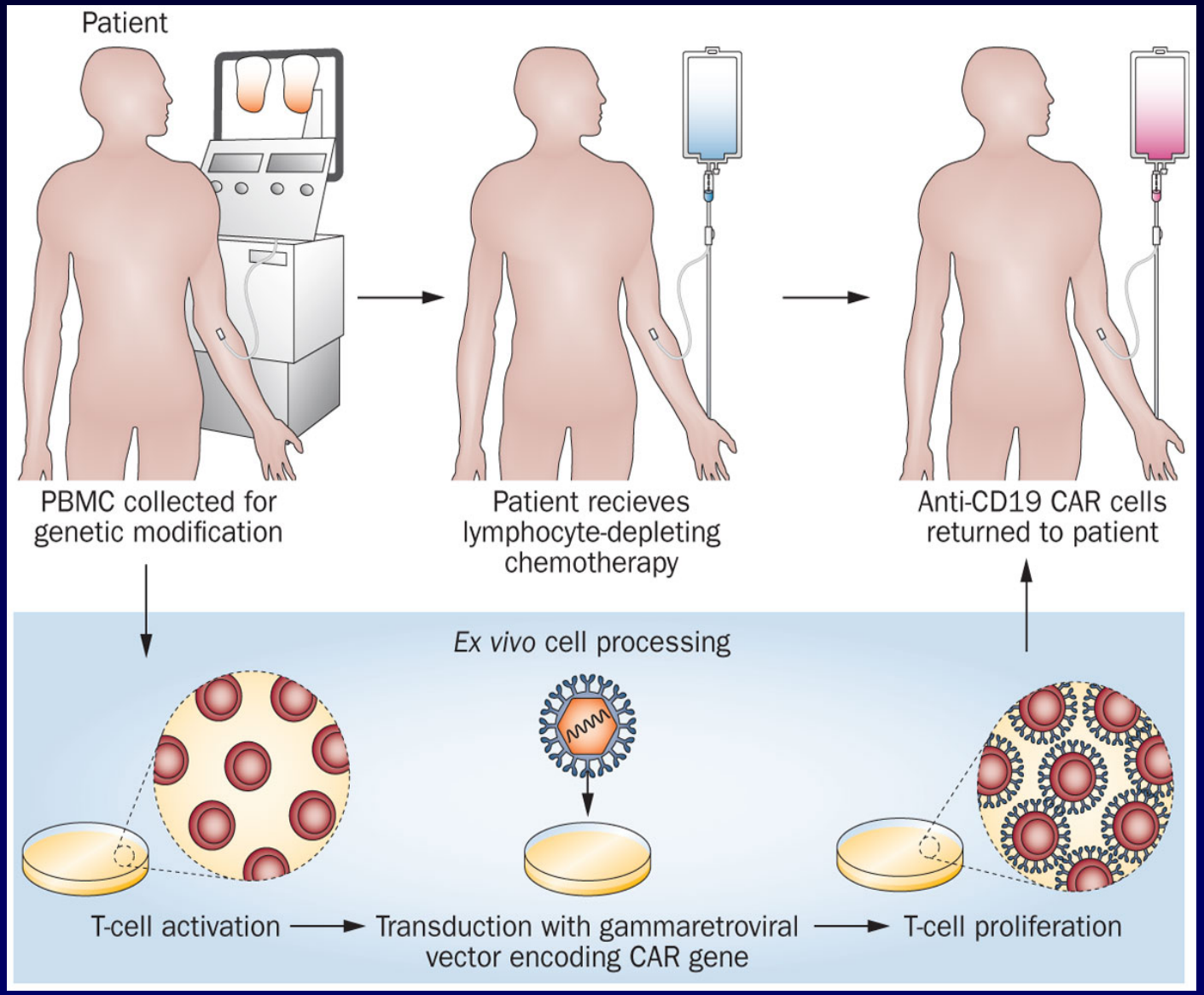


Redirecting the Specificity of T Cells



Courtesy of David Porter- U Penn

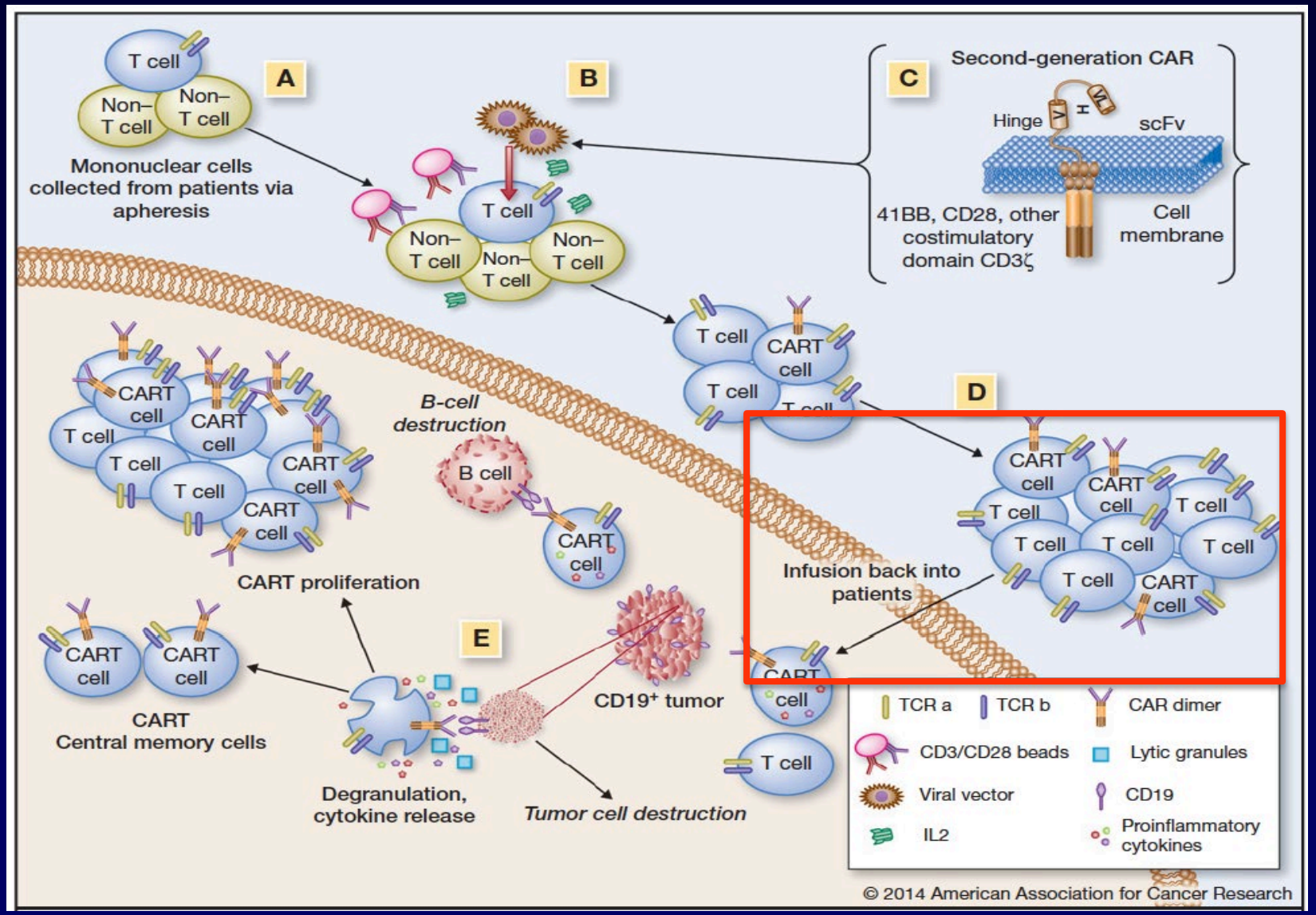
CAR T-cell Therapy



2-4 week process

Kochenderfer JN & Rosenberg SA. Nat Rev Clin Oncol 10, 267-176, 2013

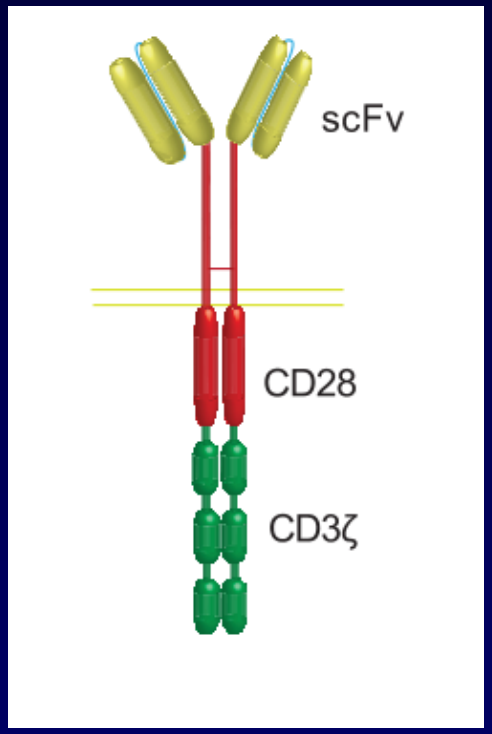
Anti-CD19 CAR T-cell effects *in vivo*



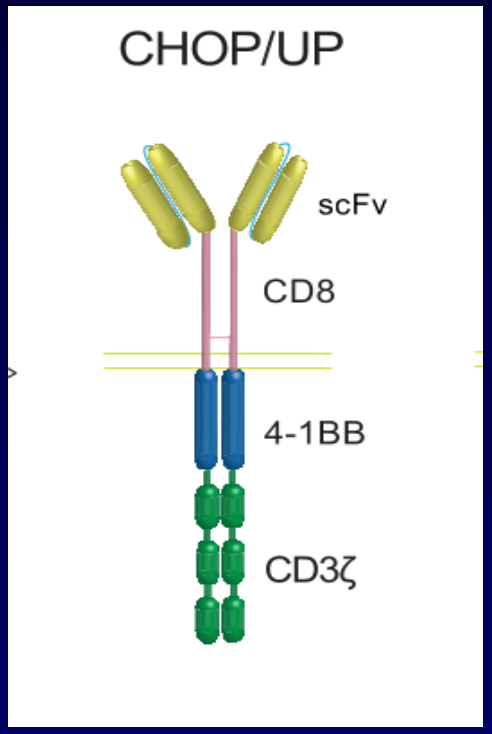
Kenderian SS et al. Cancer Res. 2014 Nov 15;74(22):6383-6389

CD19 CARS in clinical trials

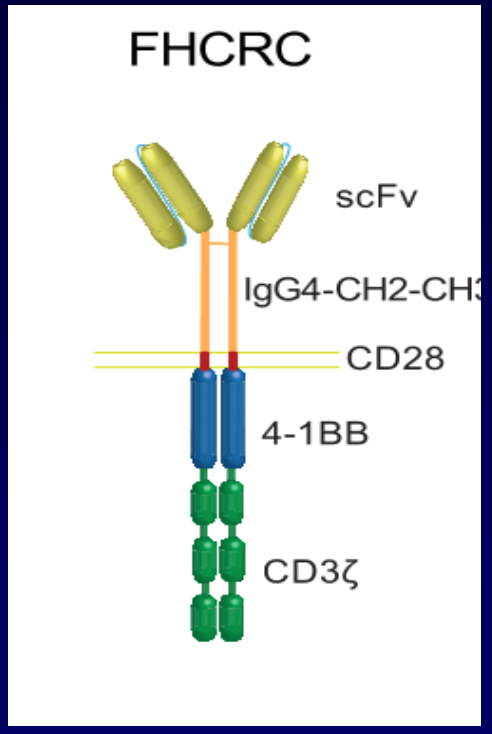
NCI



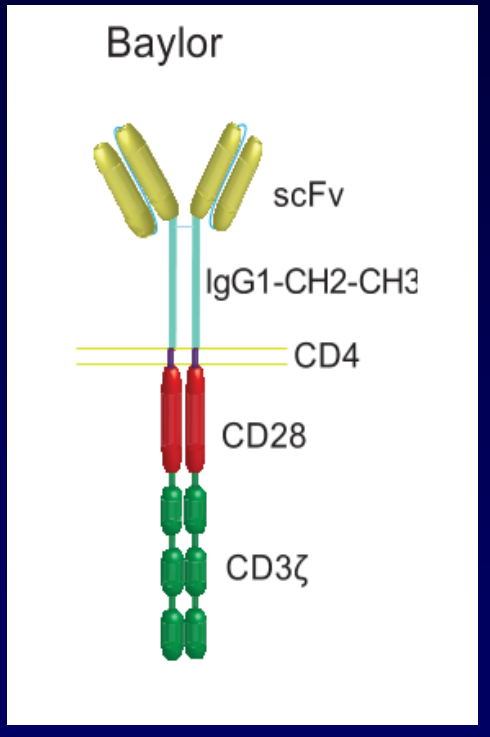
CHOP/U. Penn



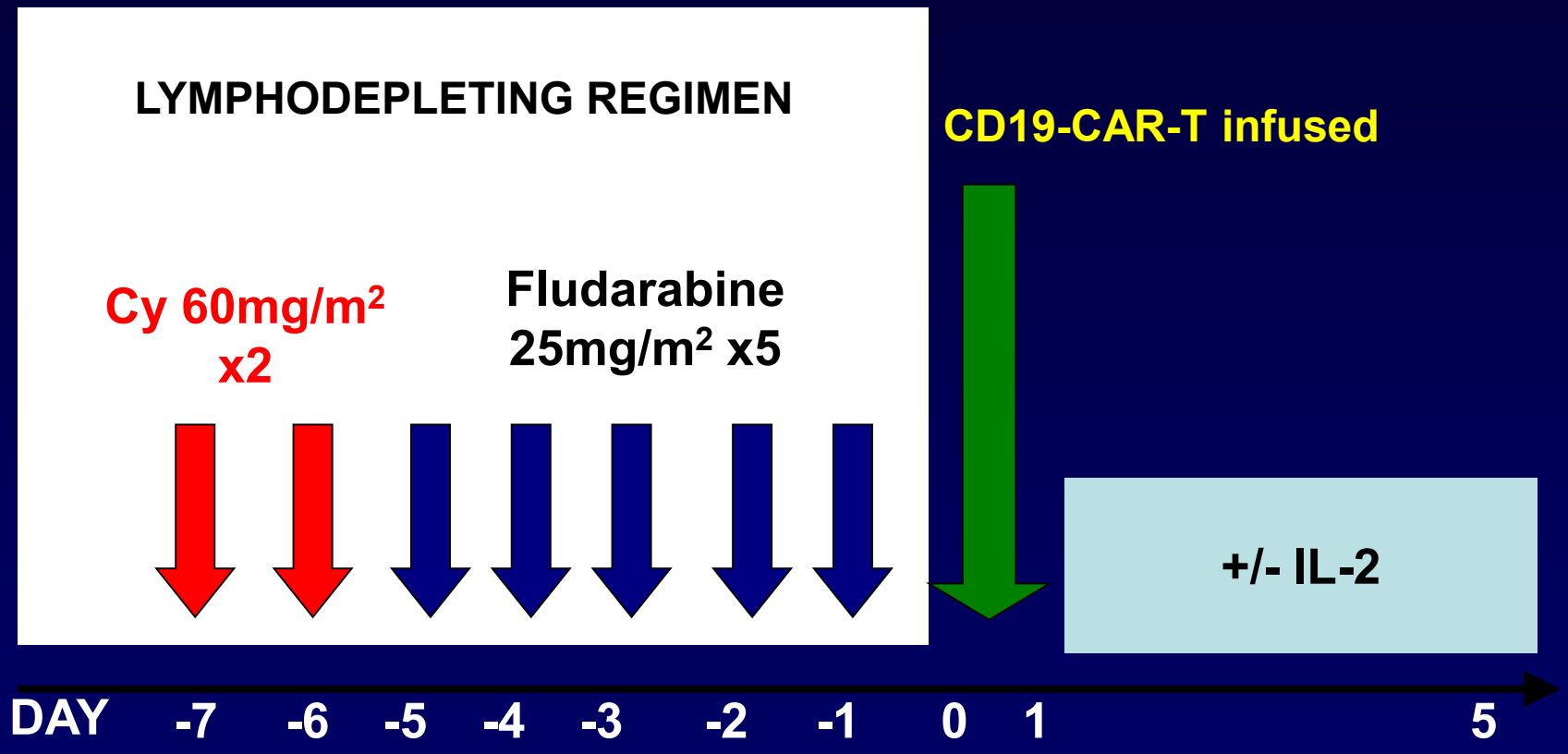
FHCC



Baylor
Bluebird Bio



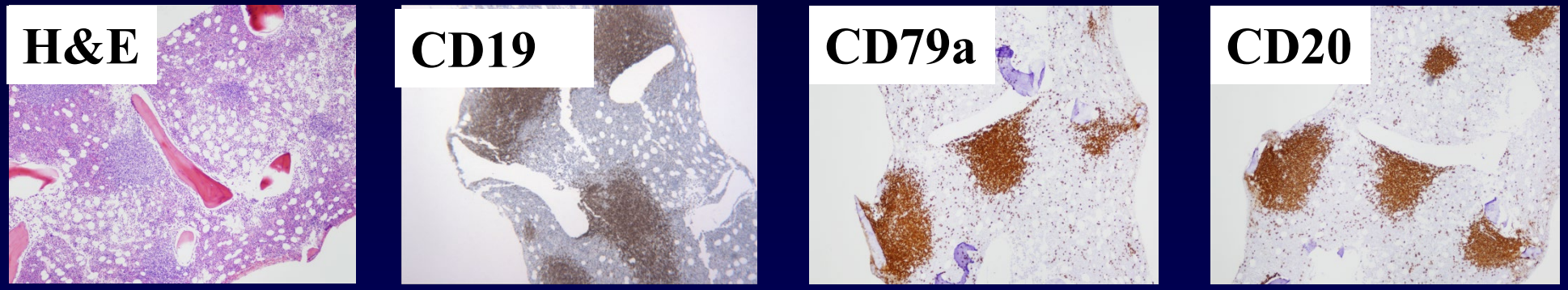
First successful CAR T cell treatment reported in NHL with CD19-CAR.CD28z (NCI)



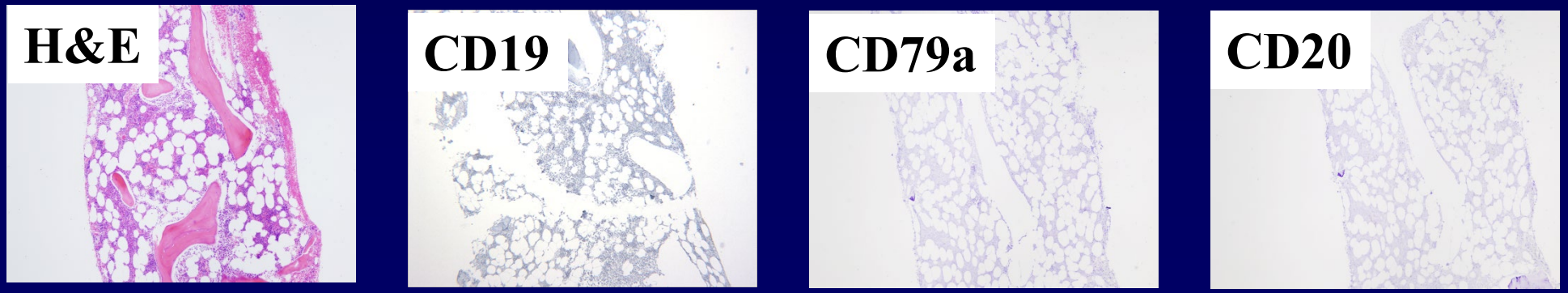
Kochenderfer, Blood 2010

Bone marrow disease cleared within 14 weeks after CAR-T cells

Before treatment: extensive involvement follicular lymphoma



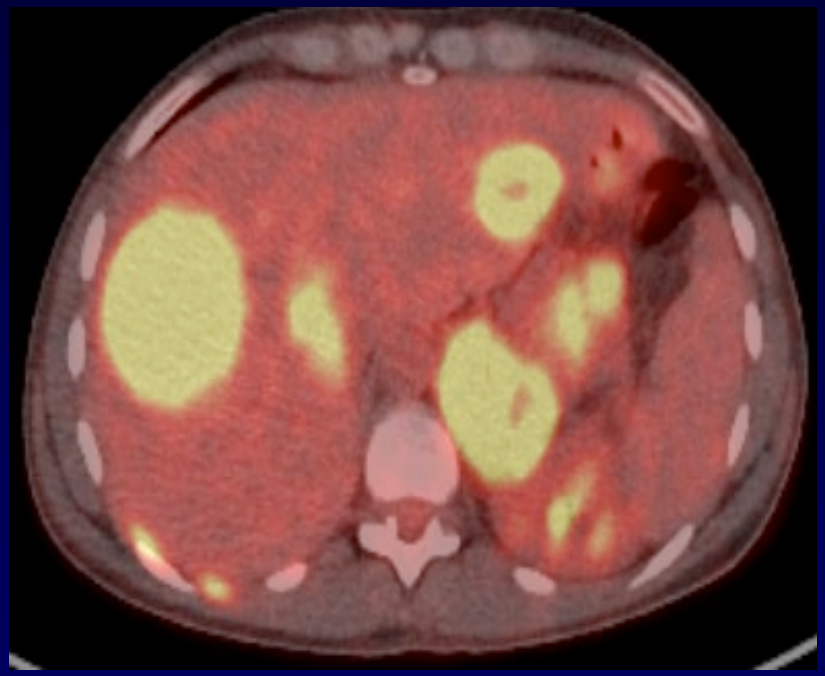
14 weeks after treatment: absence of all B-lineage cells



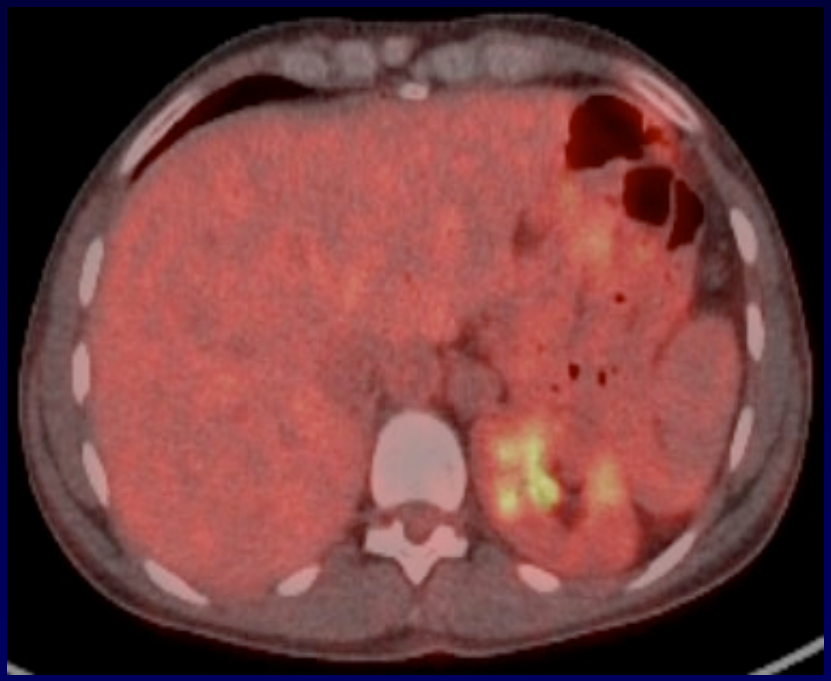
Kochenderfer, Blood 2010

Durable remissions post CD19-CAR.28z T cells but with appreciable toxicities

Before treatment



9 months after treatment



CR >21 months of chemo-refractory PMBL despite 10 prior treatments

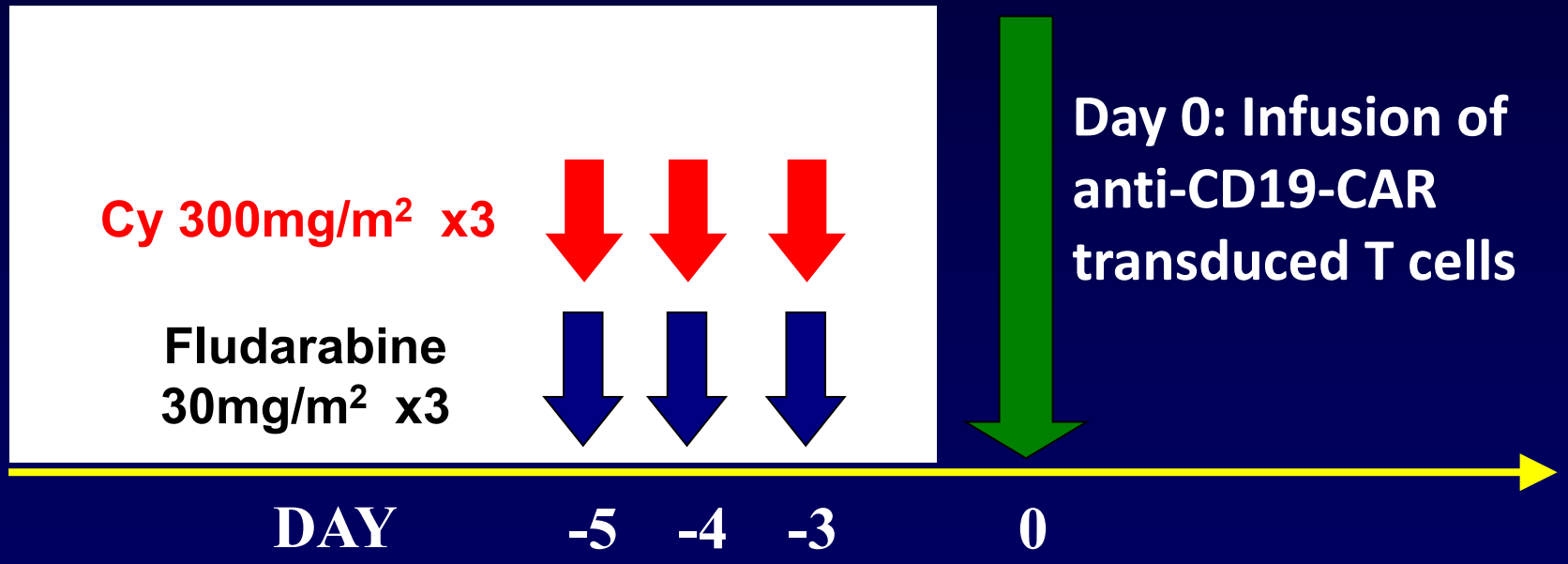
But…

All 15 patients developed SAEs (grade 3-5)

Kochenderfer, Blood 2010

CD19 CAR.28z T cells with low-dose chemotherapy to reduce toxicities- NCI

22 Advanced NHL (19 DLBCL, 2 FL, 1 MCL) ECOG 0-1



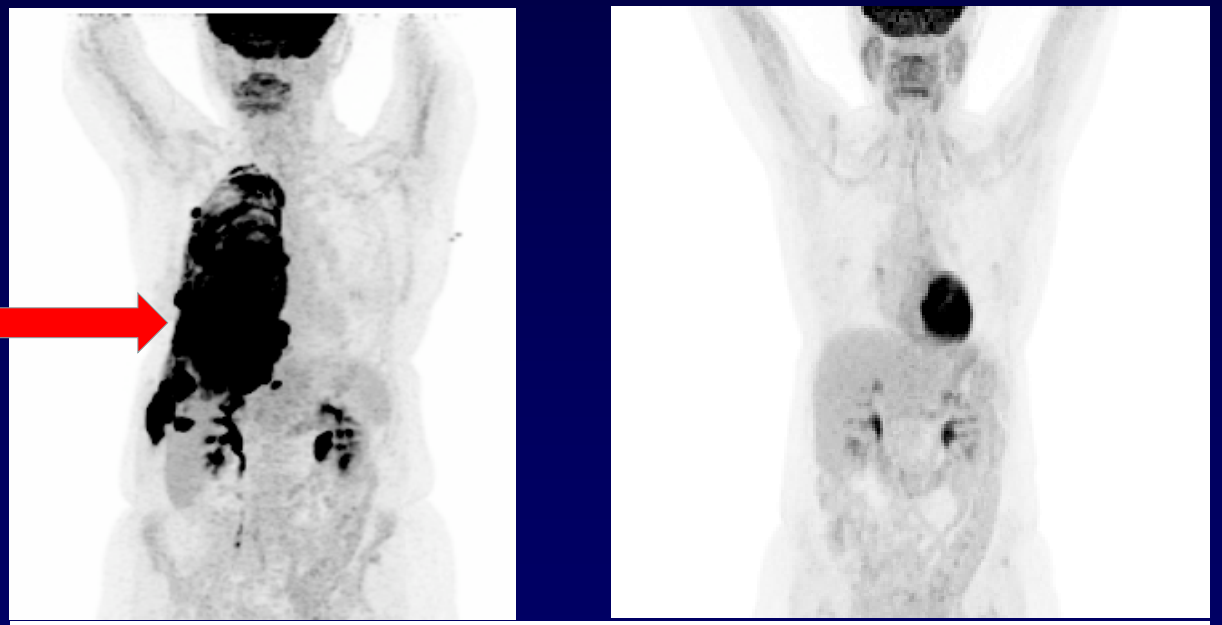
Kochenderfer et al. JCO, 2017

CD19-CAR T cells and low dose conditioning: Responses with reduced toxicities

ORR: 73%, CR in 55%, PR in 18%

55% patients grade 3-4 neurotoxicity, 18% grade 3-4 hypotension. All toxicities resolved in 2 weeks

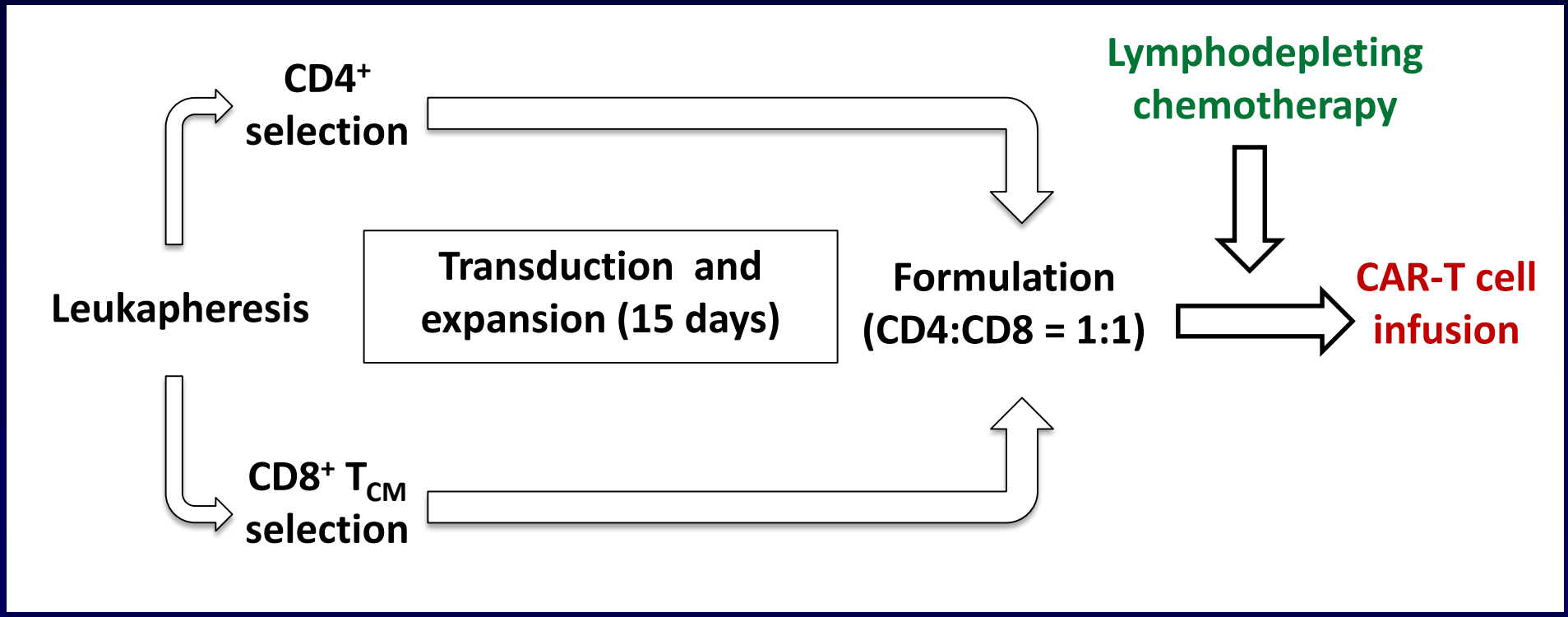
Patient 2
Chemotherapy-refractory triple-hit DLBCL



Resolution of a large pleural effusion and lymphoma masses

Kochenderfer et al. JCO, 2017

CD19 CAR.41BBz T cells for NHL: The Seattle Experience



3+3 Dose-escalation with CD19 CAR-T cell doses of $2x10^5$ - $2x10^7$/kg

Turtle et al, STM 2016 and JCI 2016

Multicenter CD19 CAR T-Cell Trials for Aggressive NHL

	Agent	Subtype	Relapsed and/or Refractory	Relapse Post-ASCT	Bridging Therapy	CAR T Design
ZUMA1[1]	Axicabtagene Ciloleucel	DLBCL PMBCL TFL	Refractory	23%	None	CD19/CD3z/ CD28
JULIET[2]	Tisagenlecleucel	DLBCL TFL	Relapsed or Refractory	49%	Allowed	CD19/CD3z/ 4-1BB
TRANSCEND[3]	Lisocabtagene Maraleucel (JCAR017)	DLBCL TFL FL Gr 3B	Relapsed or Refractory	40%	Allowed	CD19/CD3z/ 4-1BB

[1] Neelapu, et al. N. Engl J Med. 2017; 377:2531-2544
[2] Schuster et al. N. England J Med, 2017
[3] Abramson, et al. ASCO 2018; Abstract 7505.

Multicenter CD19 CAR T-Cell Trials for Aggressive NHL

	Agent	CAR T Dose	Cond. Therapy	Manufacturing Success	Treated/ Apheresed
ZUMA1[1]	Axicabtagene Ciloleucel	2 x 10^6/kg (Max 2 x 10^8)	Cy/Flu	99%	108/119 (91%)
JULIET[2]	Tisagenlecleucel	Up to 0.6-6 x 10^8	Cy/Flu or Benda	94%	111/147 (76%)
TRANSCEND[3]	Lisocabtagene Maraleucel (JCAR017)	0.5-1 x 10^8 (CD4:CD8 = 1:1)	Cy/Flu	99%	114/134 (85%)

[1] Neelapu, et al. N. Engl J Med. 2017; 377:2531-2544
[2] Schuster et al. N. England J Med, 2017
[3] Abramson, et al. ASCO 2018; Abstract 7505.

Multicenter CD19 CAR T-Cell Trials for Aggressive NHL: Responses

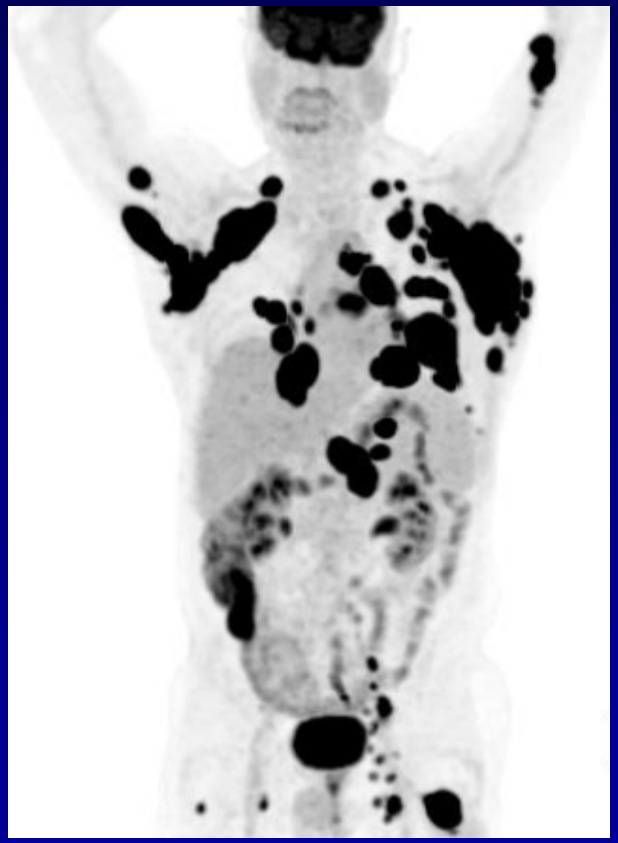
Study	Agent	N	Best ORR	Best CR rate	Follow-up mo	Durable ORR	Durable CR rate	OS at 12 mo
ZUMA1[1]	Axicabtagene Ciloleucel	108	82%	58%	12	42%	40%	59%
JULIET[2]	Tisagenlecleucel	93	52%	40%	12	34%	29%	49%
TRANSCEND[3]	Lisocabtagene Maraleucel (JCAR017)	73	80%	59%	6	47%	41%	N/A

[1] Neelapu, et al. N. Engl J Med. 2017; 377:2531-2544
[2] Schuster et al. N. England J Med, 2017
[3] Abramson, et al. ASCO 2018; Abstract 7505.

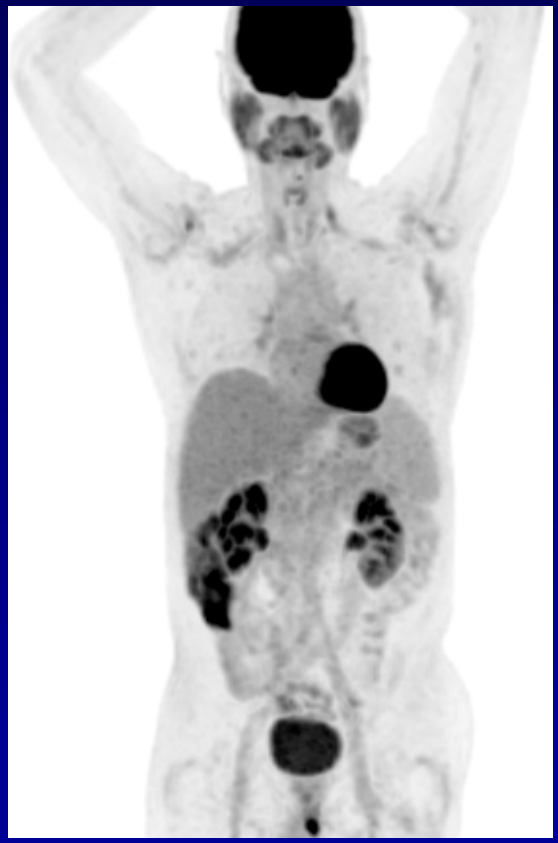
Patient Case: Ongoing 9+ mo Durable CR in Refractory DLBCL

- 62-yo M with DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-Lenalidomide
- No response to last 3 lines of therapy

Baseline



3 months



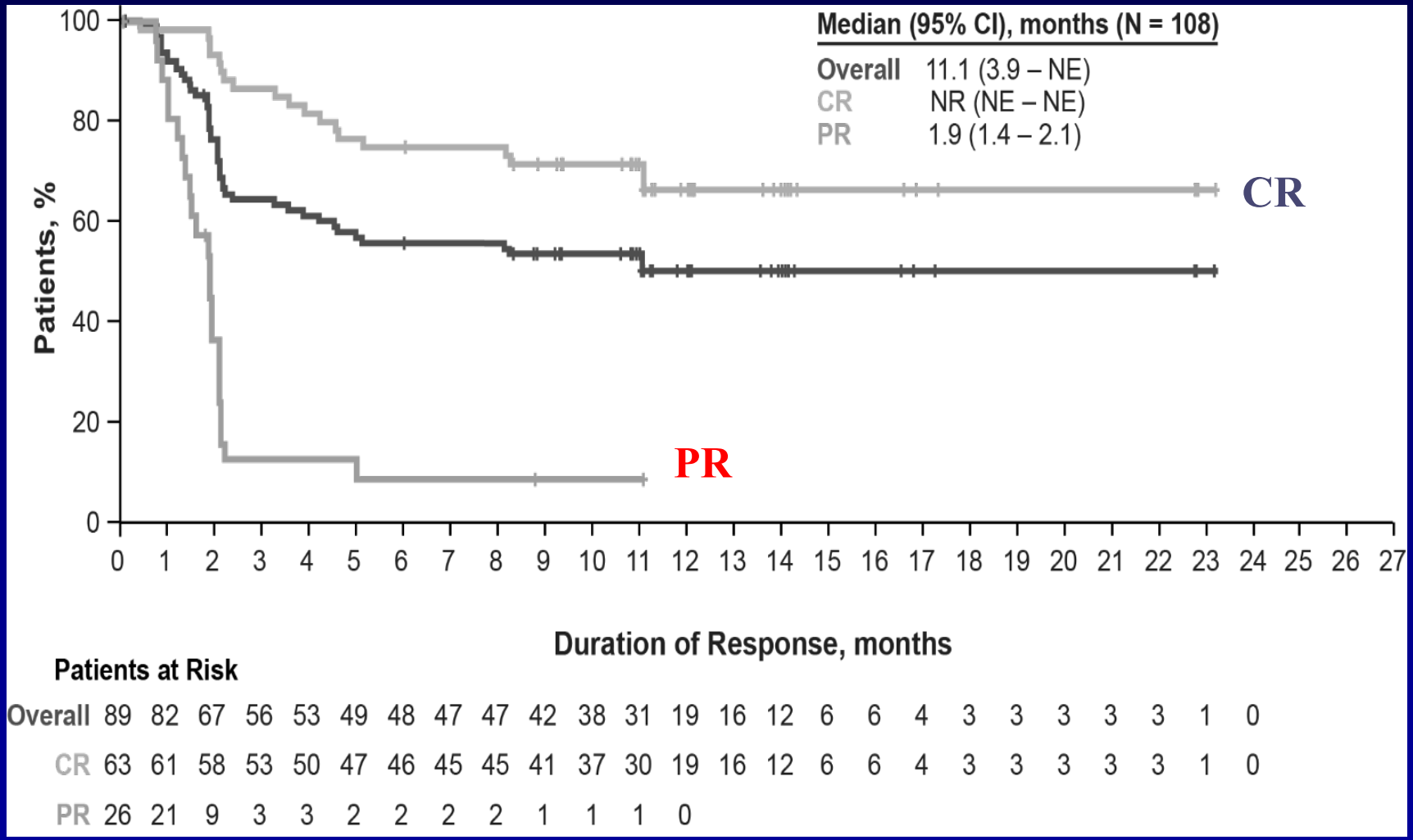
Neelapu & Locke et al ASH 2016, #LBA-6

ZUMA-1: Long Term Follow-up
Best Objective Response

	Phase 2 Primary Analysis (n = 101)		Phase 1 and 2 Updated Analysis (N = 108)	
Median follow-up, mo	8.7		15.4	
	ORR	CR	ORR	CR
Best response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 month post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days

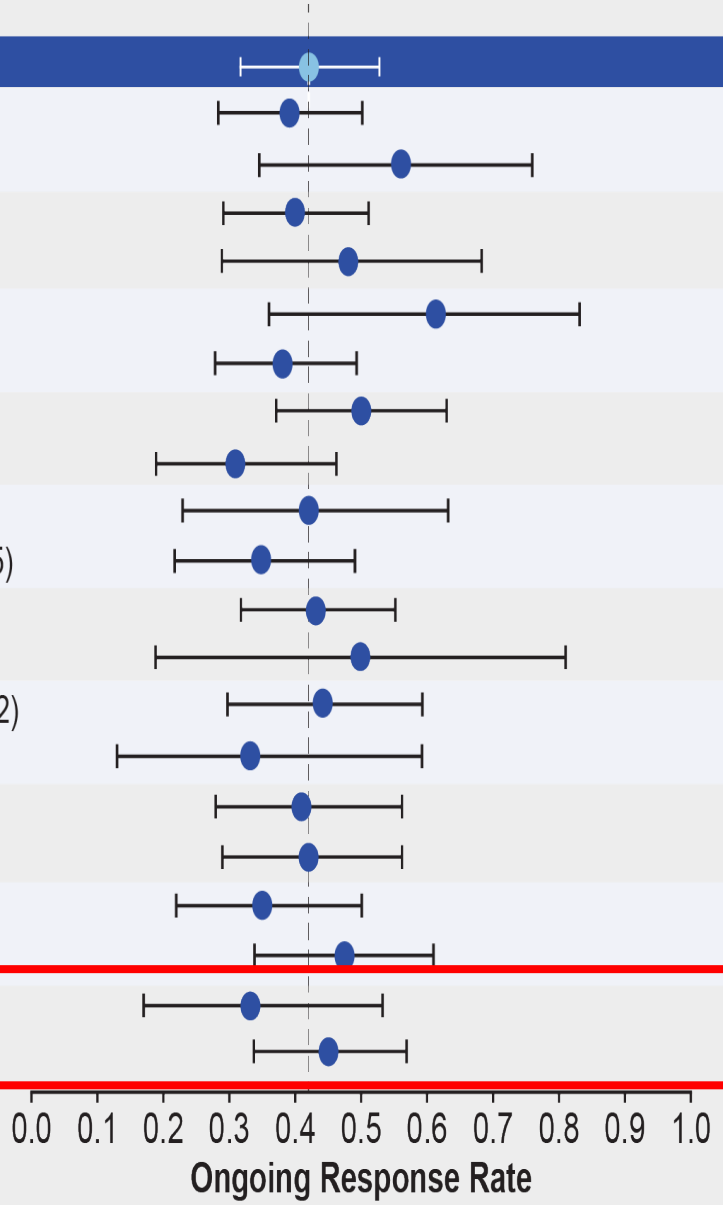
ZUMA-1: Duration of Response by Best Objective Response



- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients having ongoing CR at 24 months

ZUMA-1

Ongoing Responses (> 1 year) Across Key Covariates



		n[a]	ORR	LCI[b]	UCI
Overall (N=108)		45	0.42	0.32	0.52
Refractory Subgroup	Refractory to ≥ 2nd line therapy (N=80)	31	0.39	0.28	0.50
	Relapse post ASCT (N=25)	14	0.56	0.35	0.76
Age	< 65 Years (N=81)	32	0.40	0.29	0.51
	≥ 65 Years (N=27)	13	0.48	0.29	0.68
Disease Stage	I-II (N=18)	11	0.61	0.36	0.83
	III-IV (N=90)	34	0.38	0.28	0.49
IPI Risk Score	0-2 (N=60)	30	0.50	0.37	0.63
	3-4 (N=48)	15	0.31	0.19	0.46
Treatment History	Primary Refractory Disease (N=27)	11	0.41	0.22	0.61
	Refractory to 2 Consecutive Lines (N=55)	19	0.35	0.22	0.49
CD19 Status	Positive (N=77)	33	0.43	0.32	0.55
	Negative (N=10)	5	0.50	0.19	0.81
Cell of Origin	Germinal Center B Cell-like (GCB) (N=52)	23	0.44	0.30	0.59
	Activated B-Cell like (ABC) (N=18)	6	0.33	0.13	0.59
CD4/CD8 Ratio	>1 (N=51)	21	0.41	0.28	0.56
	≤1 (N=57)	24	0.42	0.29	0.56
Tocilizumab Use	Yes (N=49)	17	0.35	0.22	0.50
	No (N=59)	28	0.47	0.34	0.61
Corticosteroid Use	Yes (N=30)	10	0.33	0.17	0.53
	No (N=78)	35	0.45	0.34	0.57

CAR T-Cell Toxicity

- Cytokine release syndrome (CRS)
- CAR-related encephalopathy syndrome (CRES)
- B-cell aplasia
- Hemophagocytic lymphohistiocytosis (HLH)

CAR T-Cell Toxicity

Cytokine Release Syndrome (CRS)

- Early hemodynamic changes associated with capillary leak
  - High fever, hypotension, tachycardia, decrease in protein/albumin, weight gain
- Coagulopathy and increased transfusion requirements
- Increased risk of hepatic and renal dysfunction
  - Elevated AST, ALT, bilirubin, alk phos, creatinine
- Cardiac arrhythmias
- Elevated serum cytokines
- Elevated serum CRP and ferritin
- Usually responds to tocilizumab +/- steroids

Neurotoxicity

- Often presents with word finding difficulties and can progress to coma
- May be associated with cerebral edema or seizures
- Onset 2-4 days after CRS
- Usually reversible, but may be fatal
- Not clear if treatments are effective (usually treated with tocilizumab or steroids)

Neelapu, et al. Nat Rev Clin Oncol. 2018;15(1):47-62.

Multicenter CD19 CAR T-Cell Trials for Aggressive NHL: Safety

Study	Agent	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Toci usage	Steroid usage
ZUMA1[1]	Axicabtagene Ciloleucel	108	93%	13%	65%	31%	45%	29%
JULIET[2]	Tisagenlecleucel	111	58%	22%	21%	12%	15%	11%
TRANSCEND[3]	Lisocabtagene Maraleucel (JCAR017)	102	37%	1%	23%	13%	17%	21%

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 1 cardiac arrest, 1 HLH, 1 pulmonary embolism

CAR T-cells: Efficacy

- **August 30, 2017: FDA Approves tisagenlecleucel (formerly CTL019) for the treatment of children and young adults (up to 25 years of age) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.**

October 19, 2017: FDA Approves axicabtagene ciloleucel (formerly KTE-C19) for the treatment of adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment

May 1st, 2018 : FDA Approves tisagenlecleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two lines of systemic therapy (DLBCL, high grade B-cell lymphoma and DLBCL arising from FL)

CD19 CARs – Remaining Issues

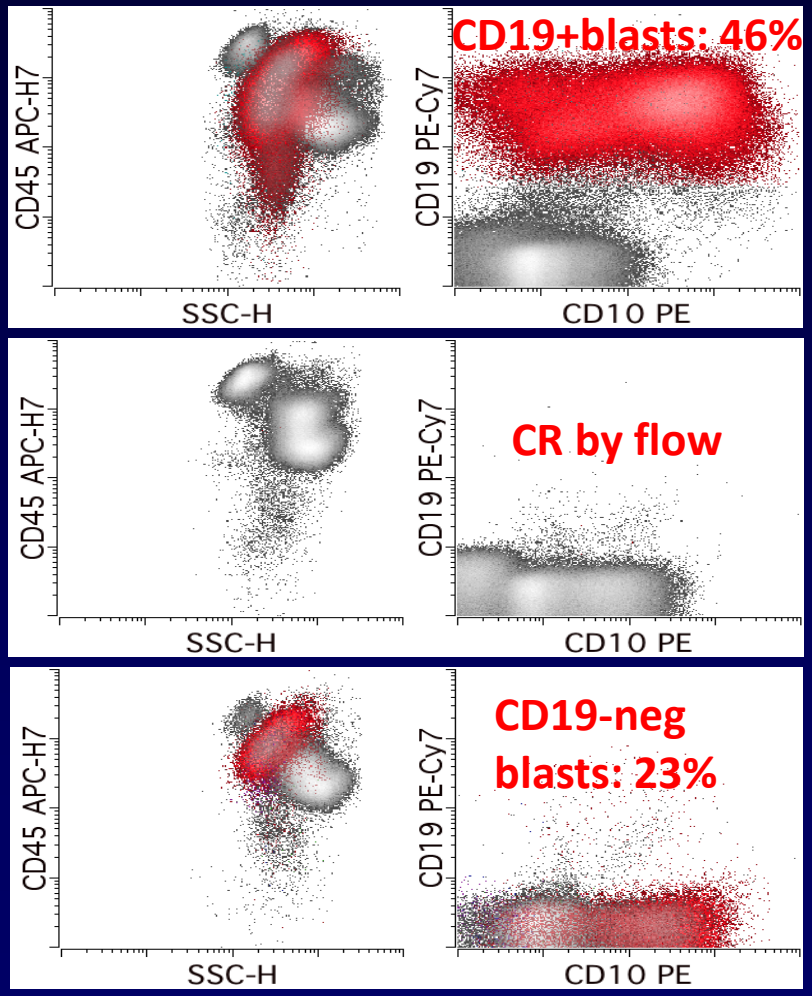
- Managing CRS/Neurotoxicity
- Complex study especially in multicenter setting
- Managing prolonged B-cell depletion
- Expensive! Insurance Issues?
- CAR attributes for potency remain unclear:
  - How many endogenous T-cell clones are needed for a response?
  - Which host's/ tumor characteristics are driving (or limiting) this response?
- Immune escape through antigen loss

CD19 antigen-negative relapse in B cell malignancies after CD19 CAR-T cells

Before CAR-T cells

Day 14 after CAR-T cells

Day 106 after CAR-T cells



CD19-neg relapse in B-ALL, NHL and CLL

in B-ALL:
MSKCC: 2/14
UPenn: 13/20
FHCRC: 2/9

40%

Turtle, J Clin Invest, 2016
Lee, ASH, 2015
Park, ASCO, 2015
Maude, ASCO, 2016
Turtle, J Clin Oncol, 2017
Evans, Br J Haem, 2015

Guidelines for CAR T-cell Therapy

Prior to CAR T cell infusion

- Baseline brain magnetic resonance imaging to rule out any central nervous system disease
- Central venous access with double or triple lumen catheter
- Cardiac monitoring by telemetry starting on the day of CAR T cell infusion and continued until CRS resolves
- Tumour lysis prophylaxis for patients with bulky tumours
- Seizure prophylaxis with levetiracetam at 750 mg orally q12h for 30 days starting on the day of infusion for CAR T-cell therapies known to cause CRES
- Hospitalization recommended for at least 7 days after CAR T-cell therapy

Monitoring after CAR T cell infusion

- Vitals q4h, strict input and output, daily weights
- Daily history and physical examination
- Daily blood counts and complete metabolic profile
- C-reactive protein and ferritin levels daily starting on day 0
- Assessment and grading of CRS should be done at least twice daily and whenever there is a change in patient's status
- Assessment and grading for CRES using the CARTOX 10-point neurological assessment should be done at least every 8 hours and should include writing a sentence twice daily
- Maintenance IV fluids with normal saline to ensure adequate hydration

Notifications and contingency orders

- Notify physician
  - ✓ SBP >140 or <90 mmHg
  - ✓ Heart rate >120 or <60 / min or arrhythmia
  - ✓ Respiratory rate >25 or <12 / min
  - ✓ Oxygen Saturation <92% on room air
  - ✓ Urine output <1500 mL/24h
  - ✓ Upward trends in creatinine or liver function tests
  - ✓ Tremors or jerky movements in extremities
  - ✓ Change in mental status (alertness, orientation, speech, and ability to write a sentence)
- For temperature greater than 38.3 ^{0}C, send blood cultures (central and peripheral) and urine for urinalysis and culture, obtain portable chest x-ray, and notify physician
- For patients with neutropenia and fever, start empiric broad-spectrum antibiotics
- Do not administer corticosteroids unless approved by physician
- If patient develops CRES, withhold oral intake and notify physician
- PRN medications
  - ✓ Acetaminophen (1st choice) or ibuprofen (2nd choice if not contraindicated) for fever > 38.3 ^{0}C
  - ✓ Cooling blanket prn fever > 38.3 ^{0}C
  - ✓ Normal saline 500 to 1000 mL bolus prn SBP <90 mmHg; may repeat once if SBP <90 mmHg after 1st bolus
  - ✓ PRN tocilizumab to be activated on physician order

Neelapu, et al. Nat Rev Clin Oncol. 2018;15(1):47-62.

Guidelines for the Management of CRS

CRS Grade	Symptom or Sign	Management
Grade 1	Fever or grade 1 organ toxicity	• Acetaminophen and hypothermia blanket for fever • Ibuprofen may be used as second option for fever if not contraindicated • Assess for infection with blood and urine cultures, and chest x-ray • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab 8 mg/kg or siltuximab 11 mg/kg IV for persistent (>3 days) and refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500 – 1000 mL normal saline • May give a second IV fluid bolus if SBP remains <90 mmHg • Tocilizumab 8 mg/kg[b] IV or siltuximab 11 mg/kg IV for hypotension refractory to fluid boluses; may be repeated if needed • If hypotension persists after two fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain echocardiogram and initiate other methods of hemodynamic monitoring • In patients at high-risk[c] or if hypotension persists after 1-2 doses of tocilizumab/siltuximab, may use dexamethasone 10 mg IV every 6h • Manage fever and constitutional symptoms as in grade 1
	Hypoxia (FiO_2<40%)	• Supplemental oxygen • Tocilizumab/siltuiximab +/- corticosteroids and supportive care as in hypotension
	Grade 2 organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab/siltuximab +/- corticosteroids and supportive care as in hypotension
Grade 3	Hypotension	• IV fluid boluses as needed as in grade 2 • Tocilizumab/siltuximab as in grade 2 if not administered previously • Vasopressors as needed • Transfer to ICU, echocardiogram and hemodynamic monitoring as in grade 2 • Dexamethasone 10 mg IV every 6h; increase to 20 mg IV every 6h if refractory • Manage fever and constitutional symptoms as in grade 1
	Hypoxia (FiO_2≥40%)	• Supplemental oxygen including high flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab/siltuximab + corticosteroids and supportive care as above
	Grade 3 organ toxicity or grade 4 transaminitis	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab/siltuiximab + corticosteroids and supportive care as above
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as in grade 3 • Methylprednisolone 1 gram/day IV may be used in place of dexamethasone • Manage fever and constitutional symptoms as in grade 1
	Hypoxia	• Mechanical ventilation • Tocilizumab/siltuximab + corticosteroids and supportive care as above
	Grade 4 organ	• Symptomatic management of organ toxicities as per standard

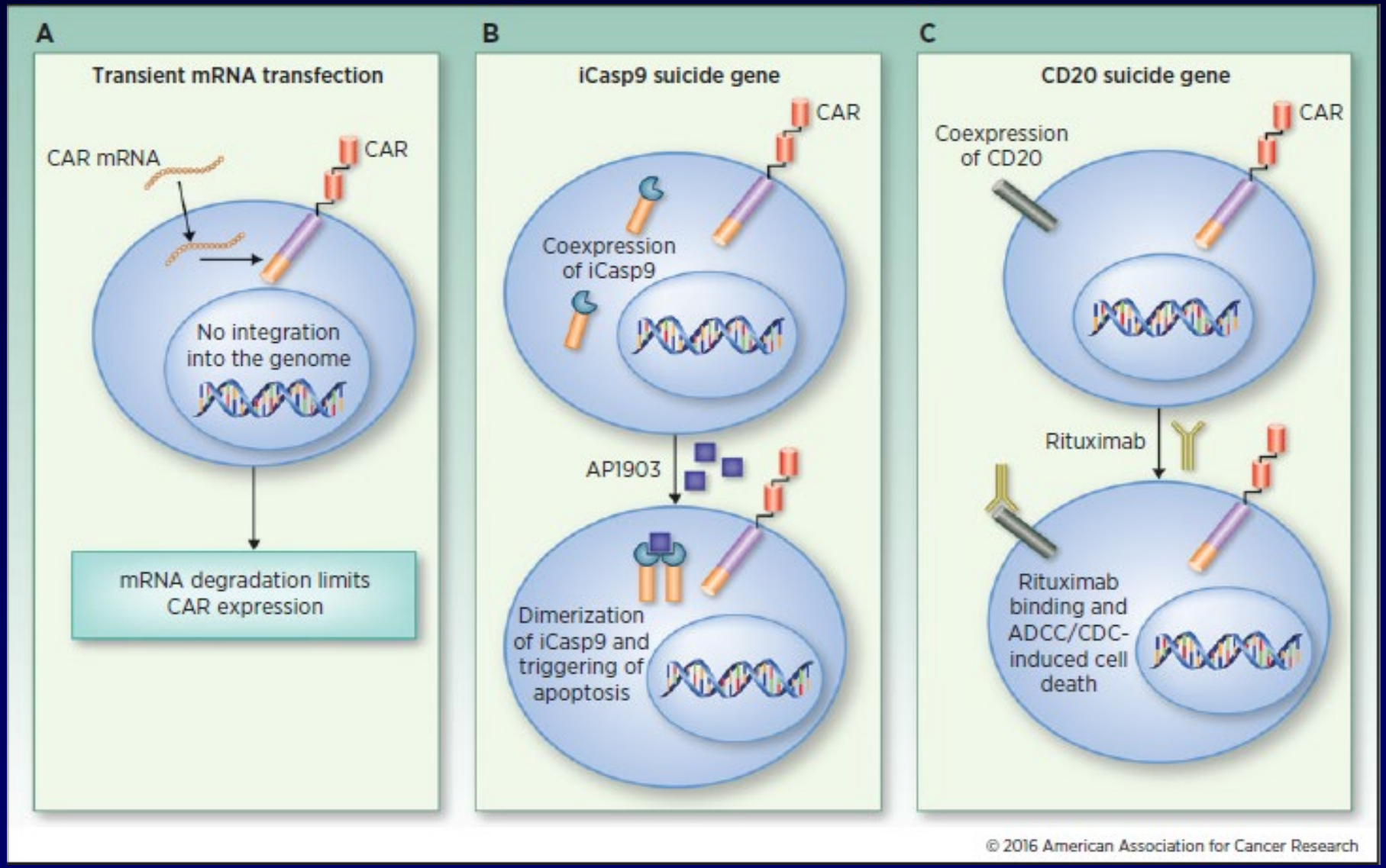
Neelapu, et al. Nat Rev Clin Oncol. 2018;15(1):47-62.

Guidelines for the Management of CRES

Grade	Management
Grade 1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam (0.25-0.5 mg IV every 8h) or haloperidol (0.5 mg IV every 6h) may be used for agitated patients with careful monitoring • Neurology consultation • Fundoscopic exam to assess for papilledema • MRI brain with and without contrast; diagnostic lumbar puncture with opening pressure; MRI spine if focal peripheral neurological deficits; CT scan of brain may be performed if MRI brain is not feasible • Daily 30 min EEG until toxicity symptoms resolve; if no seizures on EEG, continue levetiracetam 750 mg every 12h • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Box 2 • Consider tocilizumab 8 mg/kg[b] or siltuximab 11 mg/kg IV if associated with concurrent CRS
Grade 2	• Supportive care and neurological work-up as per grade 1 • Tocilizumab 8 mg/kg[b] or siltuximab 11 mg/kg IV if associated with concurrent CRS • Dexamethasone 10mg IV every 6h or methylprednisolone 1 mg/kg IV every 12h if refractory to anti-IL-6 therapy or for CRES without concurrent CRS • Consider ICU transfer if associated with grade 2 or greater CRS
Grade 3	• Supportive care and neurological work-up as per grade 1 • ICU transfer is recommended • Tocilizumab/siltuximab if associated with concurrent CRS as per grade 2 and if not administered previously • Corticosteroids as above for worsening symptoms despite anti-IL-6 therapy or for CRES without concurrent CRS; Continue corticosteroids until improvement to grade 1 and then taper • Stage 1 or 2 papilledema with CSF opening pressure < 20 mmHg, treat as per algorithm in Box 3 • Consider repeat neuro-imaging (CT or MRI) every 2-3 days if persistent ≥ grade 3 CRES
Grade 4	• Supportive care and neurological work-up as per grade 1 • ICU monitoring; Consider mechanical ventilation for airway protection • Tocilizumab/siltuximab and repeat neuro-imaging as per grade 3 • High-dose corticosteroids (e.g. methylprednisolone IV 1 g/day x 3 days followed by rapid taper at 250 mg every 12h x 2 days, 125 mg every 12h x 2 days, and 60 mg every 12h x 2 days); Continue corticosteroids until improvement to grade 1 and then taper • For convulsive status epilepticus, treat as per algorithm in Box 2 • Stage 3, 4, or 5 papilledema, CSF opening pressure ≥ 20 mmHg, or cerebral edema, treat as per algorithm in Box 3

Neelapu, et al. Nat Rev Clin Oncol. 2018;15(1):47-62.

Strategies to regulate CAR T-cells persistence…and limit "collateral damage"



Maus, M. and June, CH. Clin. Cancer Res; 2016;22:1875

Future Directions in CAR T-cell Therapy….

- Combination with checkpoint blockade antibodies

- Novel Antigenic Targets

Beyond CD19: Extending the CAR antigen repertoire

Specificity/ Construct	Author(s)	Center	Response
CD20- 1st gen no lymphodepletion	Till. Blood 2008 Jensen. Mol Ther 2010	FHCRC/ COH	DLBCL: NR
CD20- 3rd gen 28/41BB - limited lymphodepletion	Till et al, Blood 2011	FHCRC	Indolent NHL/MCL 0/3 CR
CD20- 2nd gen 41BB with lymphodepletion	Wang, Clin Immunol 2014; Zhang, Sig Trans Targ Ther, 2016	Chinese PLA General	R/R DLBCL 6/11 CR + 3/11 PR
Kappa	Ramos, JCI, 2016	Baylor	2/9 CR and 1/9 PR in NHL/CLL
CD30	Ramos et al, JCI 2017	Baylor	2/3 CR - ALCL / DLBCL

Myeloma: BCMA

Hudecek, Blood, 2010 (FHCRC)

Can the success of CAR T-cell therapy for B-cell malignancies be translated to solid tumors?

B-cell Malignancies

Solid Tumors

Yes…. but not so easily….or too fast...

Solid Tumors Targets

Cancer Site	Target antigens
Lung	Erb2, EphA2,GD3
Prostate	Erb2, Muc 1, PSMA, PSCA
Breast	Erb2, Erb3/4, Lewis Y, Mesothelin, Muc 1
Ovary	Erb3/4, Lewis Y, FR-a, Muc 1, NKG2D ligands
Brain	ErbB family, EGFRvIII, IL13Ra2, EphA2, B7H3
Melanoma	MAGE1, HMW-MAA, GD2, GD3, NY-ESO-1,
Sarcoma	GD2, NKGD2 ligands, B7H3

Selected Clinical Trials with CAR T-cells in Solid Tumors

Target (reference)	Indication	Preclinical antitumor efficacy	Clinical efficacy/safety	Ongoing trials
Solid tumor targets				
EGFRvIII (38, 70)	Glioma, glioblastoma, head and neck cancer	Human glioma cells *in vitro* and *ex vivo*, glioblastoma xenograft model	None reported	NCT02209376 NCT01454596
ERBB2 (42, 71, 72)	Glioblastoma, sarcoma	Tumor cell lines, breast cancer xenograft model	Stable disease for 12 weeks to 14 months in 24% of patients ($n = 17$)	NCT00902044 NCT01109095 NCT00889954
Mesothelin (43, 61. 62, 73)	Mesothelioma, pancreatic cancer, ovarian cancer, lung cancer	Mesothelioma xenograft model	Stable disease in 67% of patients at day 28 ($n = 6$)	NCT02159716 NCT02414269 NCT01583686
Carbonic anhydrase IX (74, 75)	RCC	RCC cells *in vitro*	Liver toxicity affected several patients	None
PSMA (folate hydrolase 1; refs. 40, 44)	Prostate cancer	Prostate adenocarcinoma murine model	Stable disease in 50% of patients treated ($n = 4$)	NCT01140373
FAP (76–78)	Mesothelioma	Murine pancreatic cancer model, lung cancer xenograft model	None reported	NCT01722149
Carcinoembryonic antigen (79)	Lung, colorectal, gastric, breast, and pancreatic cancers	Murine model of liver metastases	None reported	NCT02349724
5T4 (trophoblast glycoprotein; ref. 80)	Solid tumors	Murine models of melanoma and colon carcinoma	None reported	None

Maus, M. and June, CH. Clin. Cancer Res; 2016;22:1875

CAR T-cell Therapy for Solid Tumors

- Several clinical trials, but efficacy has been low

- The best responses reported has been in trials using CAR T-cells specific for the solid tumor antigens ***mesothelin, PSMA or ERBB2***
  - Stable disease in 24% to 67% of the patients

Factors limiting the efficacy of CAR T-cell therapy for Solid Tumors

- Identification of suitable target antigens that are tumor-specific
- Limited extravasation/penetration of infused CAR T-cells into solid masses
- "Hostile" microenvironment: Negative immuno-regulatory signals and/or cells that rendered CAR T-cells anergic/tolerant: TGF-beta, PDL1

Suitable target antigens

- Most epithelial tumor-associated antigens are shared proteins also found in normal tissues:
  - Serious adverse events can occur
  - CAR targeting her2/neu → Cardiopulmonary toxicity and death within days in one patient *(Morgan, RA et al. Mol. Ther. 2010;18:843)*
  - Long-term persistence of CAR T-cells can be potentially problematic…autoimmune damage of vital organs that would outweigh the benefits of this therapy

CAR T-cell therapy for Solid Tumors: Emerging Strategies

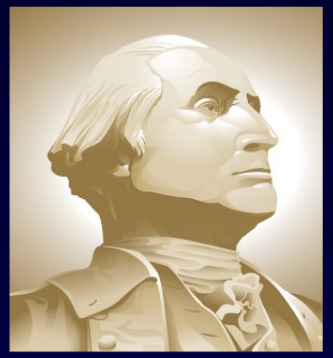
- Identification of antigens with sufficient cancer-specific expression..
  - Neo-antigens that arise from mutations in the tumor but not in healthy tissues
  - Aberrantly glycosylated self-antigens (Tn-Glycoform of membrane mucin MUC1) present mainly in tumor cells *(Posey, A. et al. Immunity 2016;44:1444)*

CAR T-cells for Solid Tumors

- Early clinical trials with CAR T-cells for solid tumors has shown a unique set of challenges for this therapy

- Lessons learned from these clinical trials (ie. minimal efficacy and adverse side effects) are informing the design of the new generation of CAR T-cells with better tumor specificity, improved migration to the tumor site and able to overcome physical and regulatory barriers in the tumor microenvironment

- ***It is not a matter of whether is going to work….it is a matter of when will work*****…..**thanks to the rapid progress in new technologies and a better understanding of the barriers that need to be surmounted to make CAR T-cell therapy for solid tumors a reality….



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THANKS

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