Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Cancer Immunotherapy in Practice

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MGH Cancer Center

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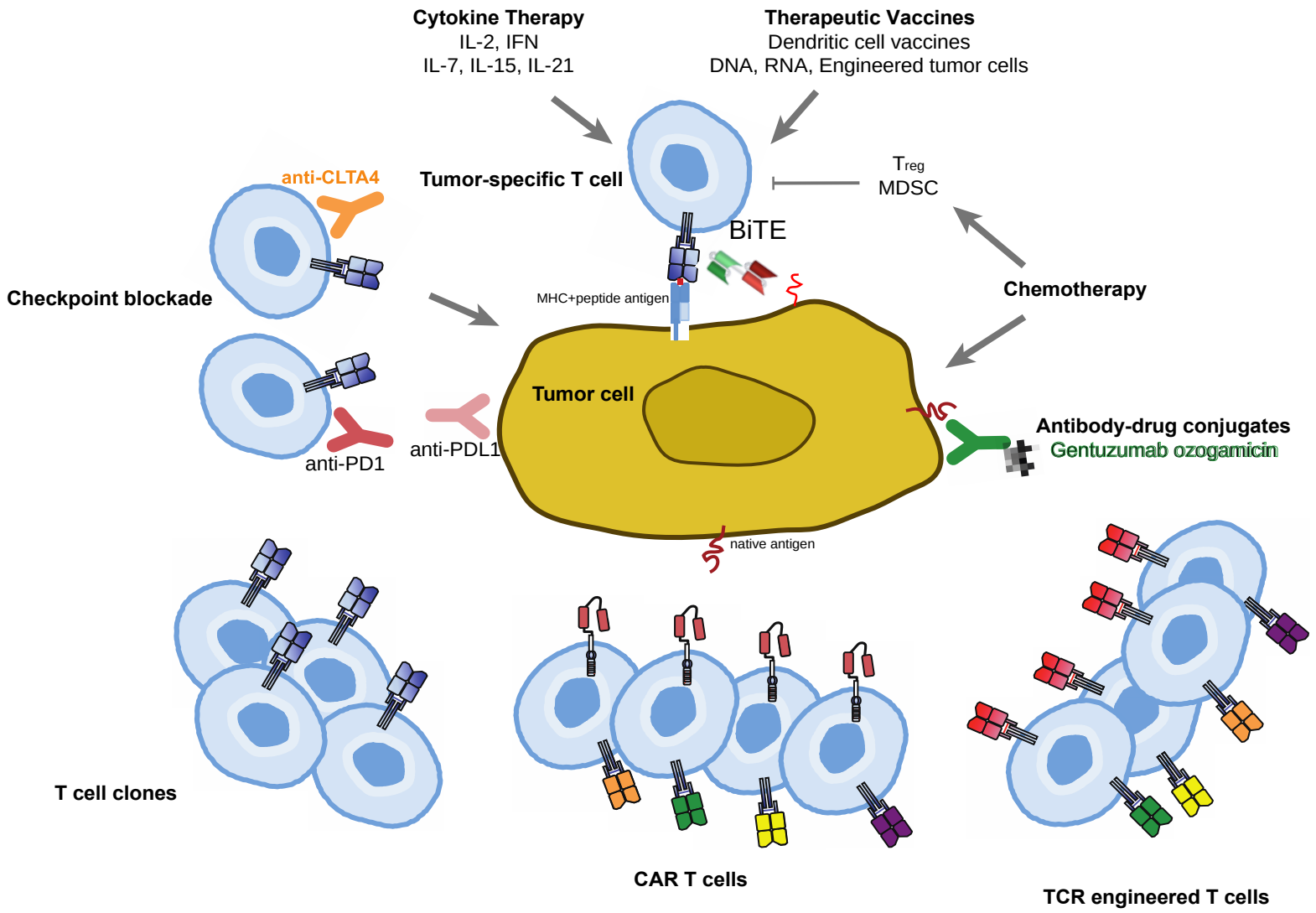
Disclosures

- Consulting Fees: Kite, Arcellx, Novartis, BMS, Iovance
- I will be discussing non-FDA approved indications during my presentation.

Learning Targets

- Overview of Cellular Therapy
- Current Indications and Evolving Use
- Toxicities Associated with Delivery of Care
- Moving Into Solid Tumors
- Infrastructure for Cellular Therapy
- Case Studies

Ways to get T cell immune responses to cancer



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We've Been Here Before..

SPECIAL REPORT

USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

A Preliminary Report

Steven A. Rosenberg, M.D., Ph.D.,
Beverly S. Packard, Ph.D.,
Paul M. Aebersold, Ph.D., Diane Solomon, M.D.,
Suzanne L. Topalian, M.D.,
Stephen T. Toy, Ph.D., Paul Simon, Ph.D.,
Michael T. Lotze, M.D., James C. Yang, M.D.,
Claudia A. Seipp, R.N., Colleen Simpson, R.N.,
Charles Carter, Steven Bock, M.D.,
Douglas Schwartzentruber, M.D.,
John P. Wei, M.D., and Donald E. White, M.S.

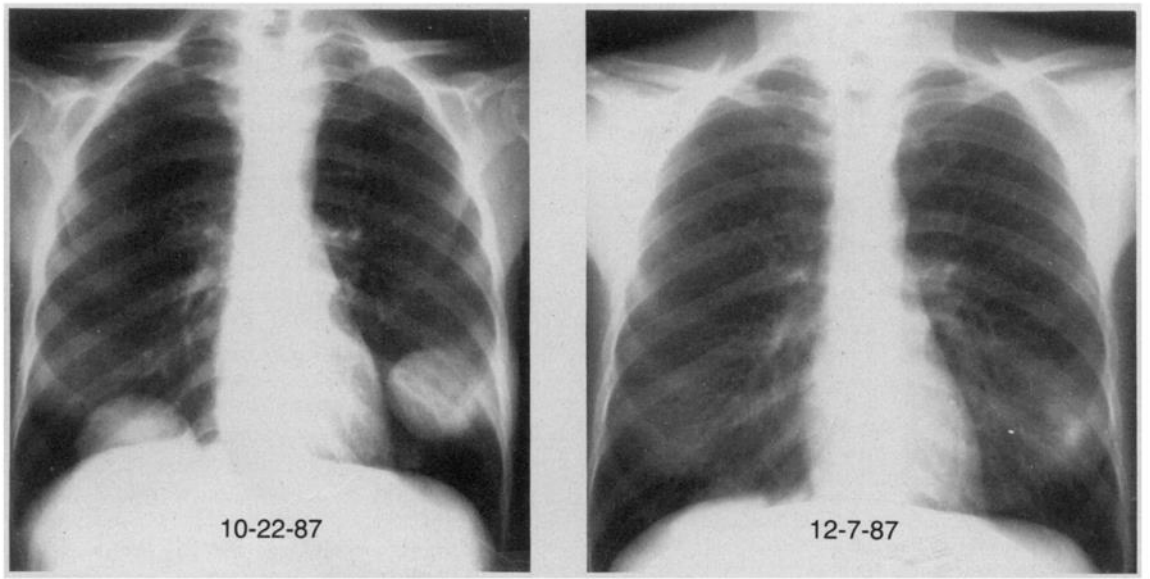

Figure 1. Pulmonary Metastases in Patient 4 before (Left) and after (Right) One Course of TIL, Interleukin-2, and Cyclophosphamide. The later chest film shows regression of the metastases. Multiple subcutaneous metastases regressed completely as well.

NEJM 1988

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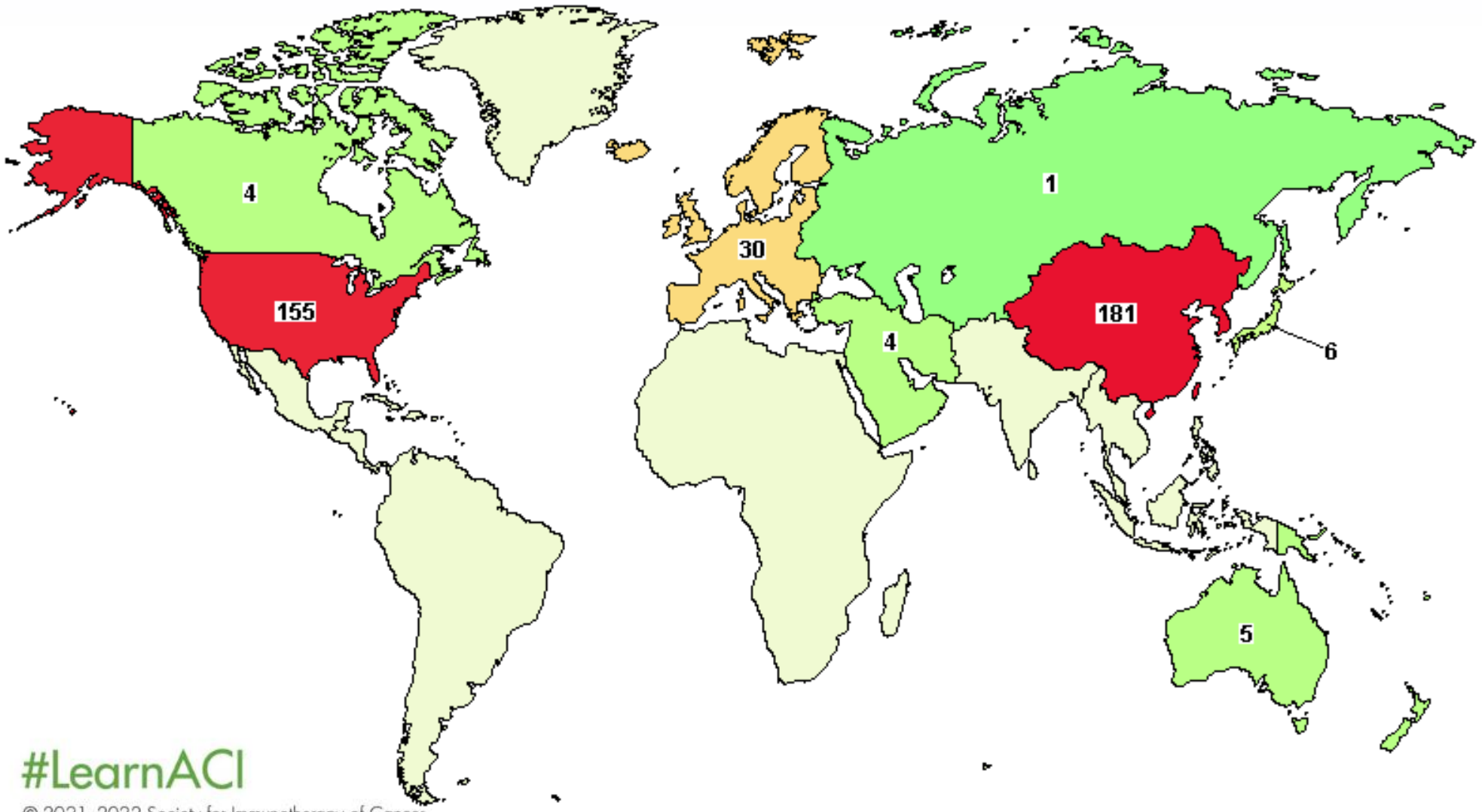
Rush Hour



Total Trials by date:

1059 – 01/24/22

370 – 04/25/19

325 – 10/29/18

317 – 09/26/18

220 – 08/27/17

183 – 04/13/17

123 – 05/19/16

88 – 12/10/15

77 – 09/2015

<5 – 2010

Map as of 04/25/19

Search term: "chimeric antigen receptor"

ClinicalTrials.gov

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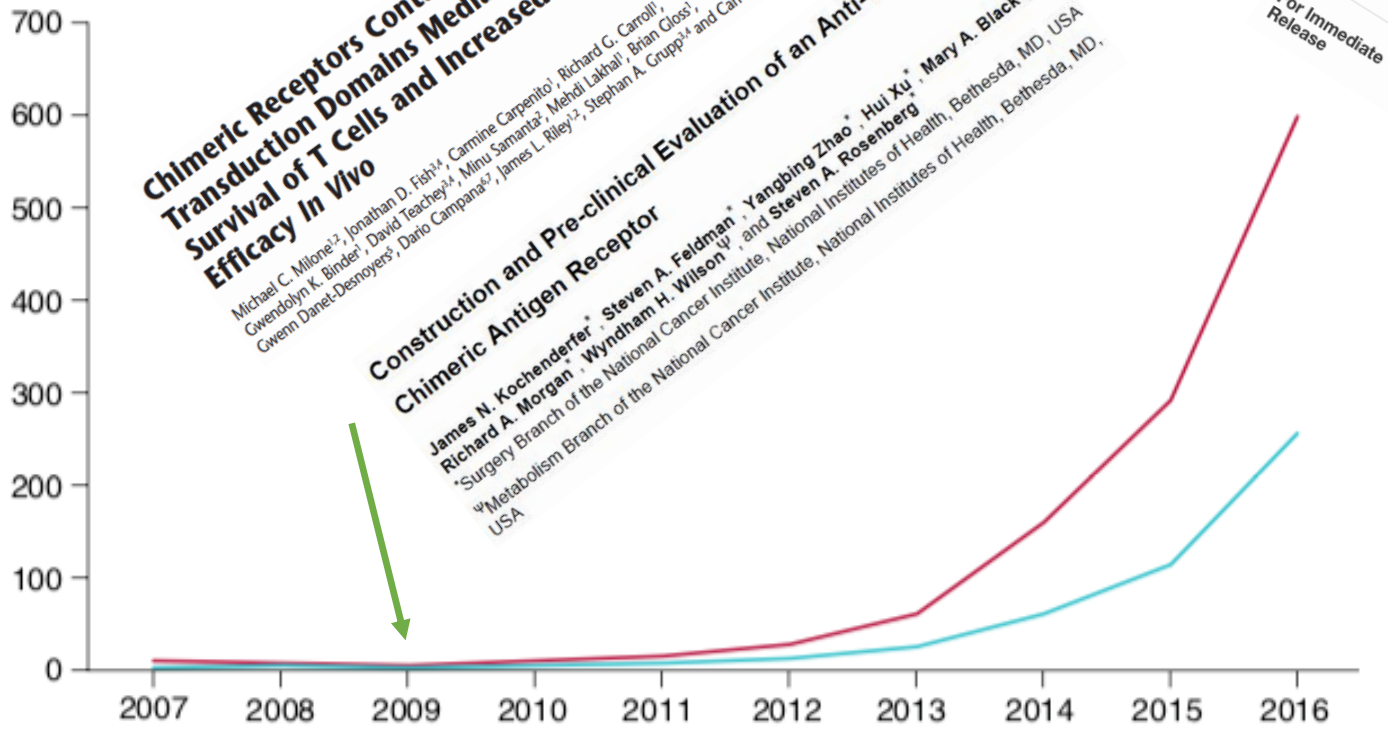
"Are we there yet?"



Chimeric Receptors Containing CD137 Signal Transduction Domains Mediate Enhanced Survival of T Cells and Increased Antileukemic Efficacy In Vivo

Michael C. Milone[1,2], Jonathan D. Fish[3,4], Carmine Carpenito[1], Richard G. Carroll[1], Gwendolyn K. Binder[1], David Teachey[3,4], Minu Samanta[2], Mehdi Lakhal[1], Brian Gloss[1], Gwenn Danet-Desnoyers[5], Dario Campana[6,7], James L. Riley[1,2], Stephan A. Grupp[3,4] and Carl H. June[1,2]

Construction and Pre-clinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor

James N. Kochenderfer*, Steven A. Feldman*, Yangbing Zhao*, Hui Xu*, Mary A. Black*, Richard A. Morgan*, Wyndham H. Wilson[ψ], and Steven A. Rosenberg*

*Surgery Branch of the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
[ψ]Metabolism Branch of the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

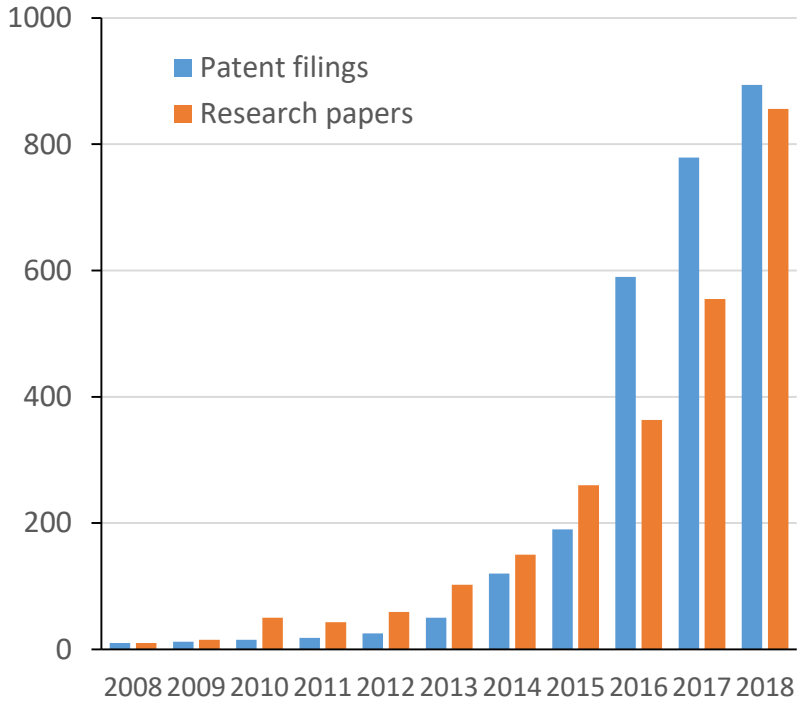
For Immediate Release

August 30, 2017

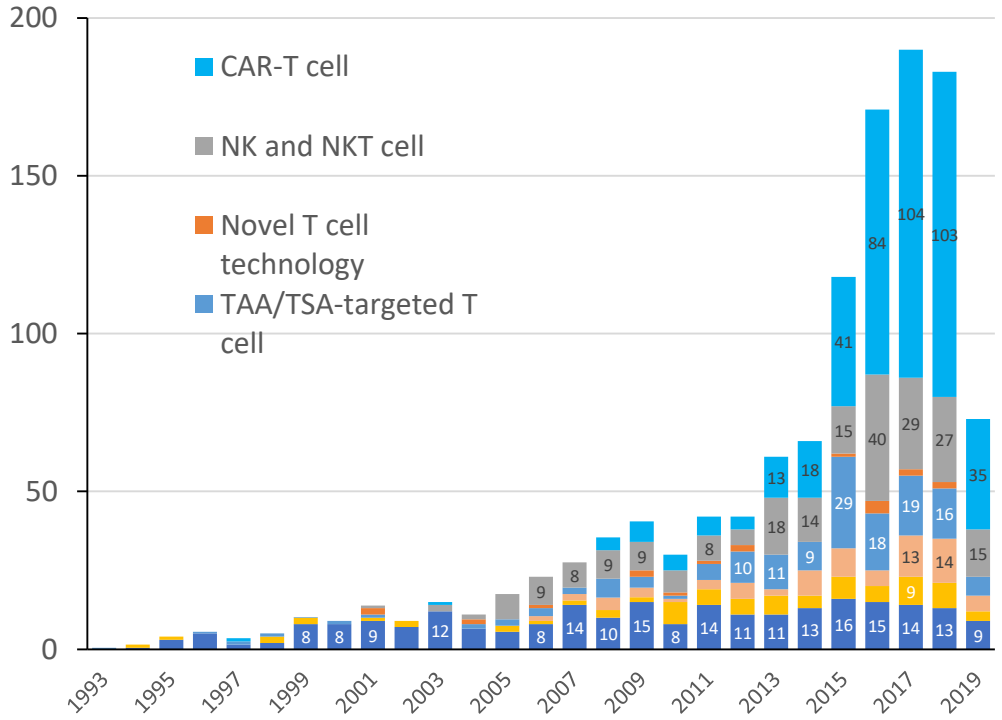
Jurgens B, Clarke NS. Nat Biotechnol April 2019

Cell therapy isn't going anywhere anytime soon:

CAR-T cell–related publications from 2008 to 2018[1,*]



Cell therapy trials for cancer from 1993 to 2019[2,†]



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1. Transformation of the CAR-T patent landscape. TC Biopharma website. https://www.tcbiopharm.com/news/perspectives/transformation-of-the-car-t-patent-landscape. Accessed October 29, 2020. **2.** Xin Yu J et al. *Nat Rev Drug Discov.* 2019;18(11):821-822.

Overview of Cellular Thearpy

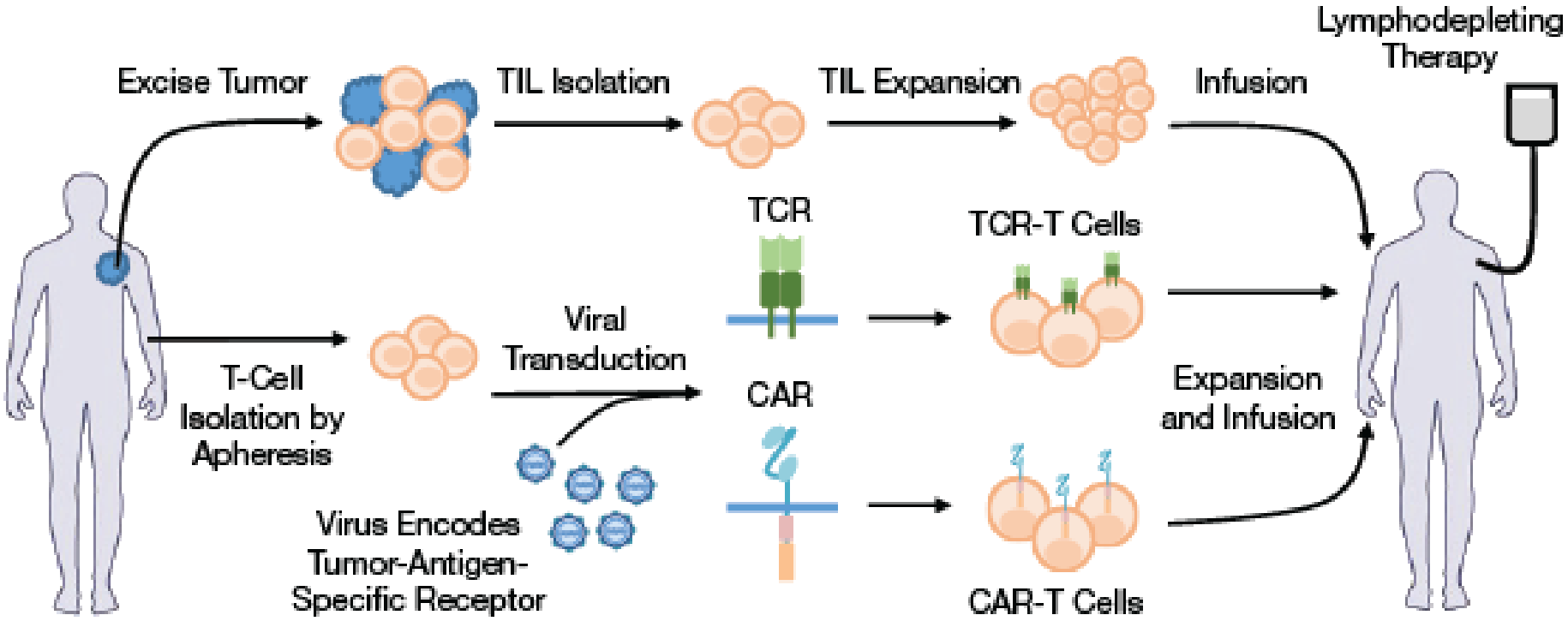
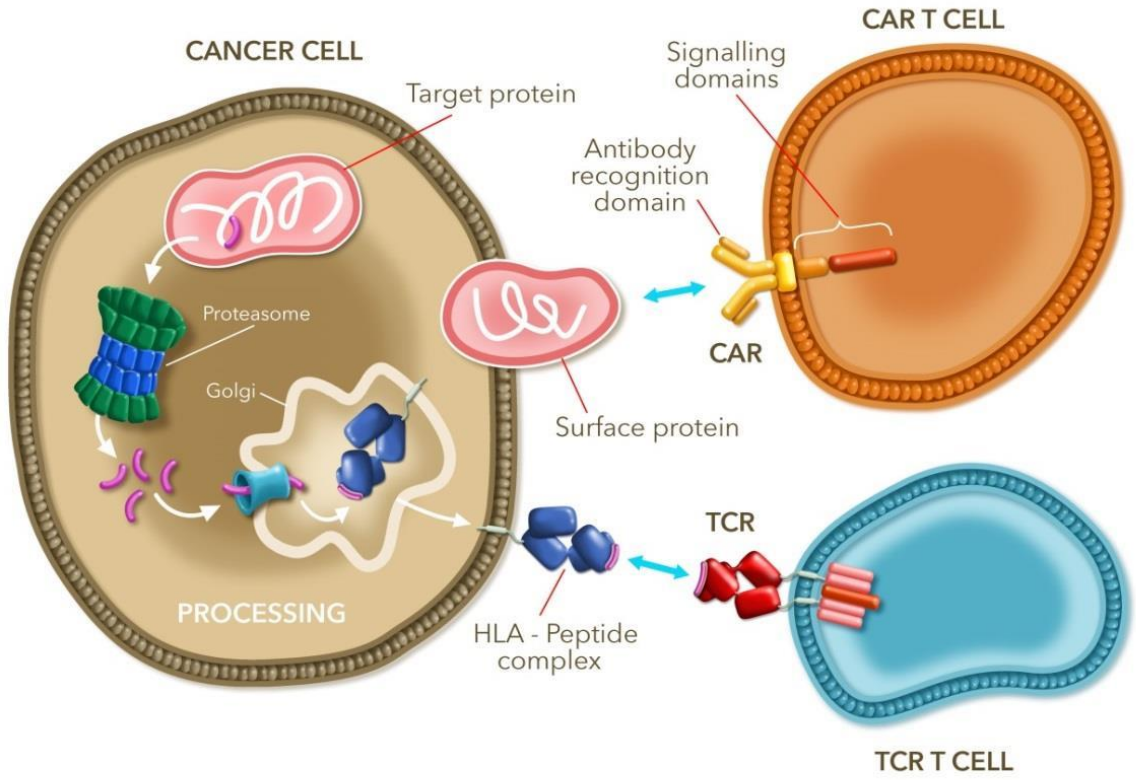


Image courtest of:
https://www.aiche.org/resources/publications/cep/2017/october/engineering-cancer-fighting-t-cells

Differing Approaches

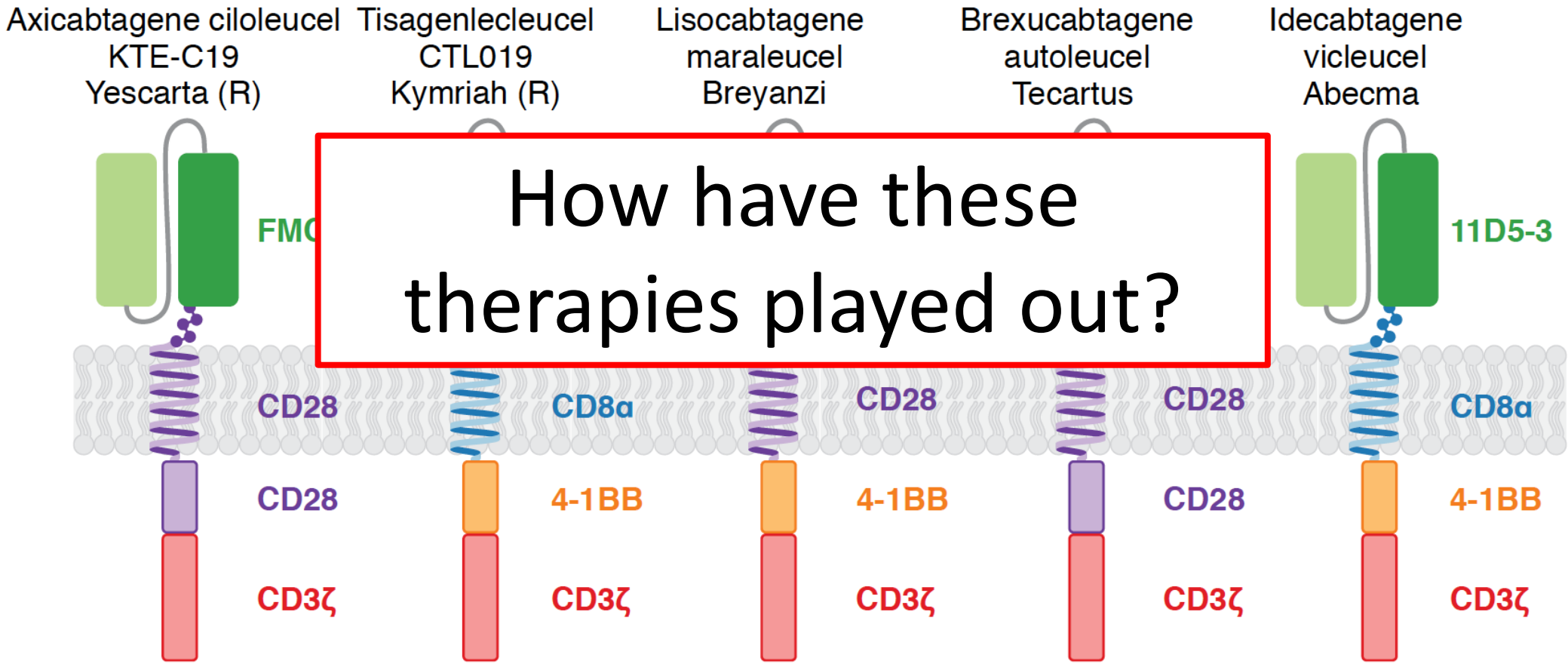
CARs are not MHC restricted but only see see surface proteins



Potentially **100%** of proteins are presented by HLA

Commercially Available CAR-T

FDA-approved CAR T cell products: molecular designs



How have these therapies played out?

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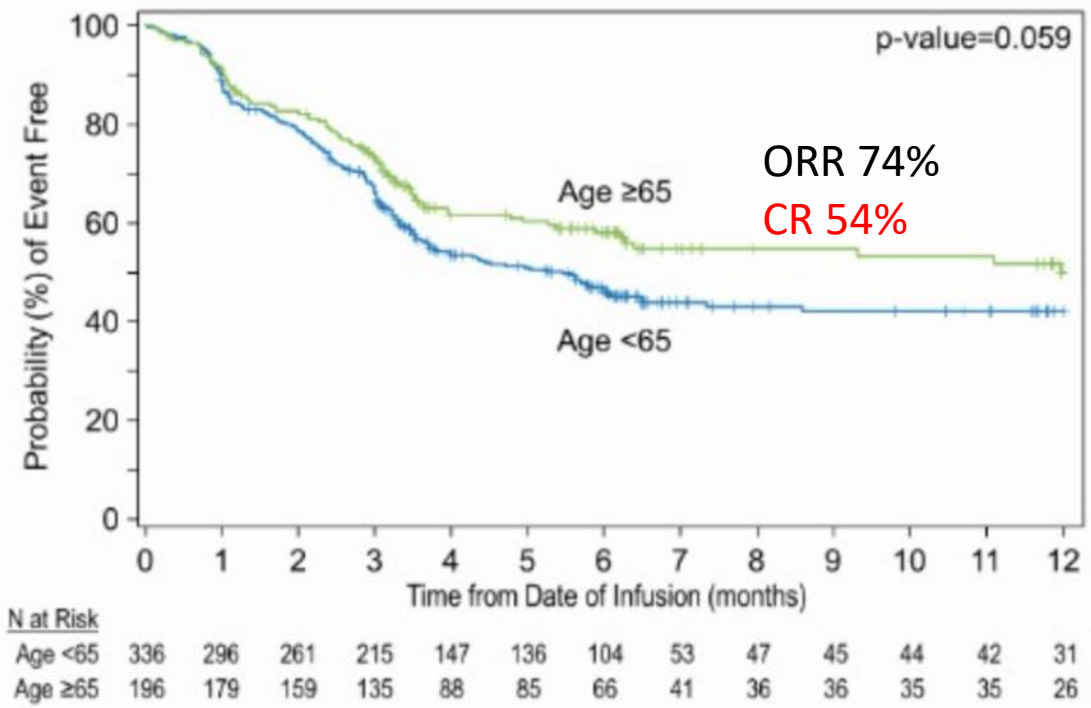
Figure by Matt Wyczalkowski

Survival Outcomes After Axi-Cel for LBCL

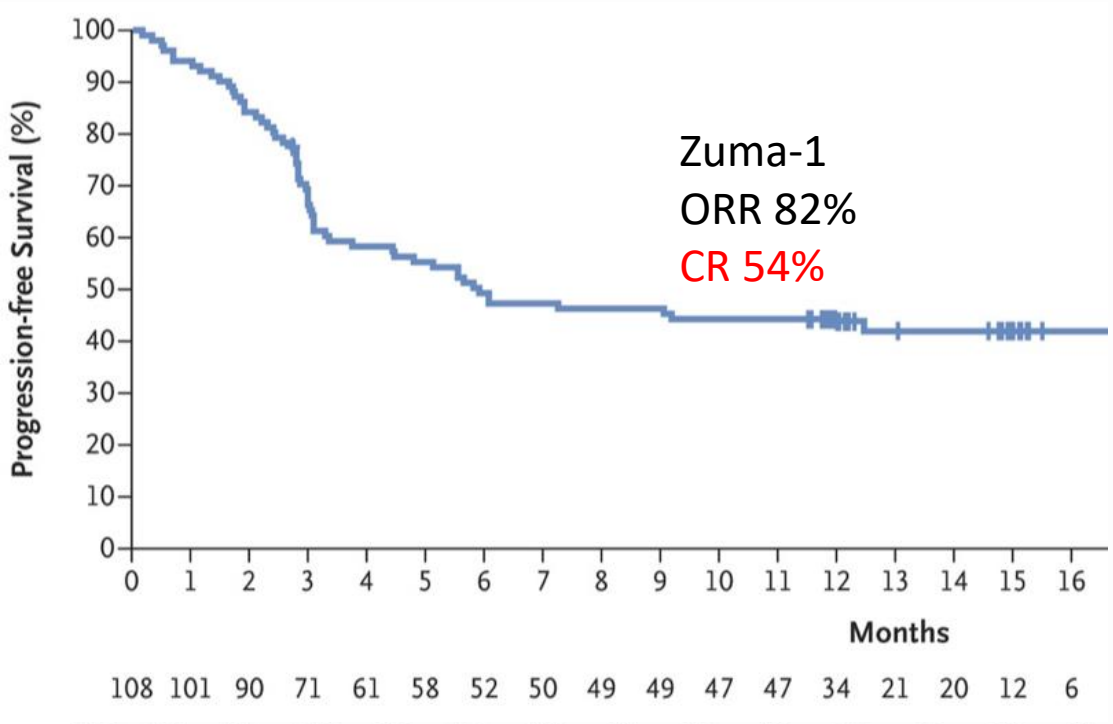
CIBMTR Registry

Progression-Free Survival



ORR 74%
CR 54%

Overall Survival



Zuma-1
ORR 82%
CR 54%

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1. Pasquini et al. ASH 2019 #764
2. Neelapu et al. NEJM 207

Multicenter Retrospective Analysis

	ZUMA-1[1]	Commercial Axi-cel[2]	JULIET[3]	Commercial Tisa-cel[2]
Patients collected, n	111	163	165	79
Patients infused, n	101	149	111	75
Median age, yrs (range)	58 (23-76)	58 (18-85)	56 (22-76)	67 (36-88)
DLBCL (including HGBL), %	76	86	79	94
ECOG 0/1, %	100	86	100	94
Prior ASCT, %	23	29	49	23
ORR, %	82 (Best)	72 (Day 30)	52 (Best)	59 (Day 30)
CR, %	58 (Best)	43 (Day 30)	40 (Best)	44 (Day 30)
Grade ≥ 3 CRS / NEs, %	13 / 31	13 / 41	22 / 12	1 / 3
Tocilizumab / steroid use, %	43 / 27	62 / 57	14 / 10	13 / 7

1. Neelapu. NEJM. 2017;377:2531. 2. Riedell. ASH 2019. Abstr 1599. 3. Schuster. NEJM. 2019;380:45

TRANSCEND NHL 001

R/R BLCL following 2 lines of therapy

Treatment

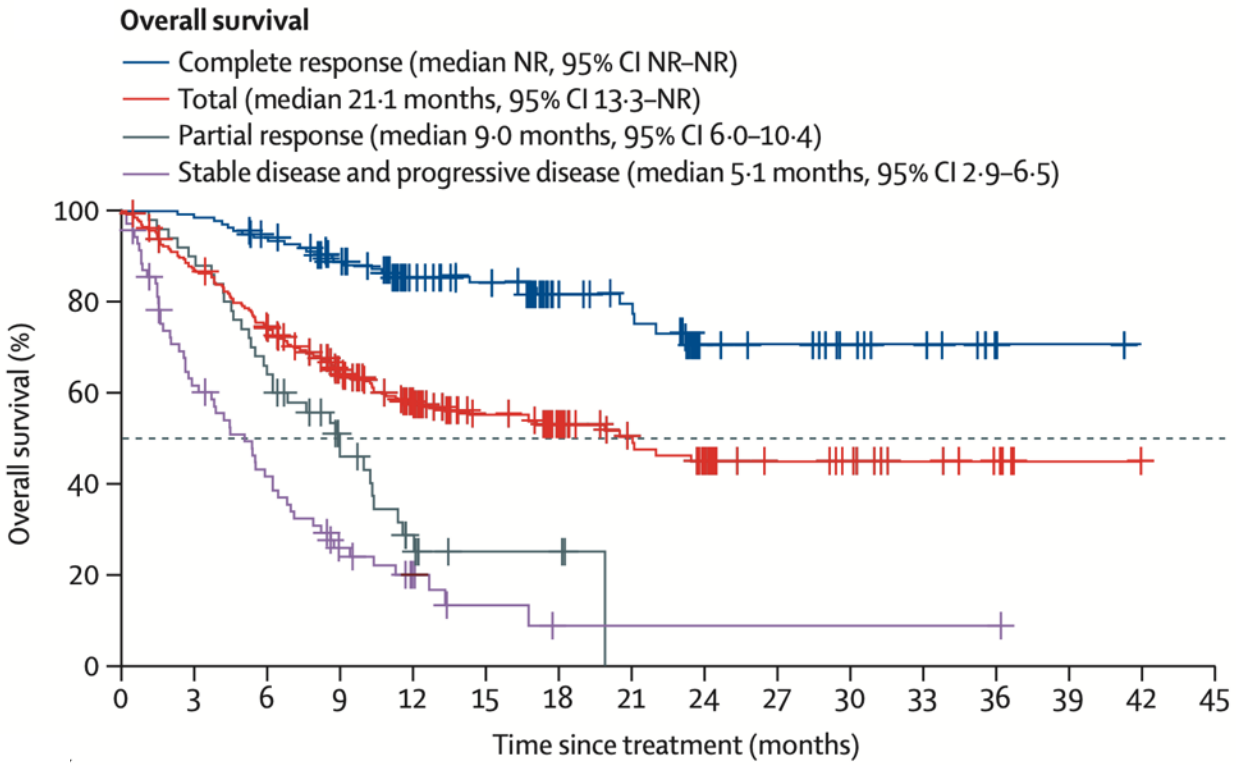
- LDC: Cy/Flu 300/30
- Cell dose: 50 to 150e6 CAR+ DL1 → DL3

Primary Endpoint

- ORR, DLTs, and AEs

Efficacy:

- 344 collected, 269 treated, 256 evaluable for efficacy
- Median f/u was 18.8 months
- ORR was 73%, CR rate was 53%
  - Median PFS was 6.8 months after a median f/u of of 12.3 months.
  - PFS at 1 year was 44%
  - Estimated 12-month OS was 58% for the total population.

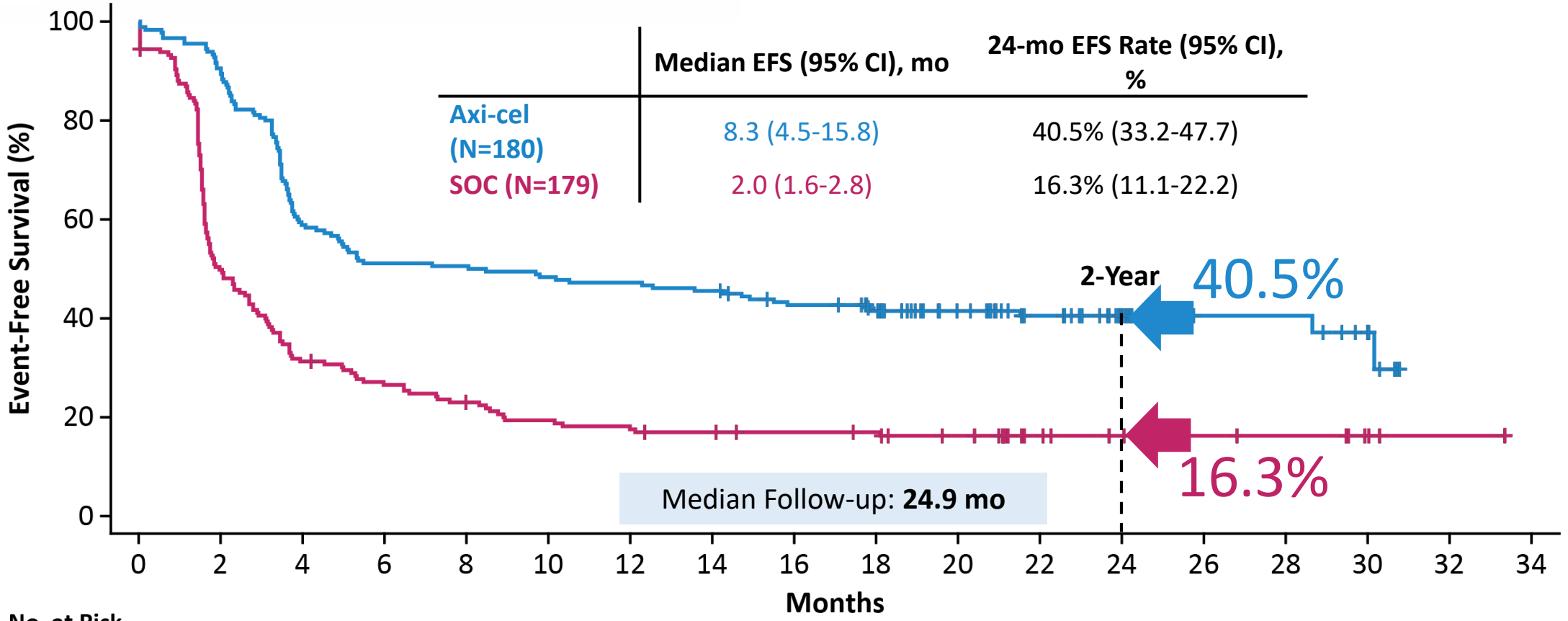


Abramson J et al. Lancet. 2020

What About Earlier CAR-T?

Primary EFS Endpoint: Axi-Cel Is Superior to SOC

HR 0.398 (95% CI, 0.308-0.514); *P*<0.0001



	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %
Axi-cel (N=180)	8.3 (4.5-15.8)	40.5% (33.2-47.7)
SOC (N=179)	2.0 (1.6-2.8)	16.3% (11.1-22.2)

No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
SOC	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

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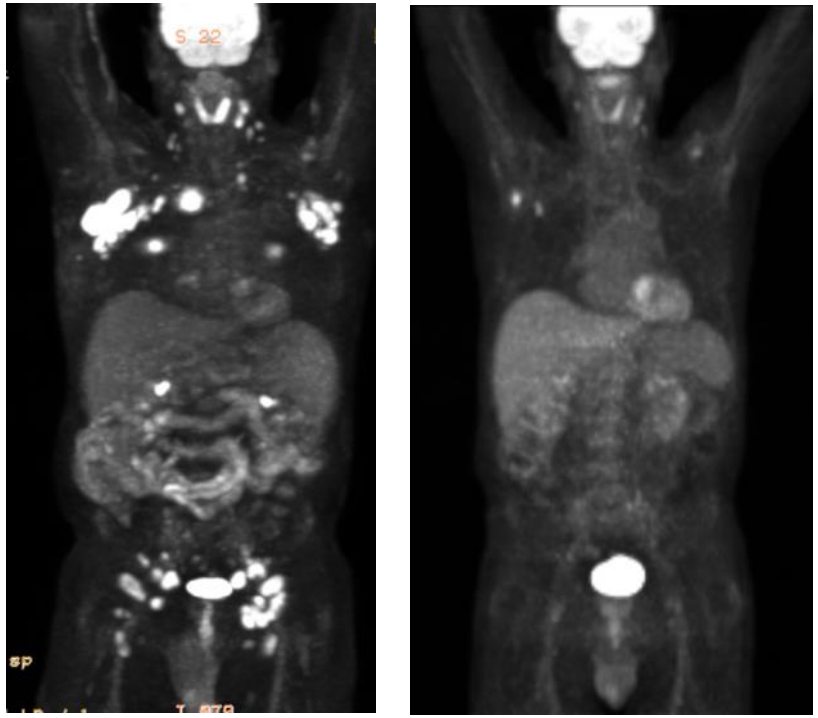
56% of SOC patients received subsequent cellular immunotherapy (off protocol)

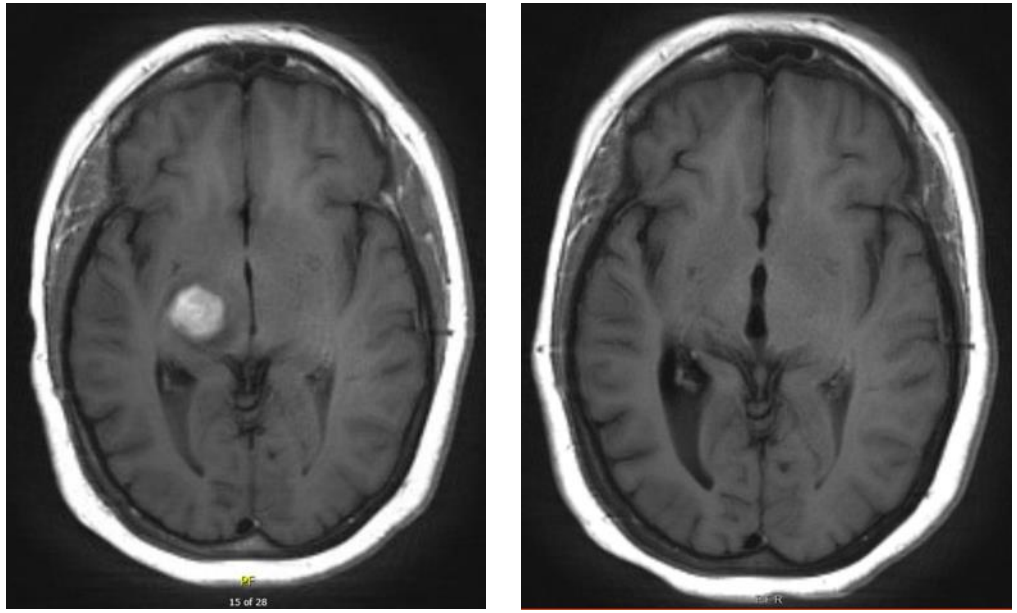
Locke et al. NEJM 2021

Pushing Into New Diseases

PTCL post allo
(NCT04136275 – MGH)

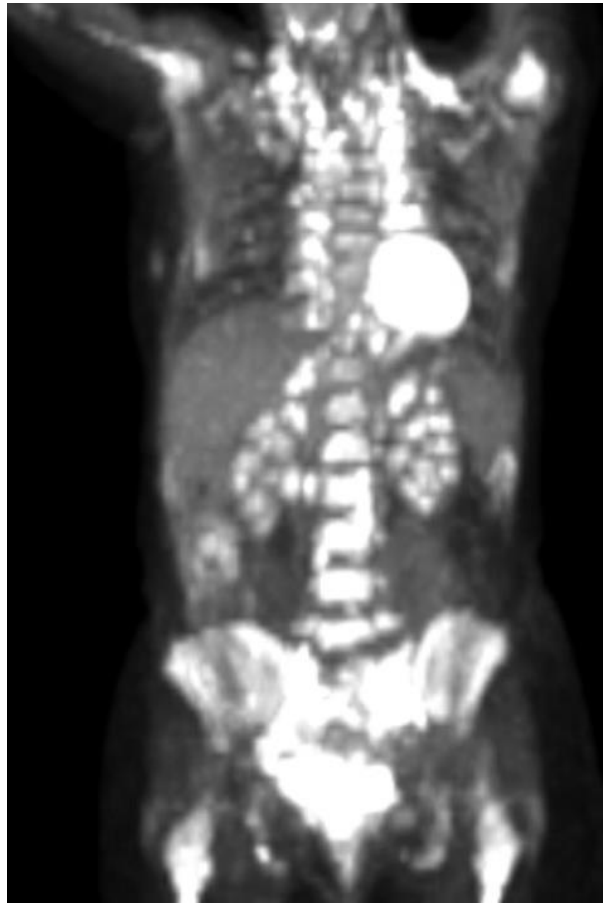


PCNSL (5 prior lines)
(NCT04134117 – MGH)

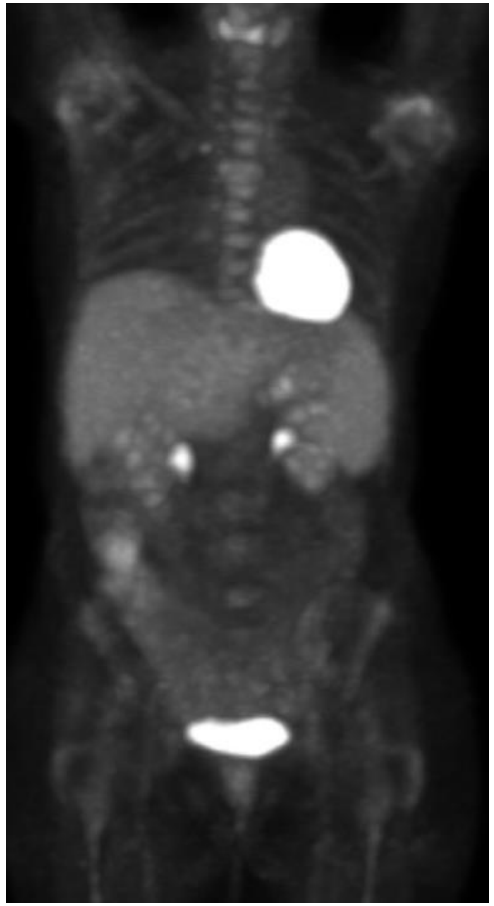


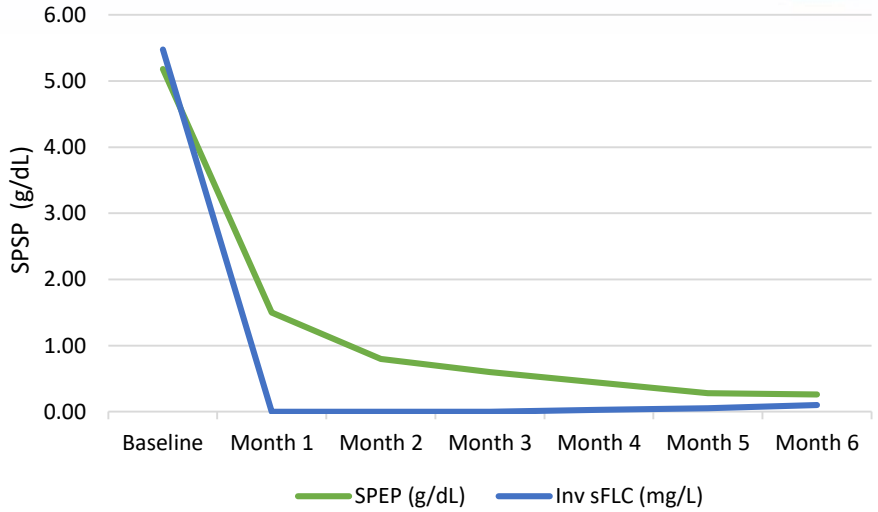
Synthetic ddBCMA Binder CAR-T - MGH

Baseline



Month 1





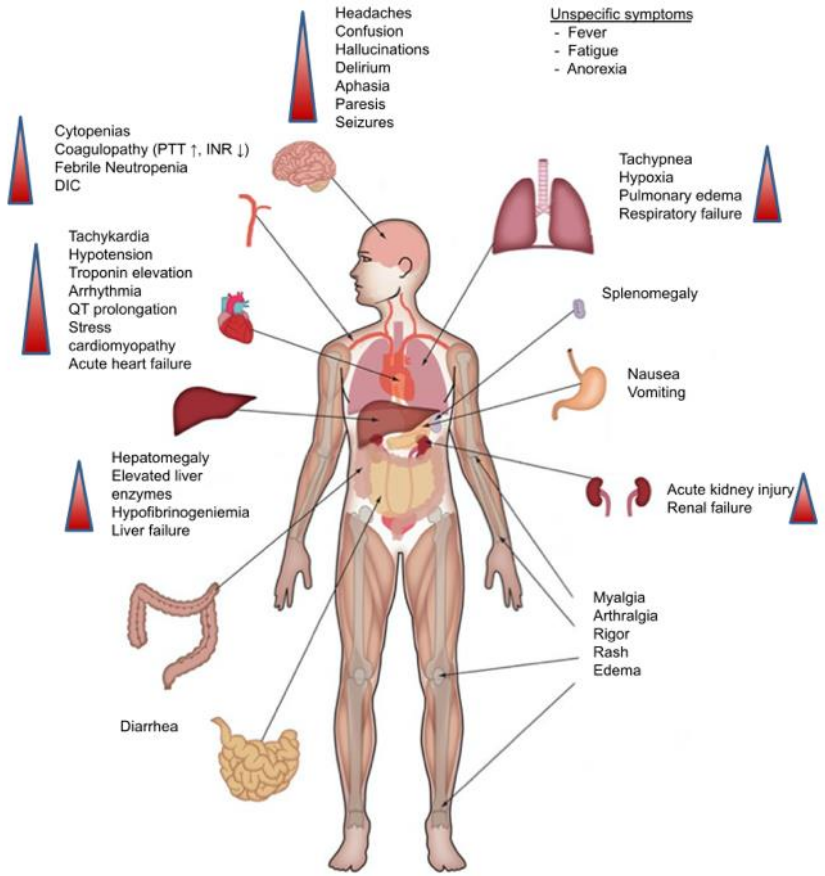
Bulky extra-medullary disease, substantial bone marrow disease (50%) at baseline with high-risk cytogenetics, penta-refractory disease and prior failed therapy with BCMA-ADC

⇒ PET-CT negative by Month 1
⇒ Bone marrow negative by Month 1
⇒ MRD-negative 10^{-4} at Month 1
⇒ Remains MRD-negative 10^{-5} at Month 6

Class Specific Toxicites

Cytokine-Release Syndrome (CRS)

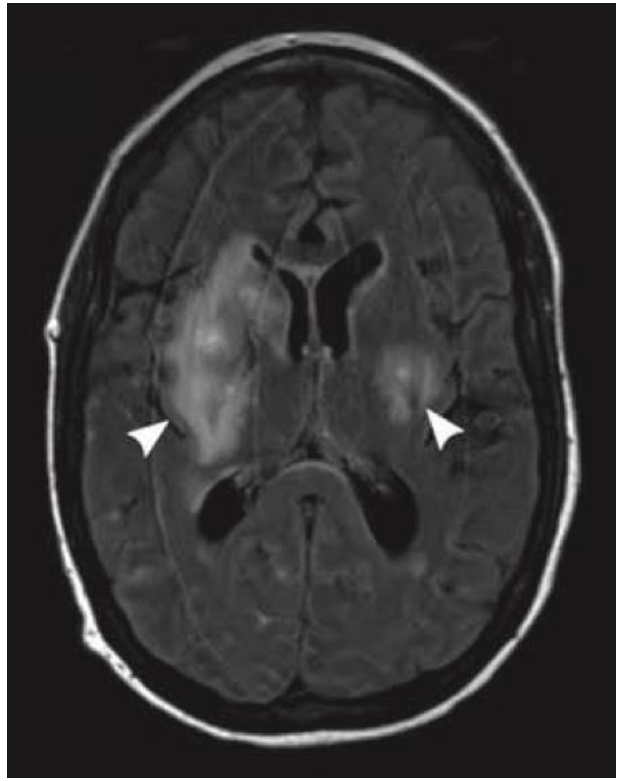
- Typical onset 2-3 days, duration 7-8 days
- Can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multiorgan system failure
- On a spectrum with macrophage activation syndrome
- Rarely, severe CRS can evolve into fulminant hemophagocytic lymphohistiocytosis
- Characterized by high levels of TNF-α, **IFN-γ**, **IL-1β**, IL-2, **IL-6**, IL-8, and IL-10
- Correlates with peak T-cell expansion



Shimabukkuro-Vornhagen et al. JITC 2018

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Typical onset 4-6 days, typical duration 14-17 days.
- Toxic encephalopathy with symptoms of mild headaches, confusion, and delirium; expressive aphasia; occasional seizures; and rarely, cerebral edema.
- Can occur in the presence of absence of systemic CRS.
- Patients with severe neurotoxicity demonstrated evidence of endothelial activation, including disseminated intravascular coagulation, capillary leak, and increased blood–brain barrier permeability.
- T-cells known to traffic into the CNS; however direct role of their presence is not fully understood.
- Primate models have demonstrated peri-vascular invasion similar to that seen on human autopsy, although not felt to be antigen mediated.
- Although limited data, no apparent increase in ICANS with active CNS disease.



Gust et al. Cancer Discov. 2017

Grading of CRS/ICANS

ASTCT Guidelines for Grading of CRS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Lee. Biol Blood Marrow Transplant. 2019;25:625.

New ASTCT Guidelines for Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (pt is unarousable)
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 nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 mins) 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
Elevated 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

Lee. Biol Blood Marrow Transplant. 2019;25:625.

New ASTCT Guidelines for Grading of ICANS: ICE Score

Parameter	Score (Points)
Orientation: year, month, city, hospital	4
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3
Following commands: ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue")	1
Writing: ability to write a standard sentence (eg, "our national bird is the bald eagle")	1
Attention: ability to count backwards from 100 by 10	1

Scoring:

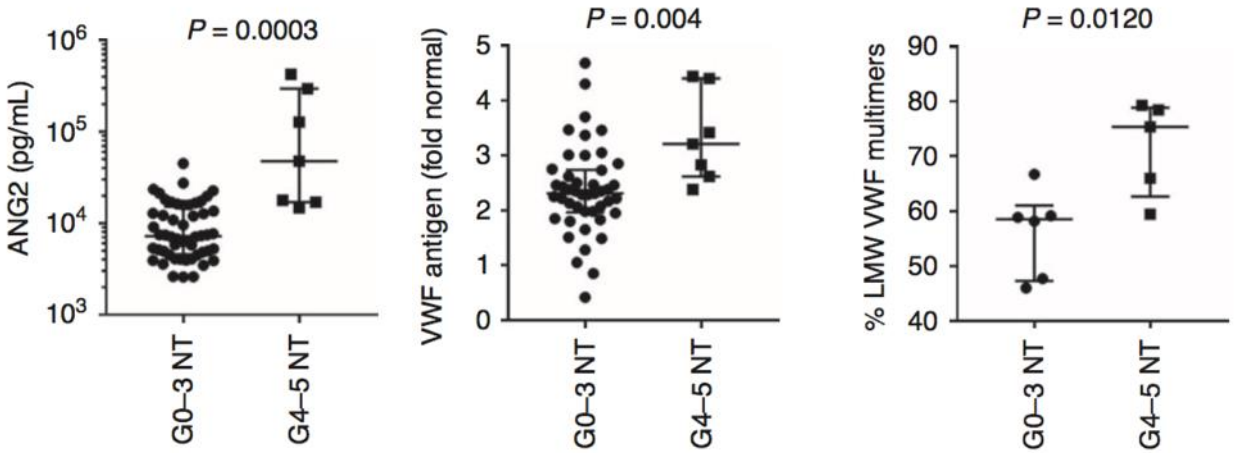
10, no impairment
7-9, grade 1 ICANS
3-6, grade 2 ICANS
0-2, grade 3 ICANS
0, patient unarousable and unable to perform ICE assessment, grade 4 ICANS

*See next slide; an ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable.

Mechanisms of Toxicity

Mechanisms of Neurotoxicity

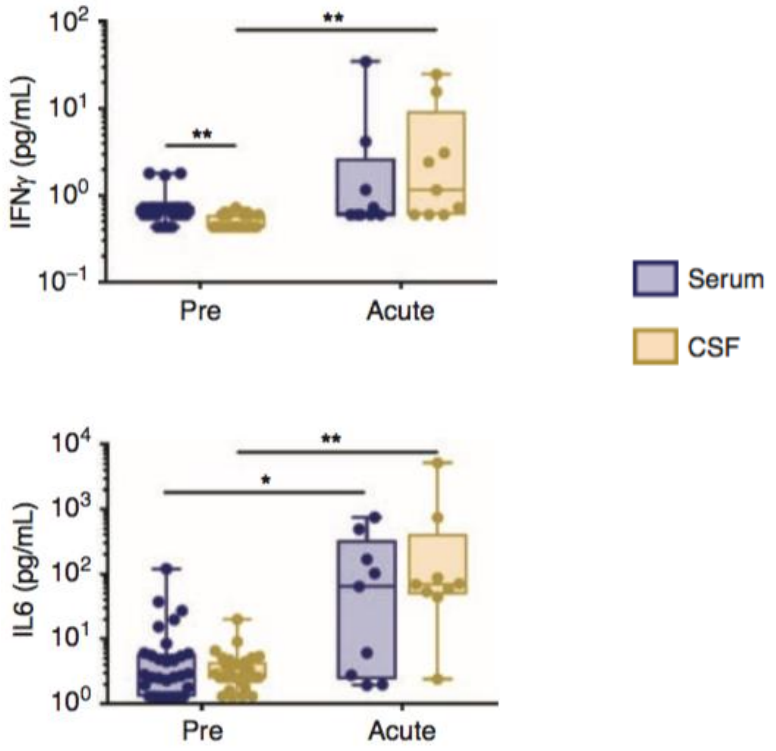
Endothelial



Increased markers of endothelial activation are seen in patients with higher grade neurotoxicity.

Patients with neurotoxicity have evidence of blood-brain barrier degradation.

Vascular/Endothelial Permeability

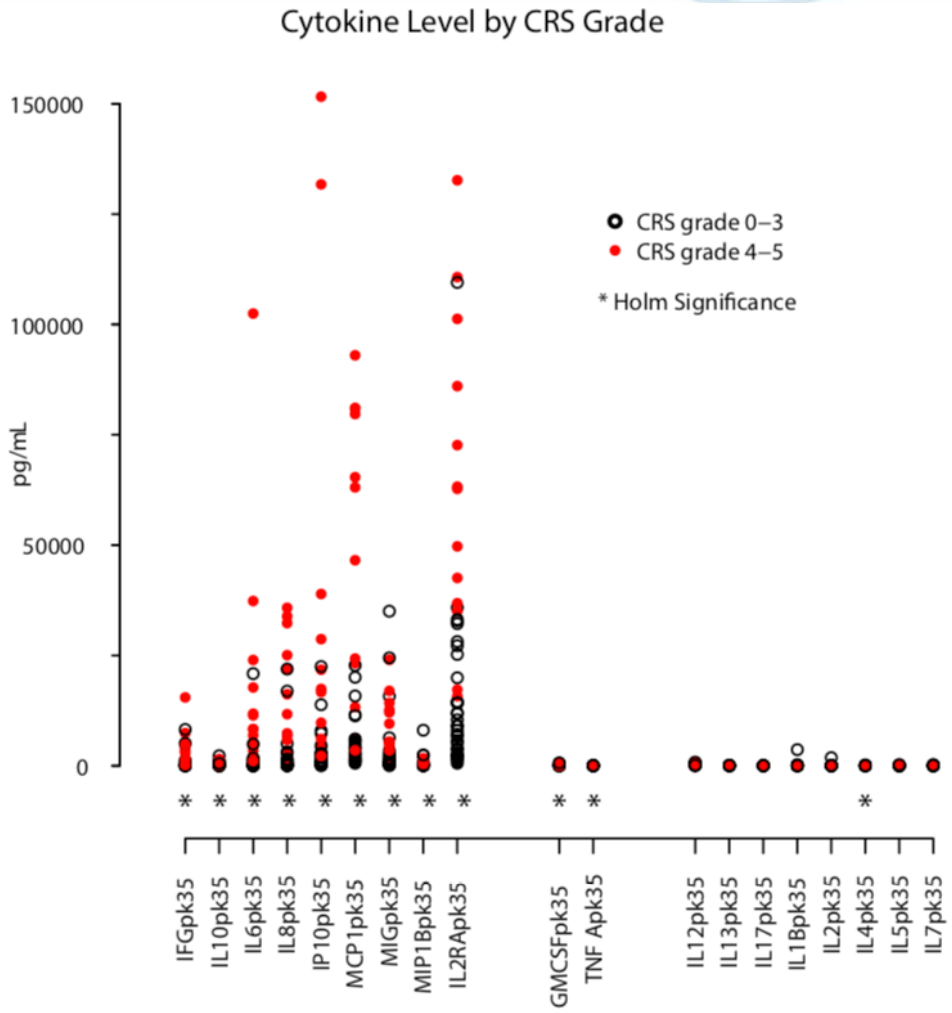


Gust et al. Cancer Discovery. 2017
Hay et al. Cancer Discovery 2017

CRS/MAS Spectrum

- Macrophage activation syndrome (MAS) appears to accompany CRS in a subset of patients.
- Characterized by high fevers, hepatosplenomegaly, liver dysfunction, renal failure, **coagulopathy**, hypofibrinogenemia, and profound hyperferritinemia.
- Histological evidence of hemophagocytosis noted on bone marrow biopsy at peak of CRS.
- Similar cytokine profiles.

CRS → **MAS**



Teachey et al. Cancer Discovery 2016

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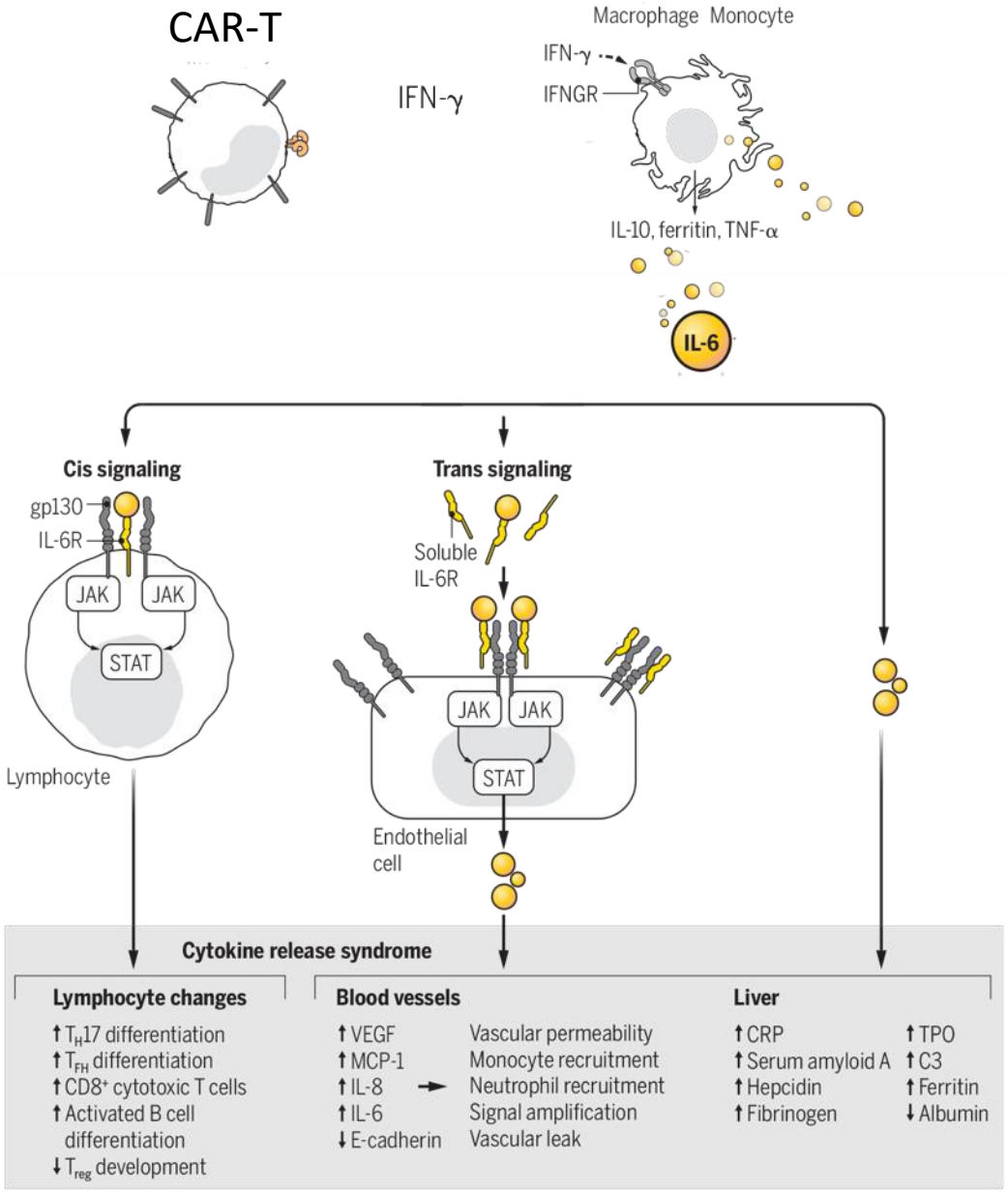

Possible Link?

- CAR-T engagement and activation
- Robust inflammatory cytokine production
  - IFNg, IL1b, GM-CSF
- Priming of macrophage/monocyte compartment with subsequent IL-6 Production
- Cis and trans IL-6 signaling leads to:
  - Further lymphoid/myeloid activation
  - Endothelial activation
  - Endothelial/vascular permeability (including pericyte regulation of blood-brain barrier)
  - CNS glial cell activation (macrophage derived)

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Figure modified from Moore JB, June CH, Science May 2020

Solid Tumor Studies On the Move

As of 11/15/21:

Although likely an under-estimate:

There are 1021 clinical trials currently listed under "**chimeric antigen receptor**"

As of 10/30/2020

372 studies are listed within the US. →
- 31 of which are targeting "carcinomas" → 232, 17 targeting "carcinoma"

There are 1399 clinical trials currently listed under "**T Cell Receptor**"

672 studies are listed within the US. →
- 115 of these are targeting "carcinomas" → 357, 73 targeting "carcinoma"

There are 438 clinical trials currently listed under search term "t**umor infiltrating lymphocyte**"

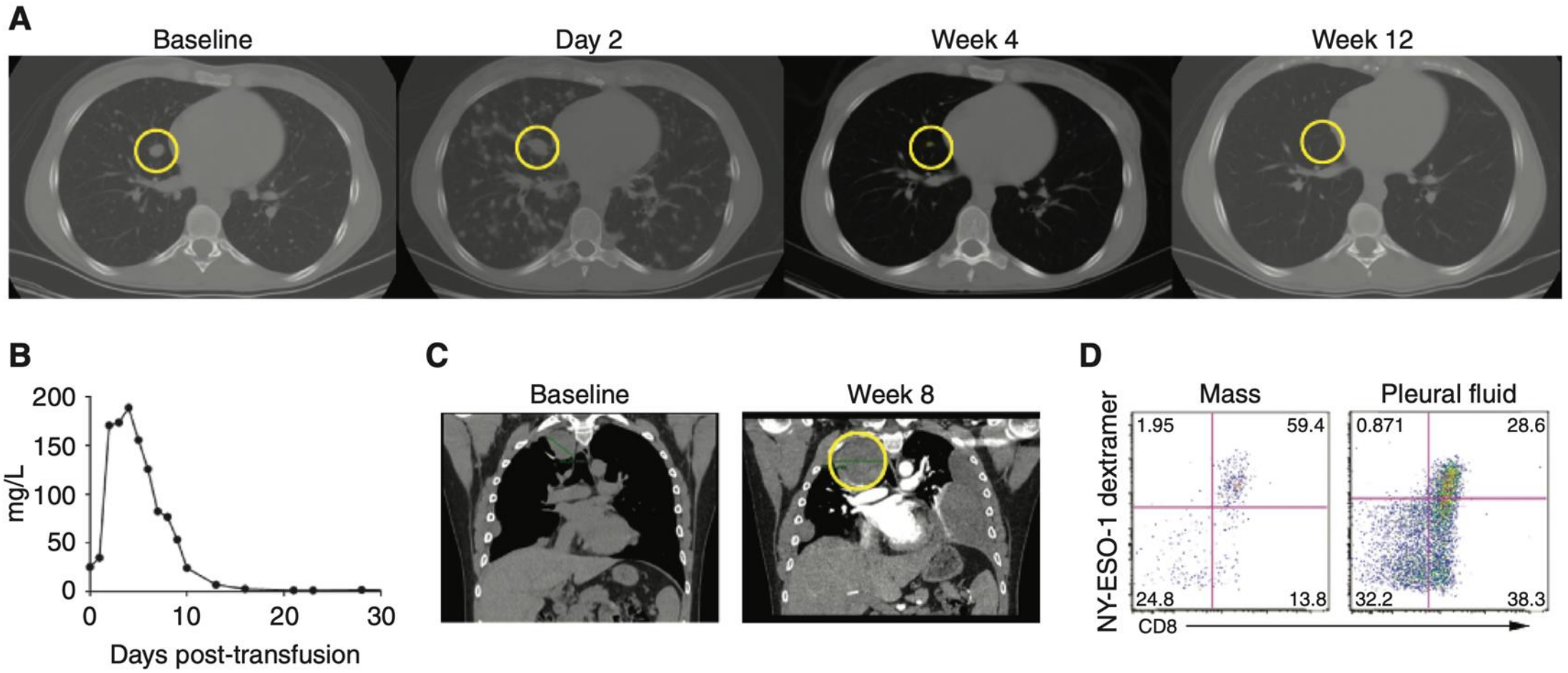
247 studies are listed within the US studies are listed with the US.
- 95 of these are targeting "carcinomas" → 234, 89 targeting "carcinoma"

www.clinicaltrials.gov

Targets in Development for Solid Tumors

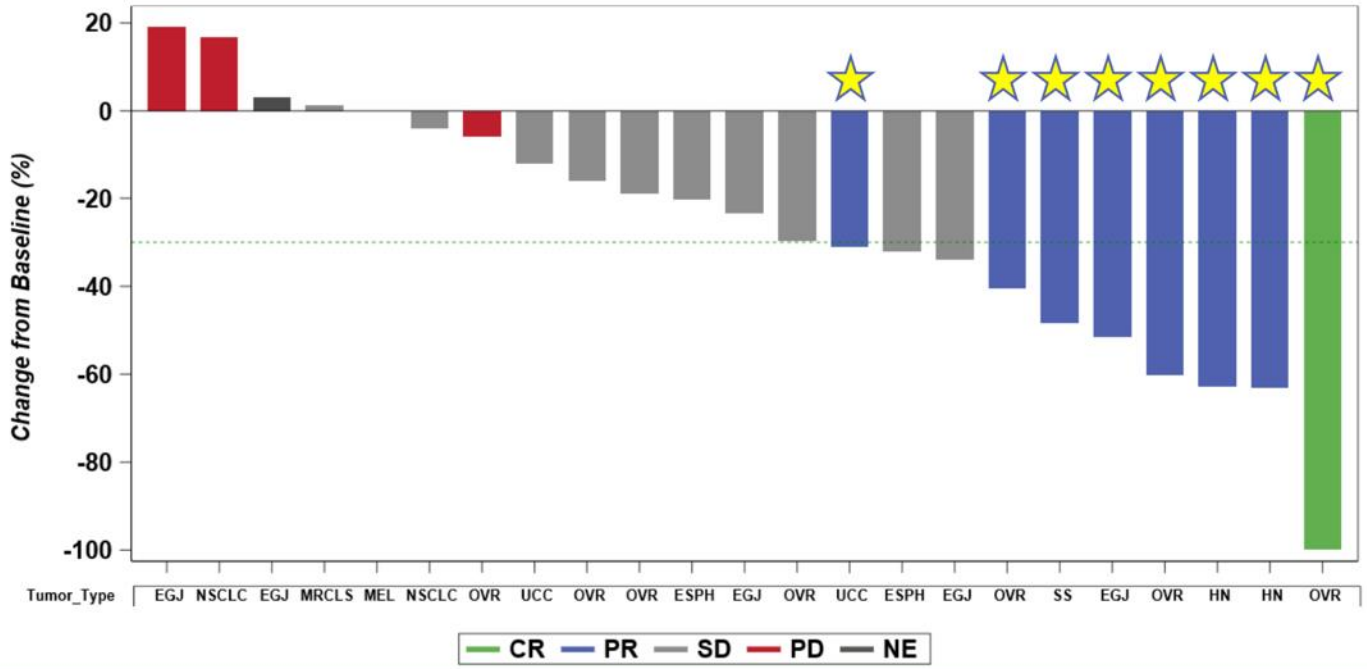
Target	Potential Indication	Potential for local delivery?
CD70	Renal Cell, AML	-
EGFRvIII	GBM	+
Mesothelin	Pancreatic, ovarian, lung	+
PSMA	prostate	-
PSCA	GI, prostate	-
IL-13Ra2	GBM	+
FR	Breast, ovarian	+
B7H3	GBM, breast	+
MUC (1,16)	Ovarian, GBM, breast	+
Her2	GBM, (others)	+ (-)
GD2	Neuroblastoma, DIPG	-/+

Demonstration of efficacy: NY-ESO TCR



Cancer Discov August 1 2018

MAGE- A4 aTCRs

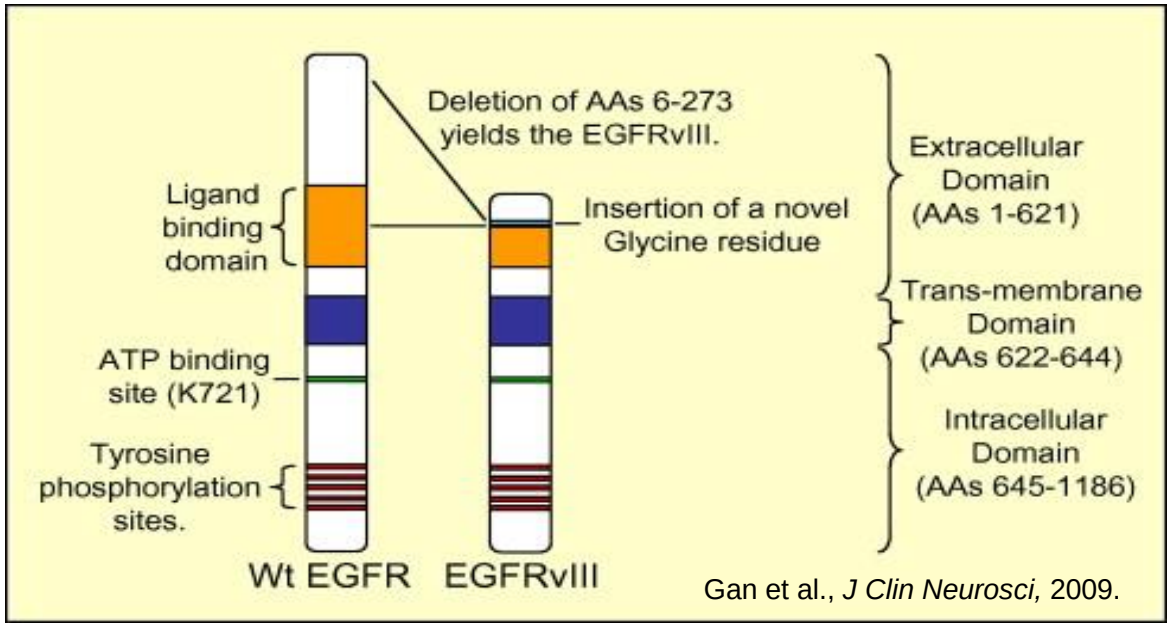


2021 ESMO congress

- Overall response rate of 36% (8/22*) with majority of patients experiencing antitumor activity
- A complete response in a patient with ovarian cancer – and partial responses in ovarian (2), head and neck (2), EGJ, bladder, and synovial sarcoma cancers

Nue

NCT02209376 Phase 1 Study of a single intravenous dose of EGFRvIII CART in patients with recurrent EGFRvIII+ GBM



Gan et al., *J Clin Neurosci,* 2009.

EGFRvIII is an oncogenic mutation

Occurring in ~20% of patients with glioblastoma

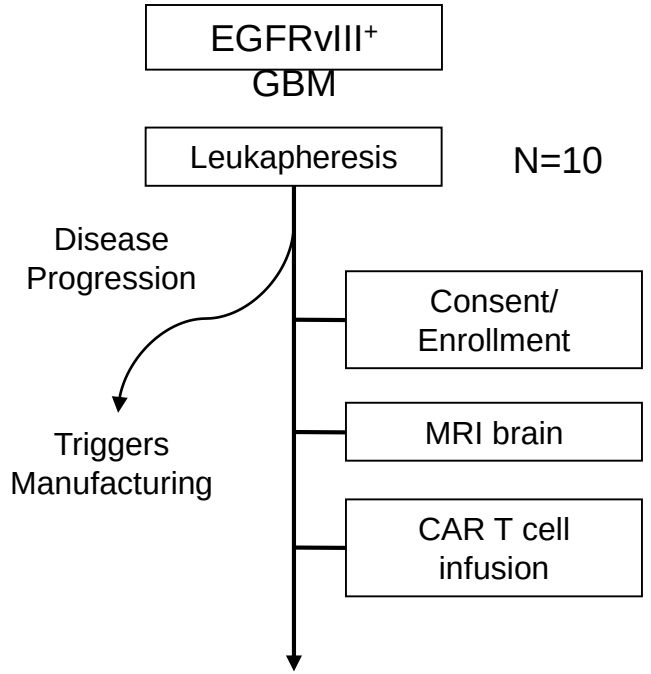
Frequently also with amplification of wt EGFR

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma

Donald M. O'Rourke,[1] MacLean P. Nasrallah,[2*] Arati Desai,[3*] Jan J. Melenhorst,[4*] Keith Mansfield,[5*] Jennifer J. D. Morrissette,[6] Maria Martinez-Lage,[2†] Steven Brem,[1] Eileen Maloney,[1] Angela Shen,[7] Randi Isaacs,[5] Suyash Mohan,[8] Gabriela Plesa,[4] Simon F. Lacey,[4] Jean-Marc Navenot,[4] Zhaohui Zheng,[4] Bruce L. Levine,[4] Hideho Okada,[9] Carl H. June,[4] Jennifer L. Brogdon,[5] Marcela V. Maus[10‡]



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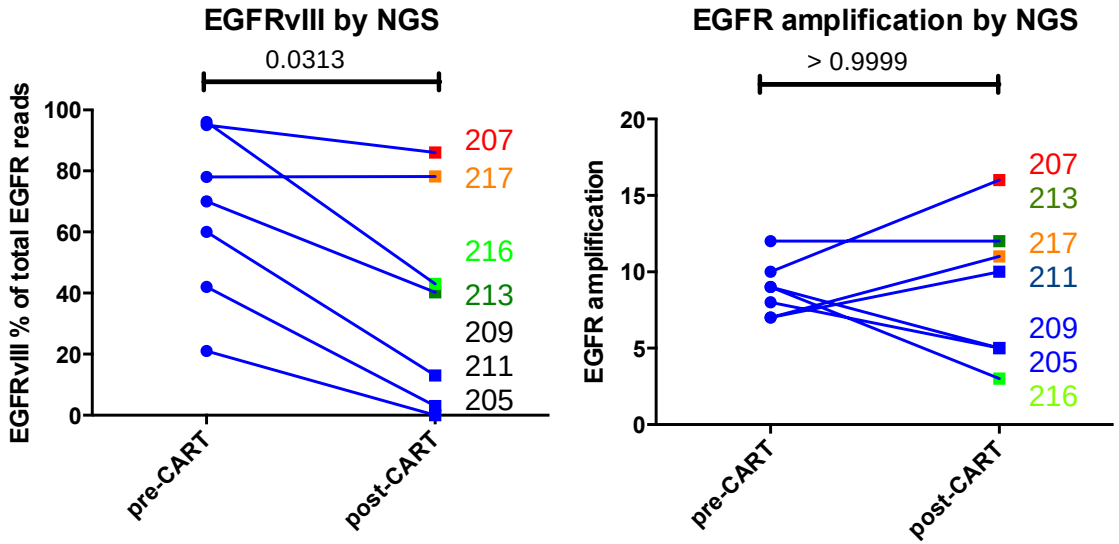
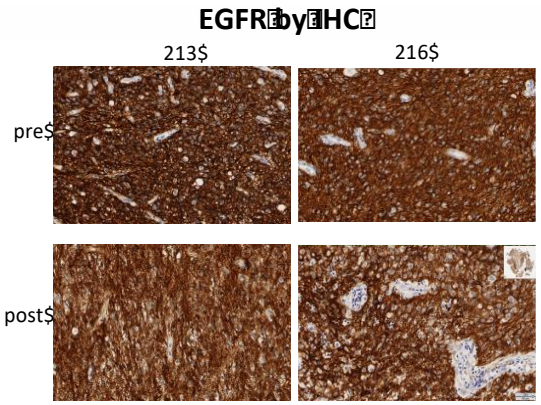
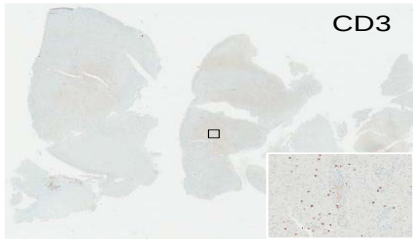
CART-EGFRvIII traffic to tumor, target antigen, but there is antigen heterogeneity and Treg infiltration

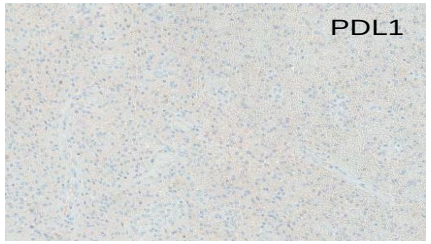


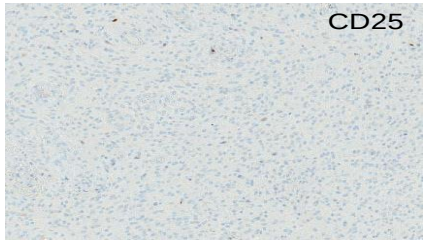


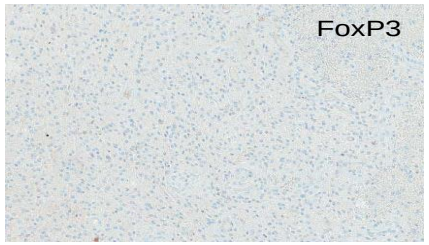
Pre

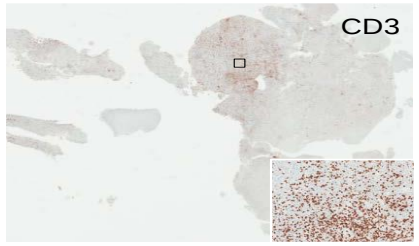
Post

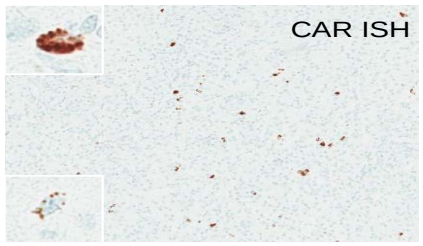


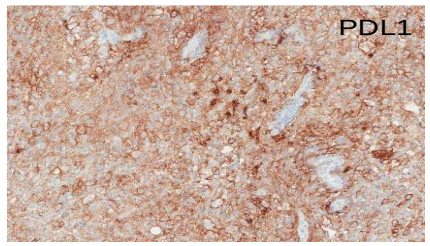


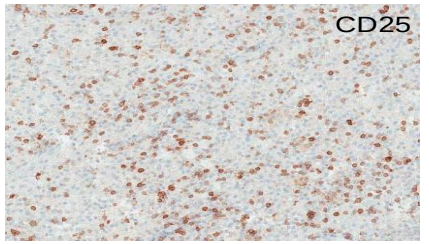


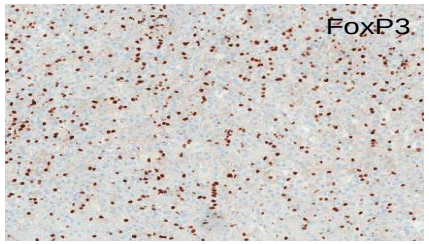






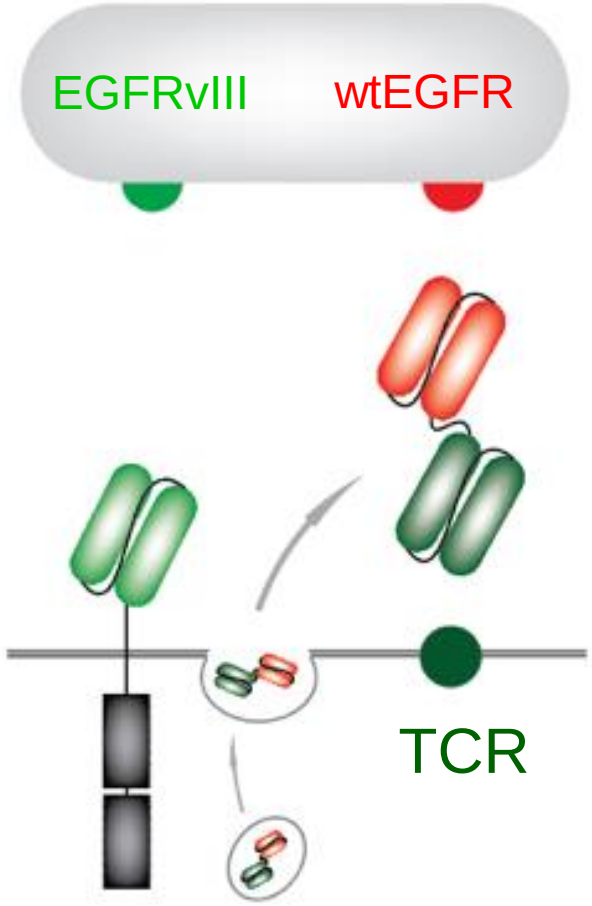






CAR T cells for solid tumors need to overcome heterogeneity and immunosuppressive environment: CAR-TEAM design

CAR targets tumor-specific target



T-cell **E**ngaging **A**ntibody **M**olecule

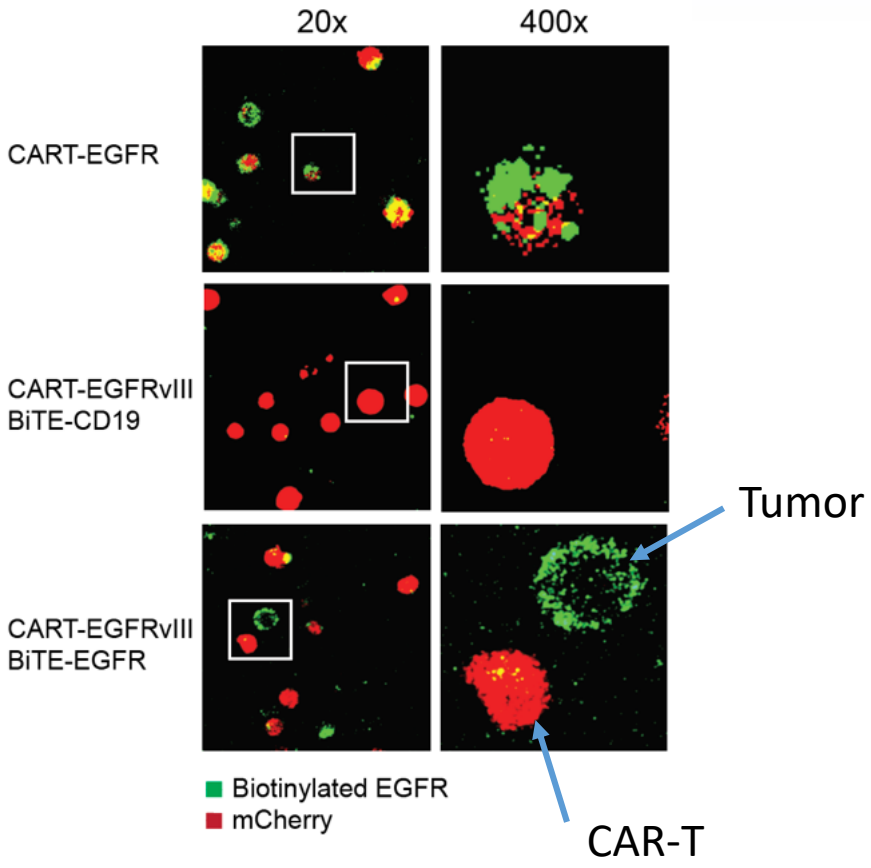
TEAM can target the "undruggable"

- Local site
- Rapid clearance
- Can re-direct Tregs

CAR-TEAM design
T cell Engaging Antibody Molecule

Choi BD. Nat Biotechnol. 2019

CAR T cells for solid tumors need to overcome heterogeneity and immunosuppressive environment: CAR-TEAM design



T-cell **E**ngaging **A**ntibody **M**olecule

TEAM can target the "undruggable"

- Local site
- Rapid clearance
- Can re-direct Tregs

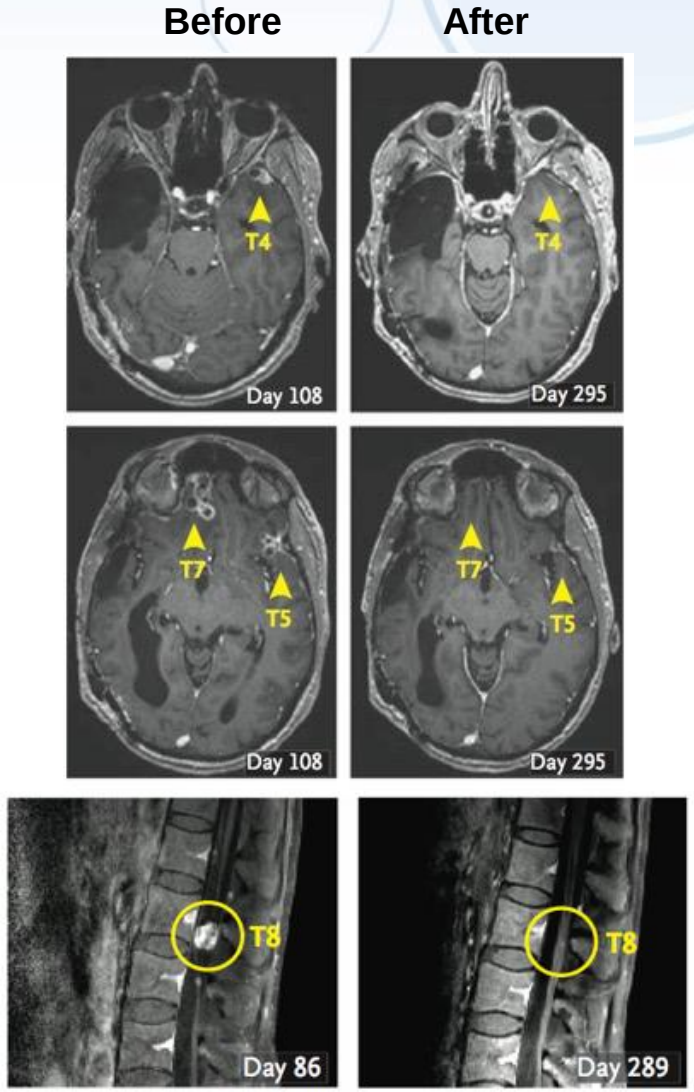
Opening @ MGH 2022

Choi BD. Nat Biotechnol. 2019

CAR T can be effective with multiple doses and **local administration**

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S., Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A., Julie R. Ostberg, Ph.D., M. Suzette Blanchard, Ph.D., Julie Kilpatrick, M.S.N., Jennifer Simpson, B.A., Anita Kurien, M.B.S., Saul J. Priceman, Ph.D., Xiuli Wang, M.D., Ph.D., Todd L. Harshbarger, M.D., Massimo D'Apuzzo, M.D., Julie A. Ressler, M.D., Michael C. Jensen, M.D., Michael E. Barish, Ph.D., Mike Chen, M.D., Ph.D., Jana Portnow, M.D., Stephen J. Forman, M.D., and Behnam Badie, M.D.



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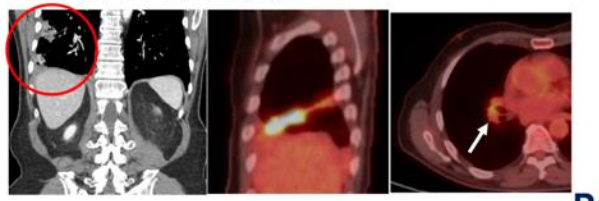
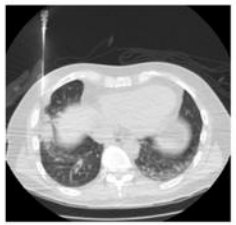
Demonstration of efficacy: CAR

Multi-modality CAR T for solid tumors

MSLN CAR T-cells + anti PD-1 agent
Complete response – 22 months

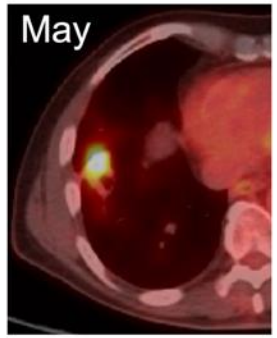
Post chemotherapy
Pre CAR T-cells



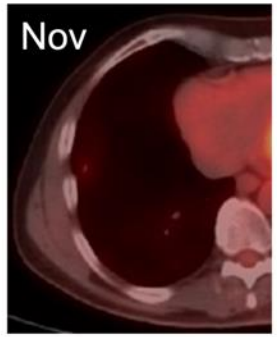


CAR T-cells administered in interventional radiology

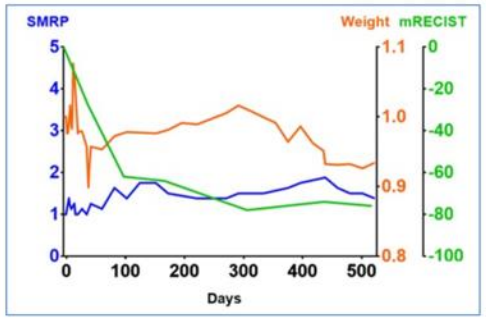
Partial response with CAR T cells alone



Post CAR T-cells



Addition of anti-PD-1 antibody



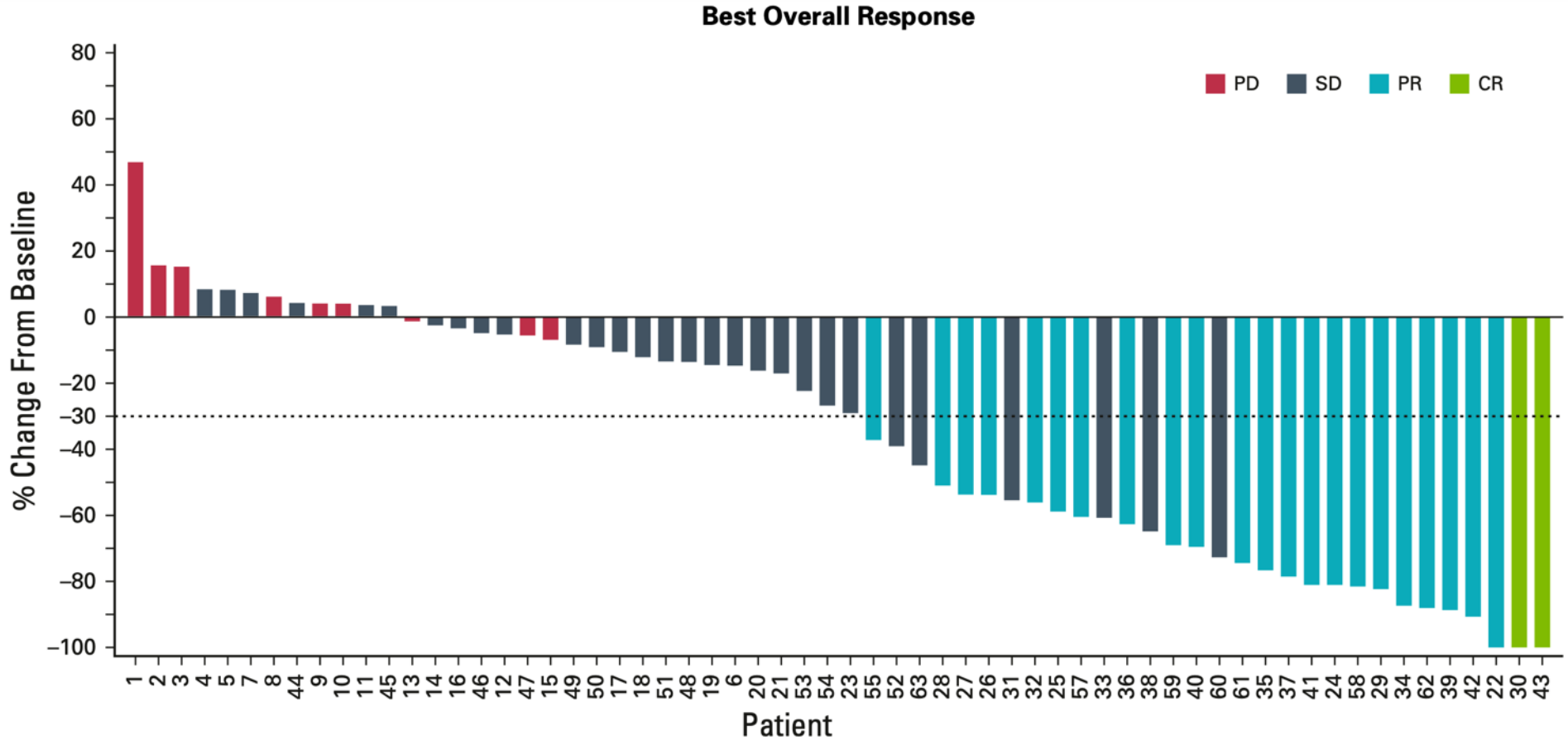
Observed both after CAR T-cell infusion and after anti-PD1 therapy:

- T-cell clonal expansion
- Clonal fold expansion
- New IgG responses

Unpublished data

Courtesy of Prasad S. Adusumilli, MD, FACS, MSKCC 2020

TILs in Checkpoint Refractory Melanoma



Median duration of response was not reached after 18.7-month median study follow-up (range, 0.2-34.1 months).

Sarnaik AA. JCO 2021

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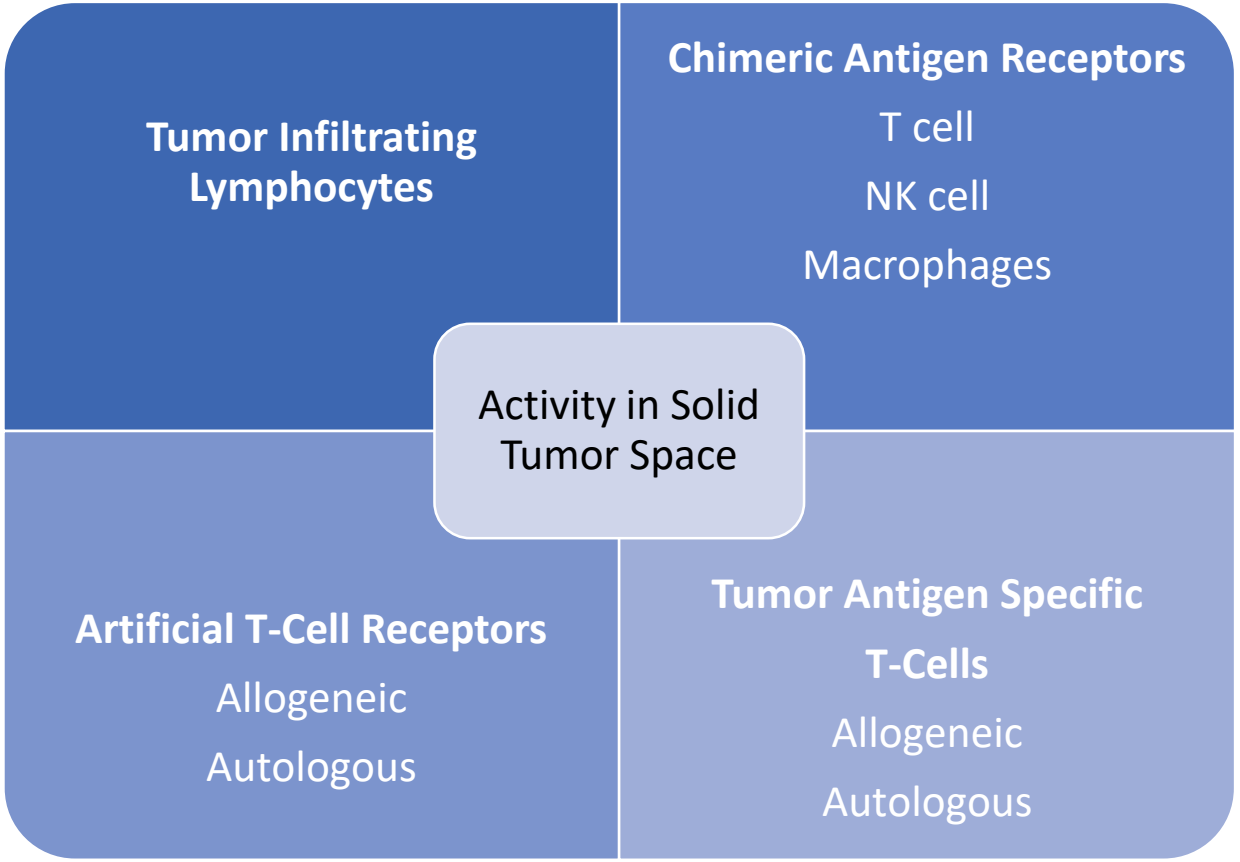
Growing and Complicated Space



Pipeline

- TCR mimetics
- Syn-notch "synthetic" switches
- Gated CARs
- Combination therapies
- Gene edited (above allogeneic products)
- iPSC & Cord Blood derived products

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Image courtest of: https://www.aiche.org/resources/publications/cep/2017/october/engineering-cancer-fighting-t-cells

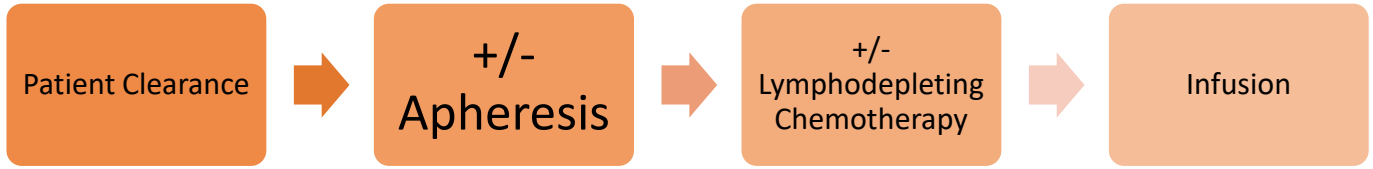
How Do We Organize This Evolving Field?

Challenges in Solid Tumors & Beyond

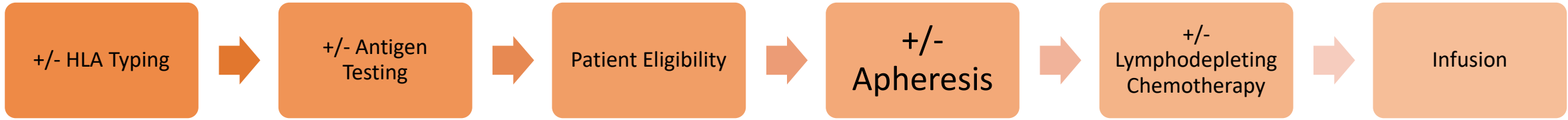
- Target selection (on target/off tumor)
- Tumor heterogeneity
- Tumor microenvironment and acquired resistance
- T-cell trafficking
- Manufacturing, delivery and scale
- **VOLUME**

Difficulties in Patient Workflows: Pre-infusion

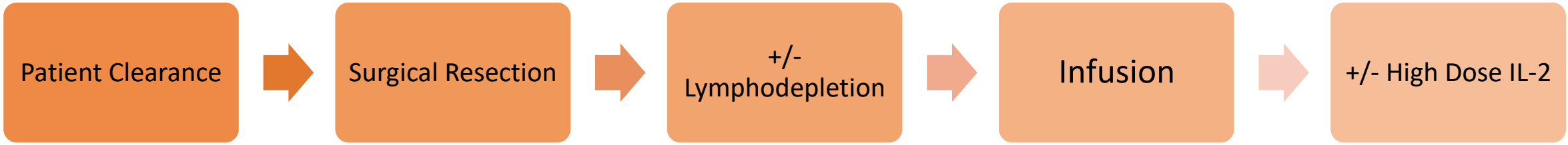
Commercial CAR-T (Ag testing not technically required)



Solid Tumor IEC (Ag pre-screen)



Non-Gene Modified



How do we build a program that will adapt and adequately address this evolving field?

Is it time to carpool?

Legal, Financial, Contracting

Platform Specific Expertise & Knowledge Sharing

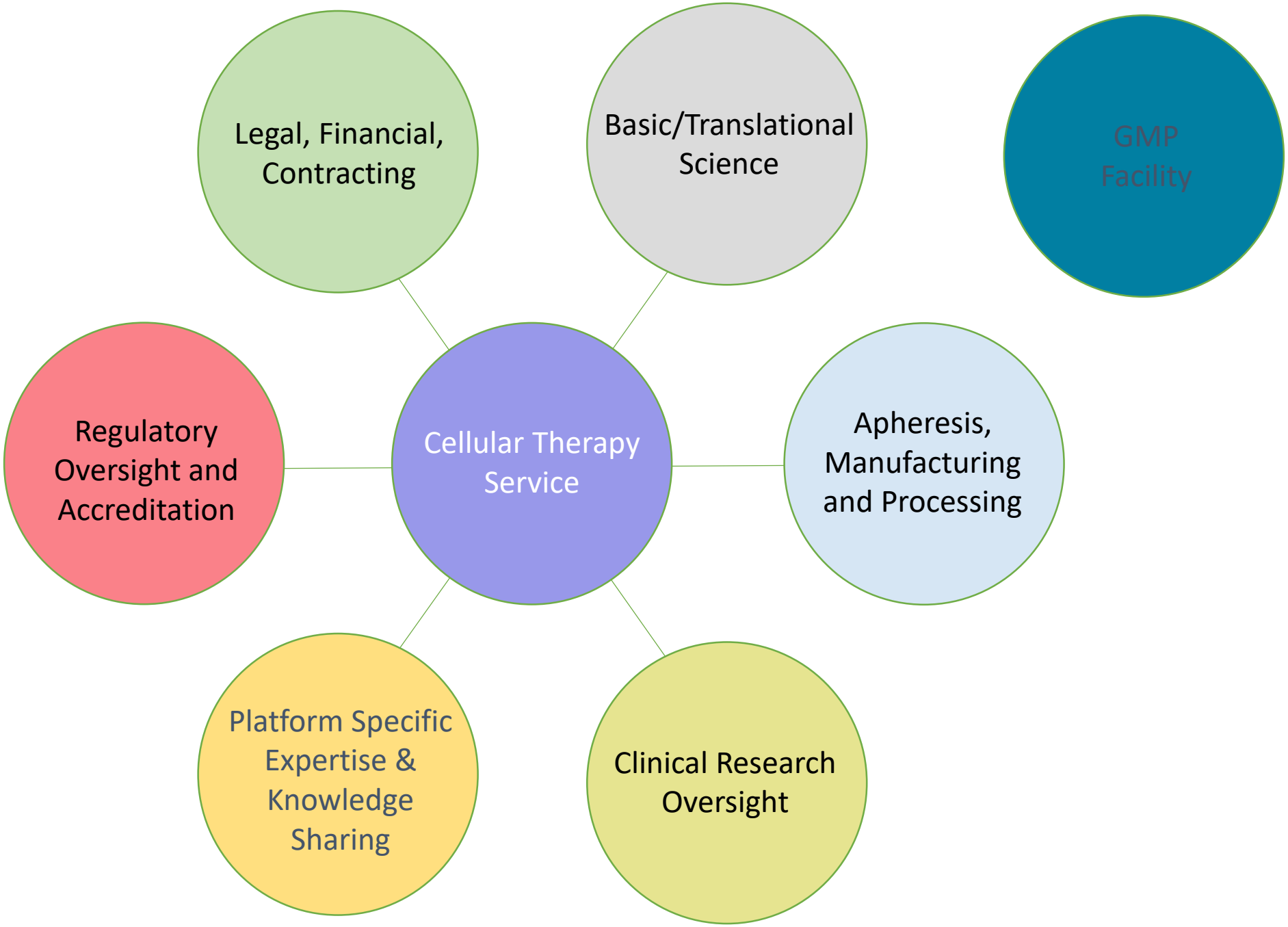
Basic/Translational Science

Apheresis, Manufacturing and Processing

Regulatory Oversight and Accreditation

Disease-centric Silos

Clinical Research Oversight


Legal, Financial, Contracting
Basic/Translational Science
GMP Facility
Regulatory Oversight and Accreditation
Cellular Therapy Service
Apheresis, Manufacturing and Processing
Platform Specific Expertise & Knowledge Sharing
Clinical Research Oversight

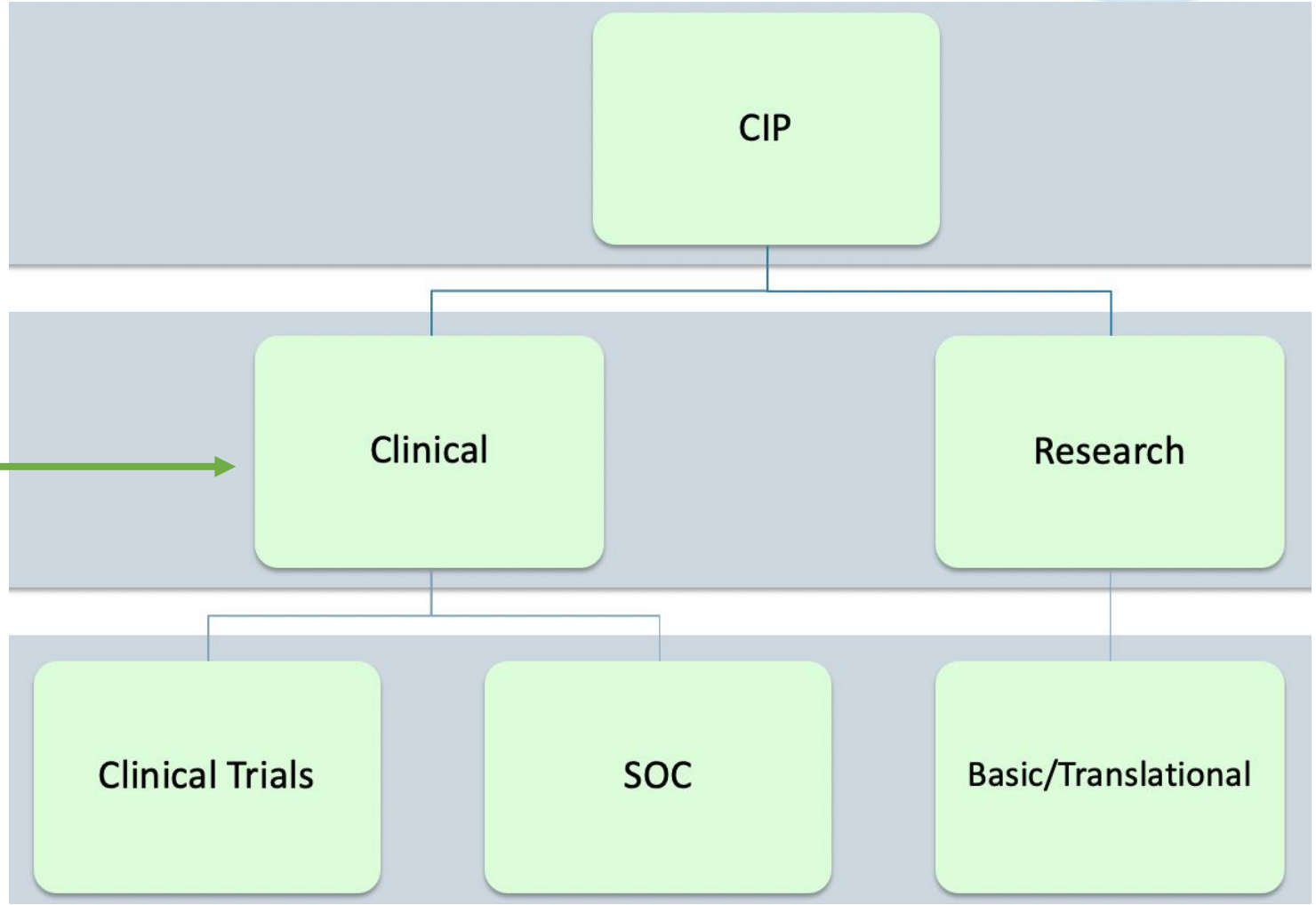
The IEC Dealership

Provides Overlapping Infrastructure

Funnels patients into clinical apparatus

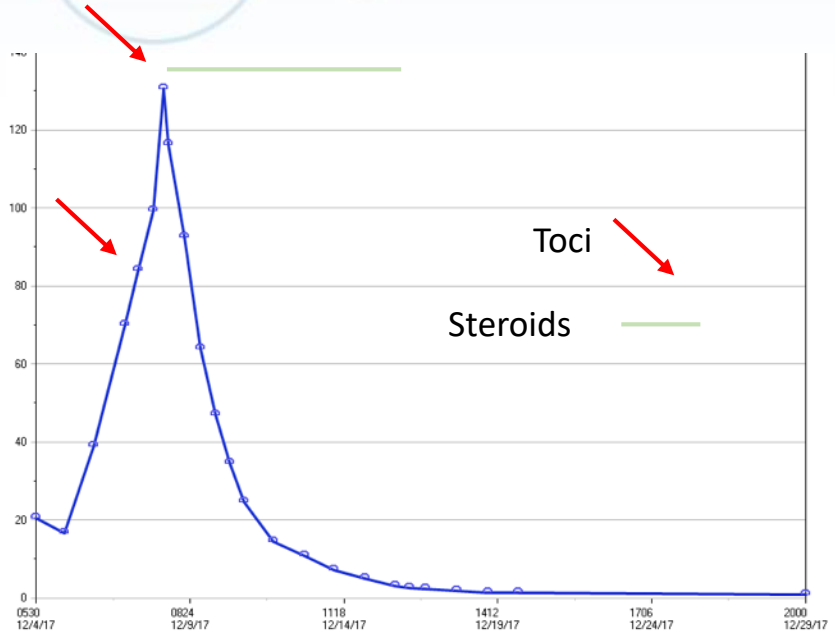
Provides clinical care and data reporting

Disease Specific Silos → HLA/Ag Pre-Screen (if needed) →



Case Examples

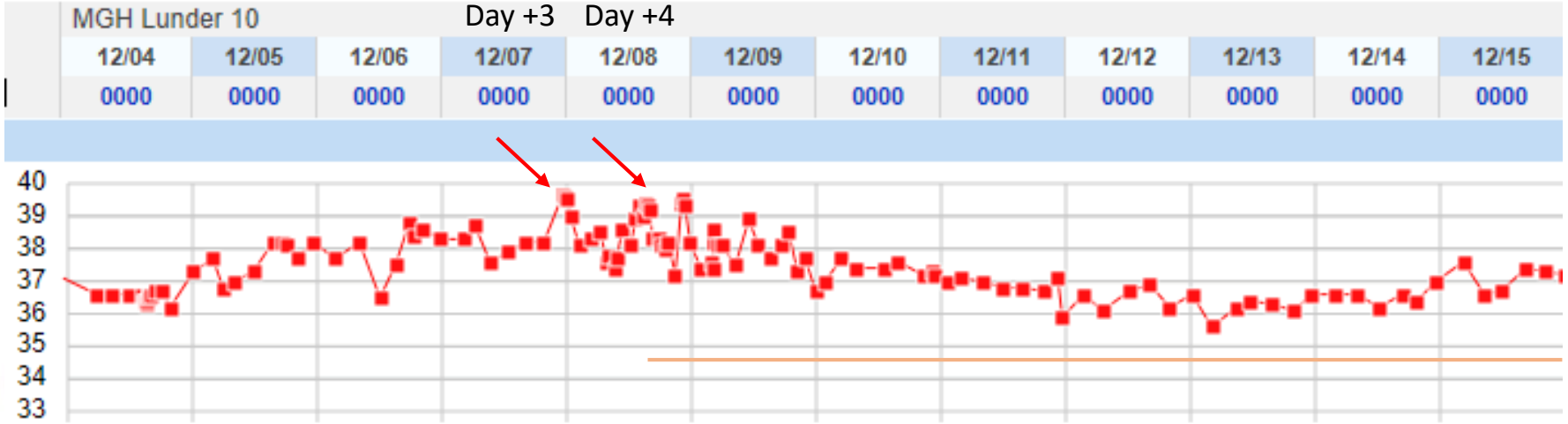
Patient 1 – CRS + Neurotox

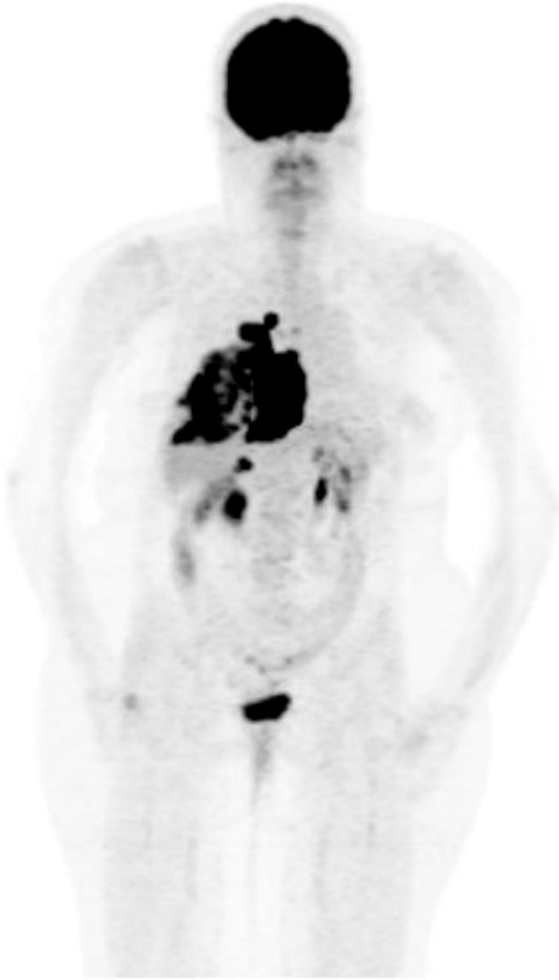


75-year-old female with R/R DLBCL

Treatment History:

- 3/14/14: DLBCL Diagnosed
- 04/201—10/2014: R-CHOP + HD MTX
- 07/2016: Relapsed disease
- 08/2016-10/2016: R-ICE
- 12/1/16: D0 BEAM ASCT
- 10/2017: Relapsed disease
- 12/4/17: CAR-T D0 infusion





PET 2 months prior to infusion

Clinical Course

12/10 (+6):

- Patient increasingly confused, new aphasia and increasing lethargy **(grade 1 CRS, grade 3 ICANS).**
  - EEG reportedly c/w global dysfunction atypical of pure delirium. Short burst of epileptiform activity.

12/11 (+7): Remained minimally responsive, continued on ppx AEDs and steroids

- CNS imaging negative.

12/12 (+8): Improving MS, opened eyes, moved extremities, still would not follow commands.

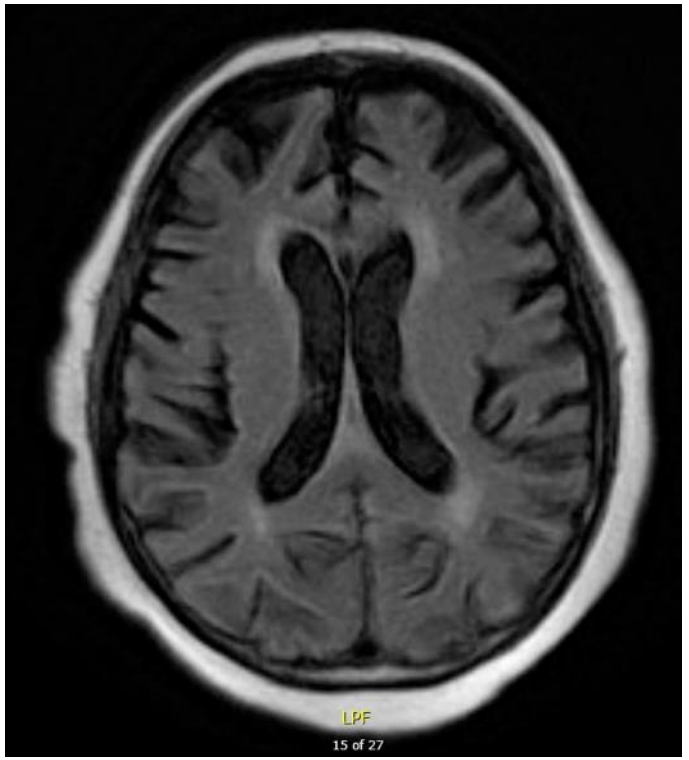
12/13 (+9): Began to respond to commands.

12/17 (+13): More conversant, stated she was at "MGH" and woke up at 6am stating "I want to get better."

12/19 (+15): Responding to commands, speaking to family in short bursts.

12/20 (+16): Discharged to rehab, speaking full sentences.

D+912: Remains in CR!



T2 Space Flair w/DWI

Gust et al. Cancer Discovery 2017.

Questions?

mfrigault@partners.org