Chimeric Antigen Receptor (CAR) T Cell Therapy Toxicity

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Conflict of Interest Disclosure

Lori Muffly MD MS

- Consulting Fees: Pfizer, KITE
- Contracted Research: Baxalta, Adaptive, Astellas
- Ownership Interest: Corvus (stock)

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Objectives

- Overview of CAR T Cell Therapy
- Common CAR T Cell Toxicities:
  - Cytokine Release Syndrome (CRS)
  - Neurological Toxicity (Neurotox)
  - On target, off tumor side effects
  - Cytopenias and infections
- The Patient Experience

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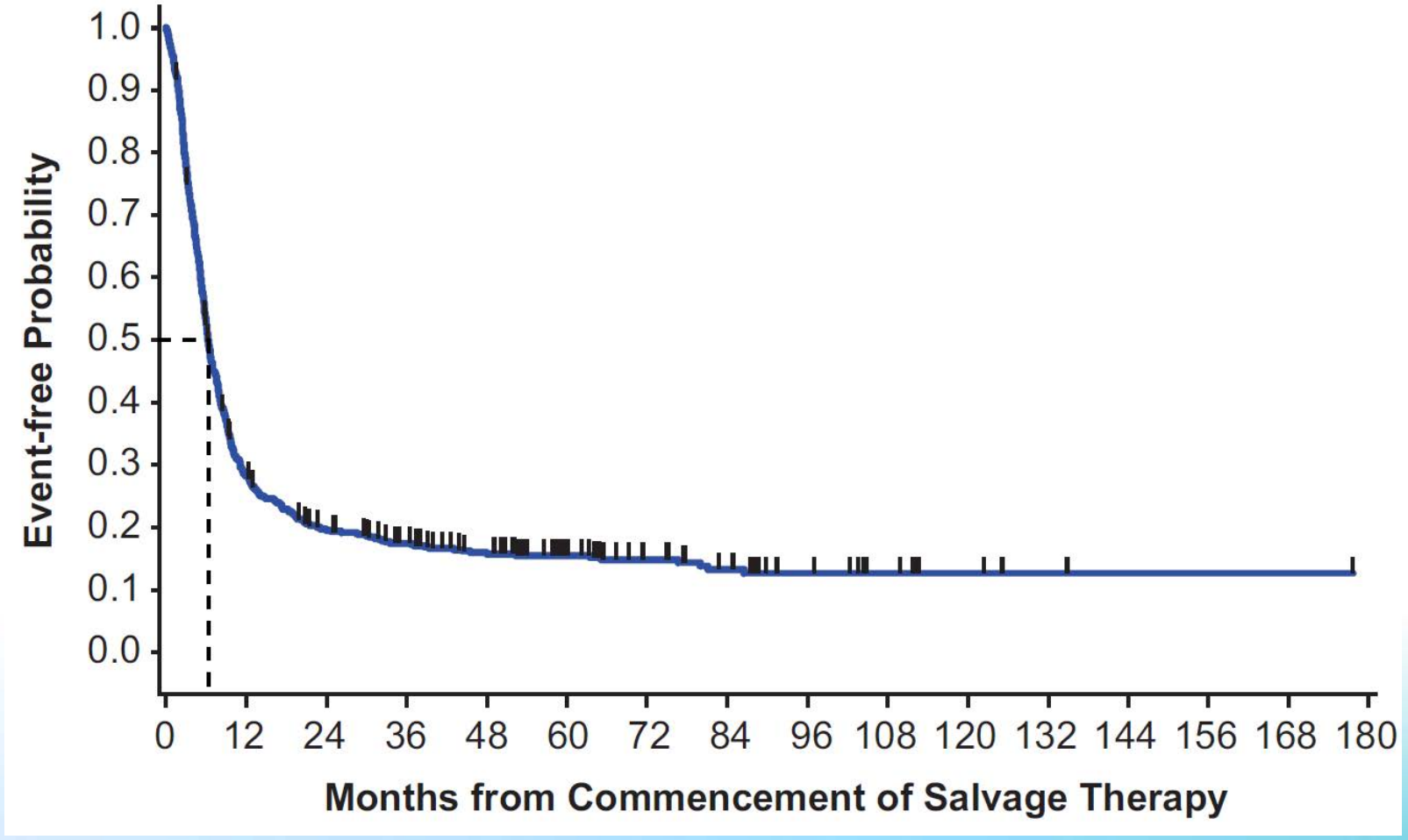
Case Presentation: Mr. W.

- 58 year old rancher diagnosed with B-cell acute lymphoblastic leukemia (ALL) in May, 2018
- Initial remission with chemotherapy quickly followed by relapse in the marrow and skin
- No response to salvage blinatumomab or inotuzumab
- March, 2019: Skin involvement throughout trunk, face, neck; circulating blasts; declining KPS
- Enrolled onto CCT5001: Phase 1 Dose Escalation Study of CART 19-22 in Adults with Relapsed or Refractory Diffuse Large B-cell Lymphoma or Acute Lymphoblastic Leukemia (NCT 03233854)

Refractory Blood Cancers Continue to Have Very Poor Outcomes



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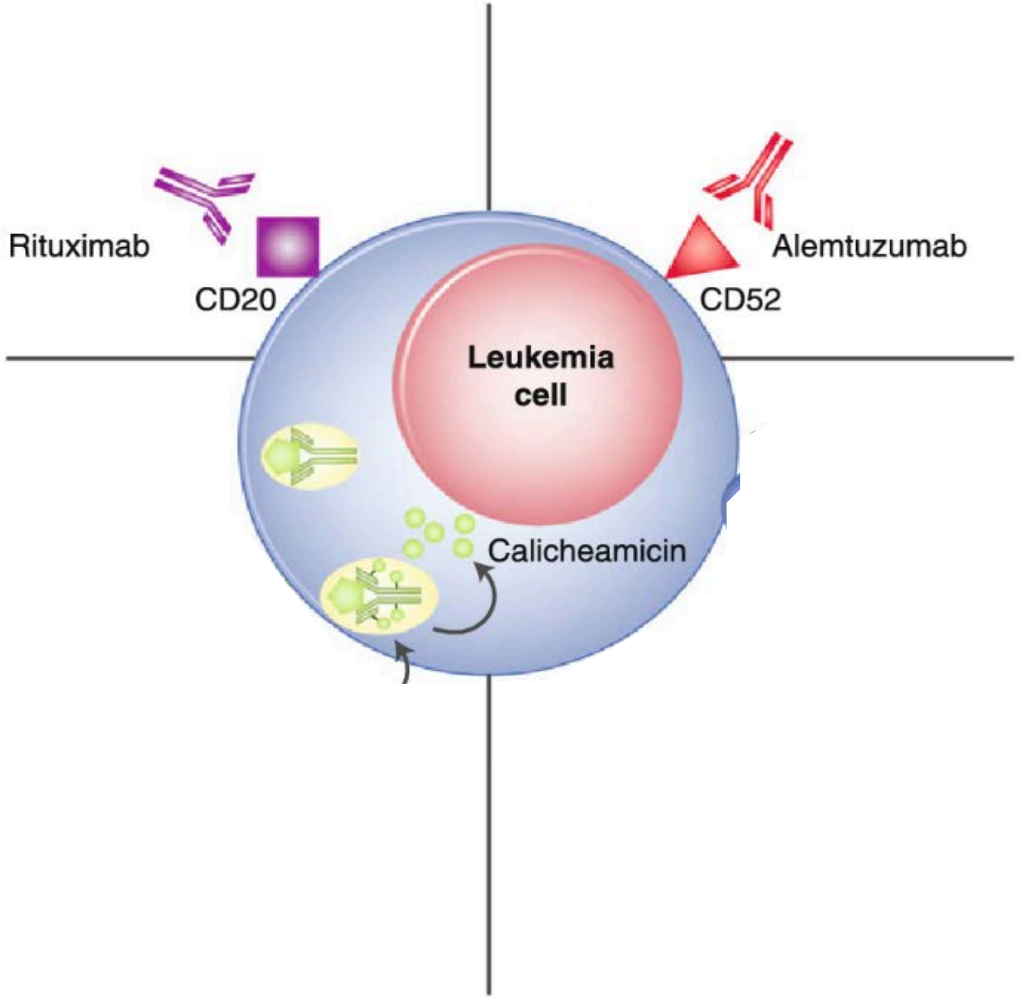
Crump M, et al. Blood. 2017

Success with Targeting Tumor Antigens in Blood Cancers



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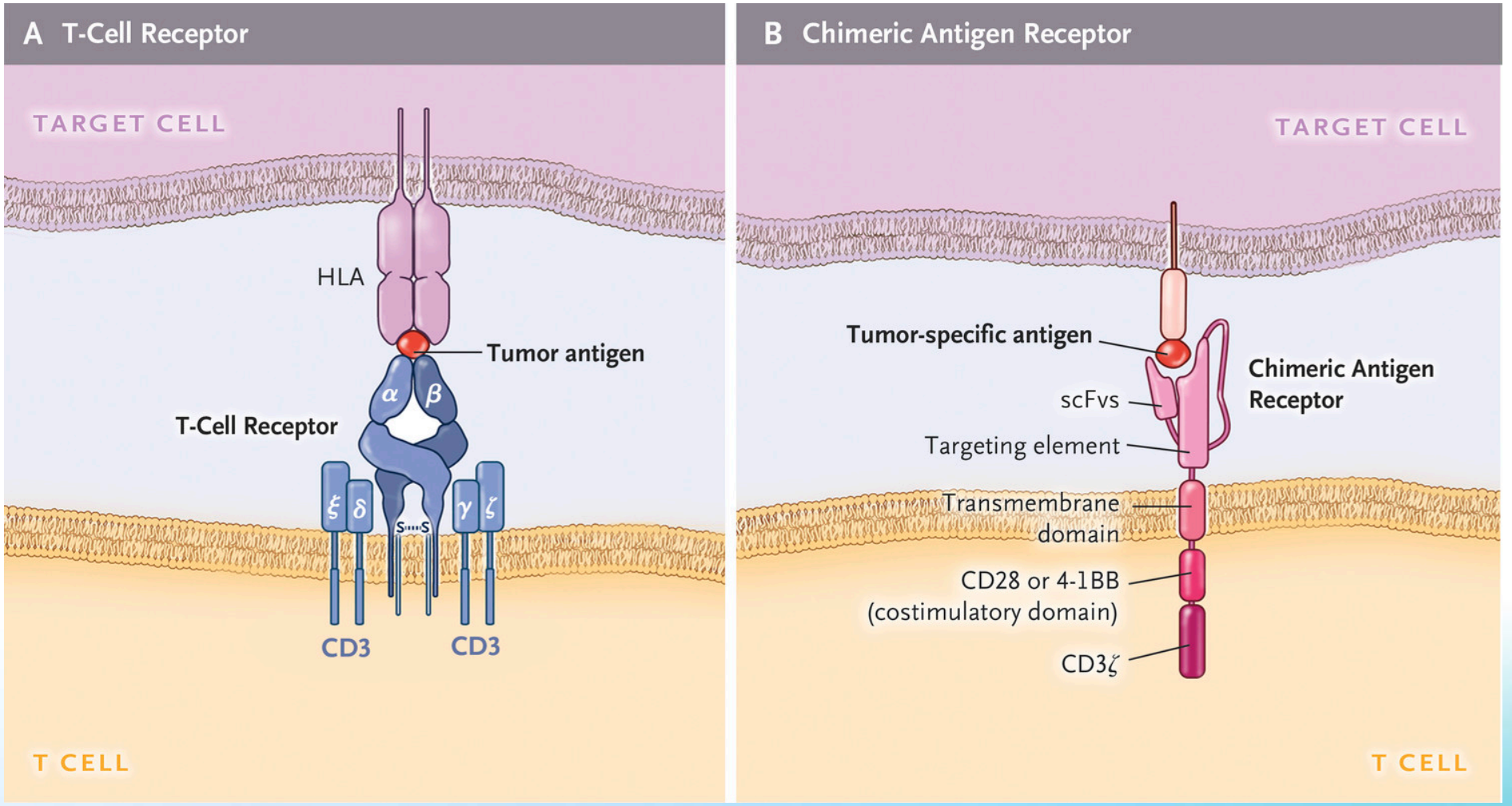
Structure of CARs and T Cell Receptors



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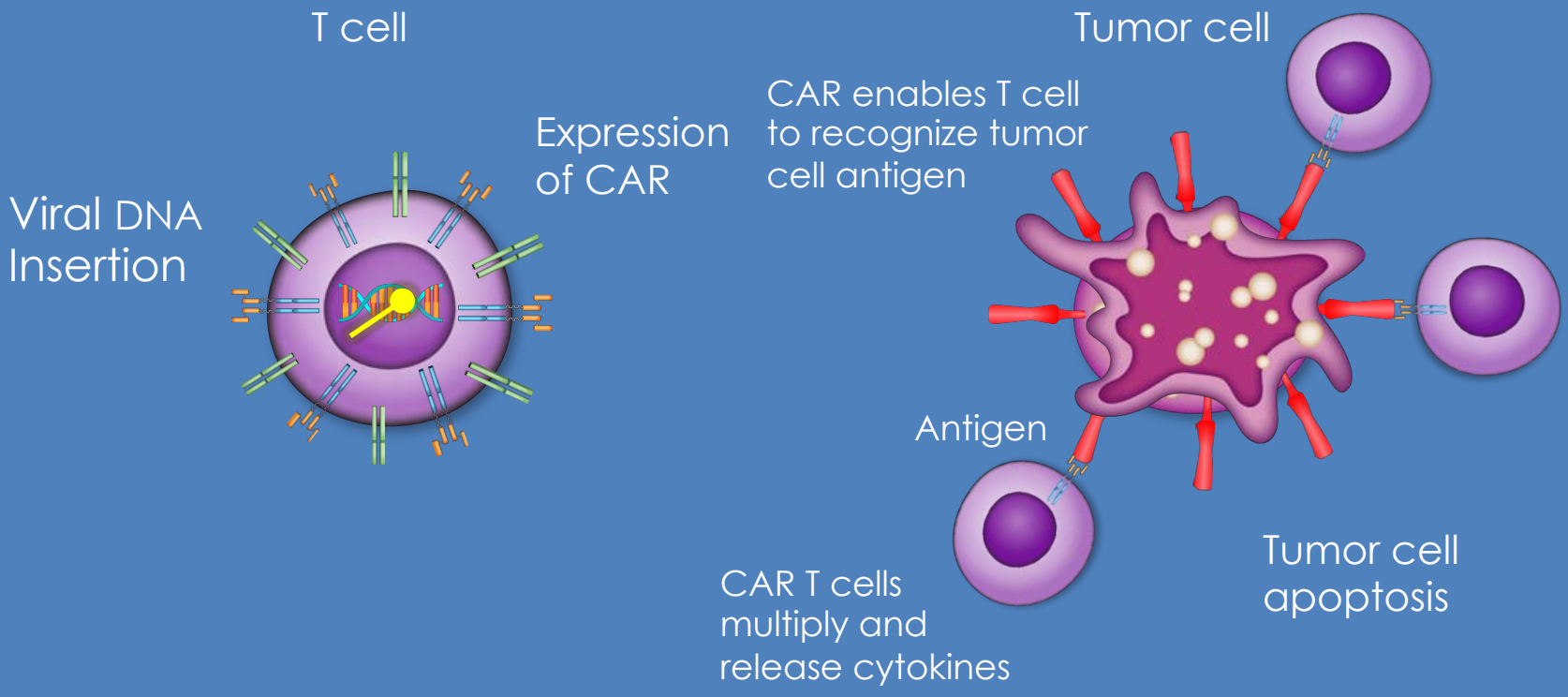
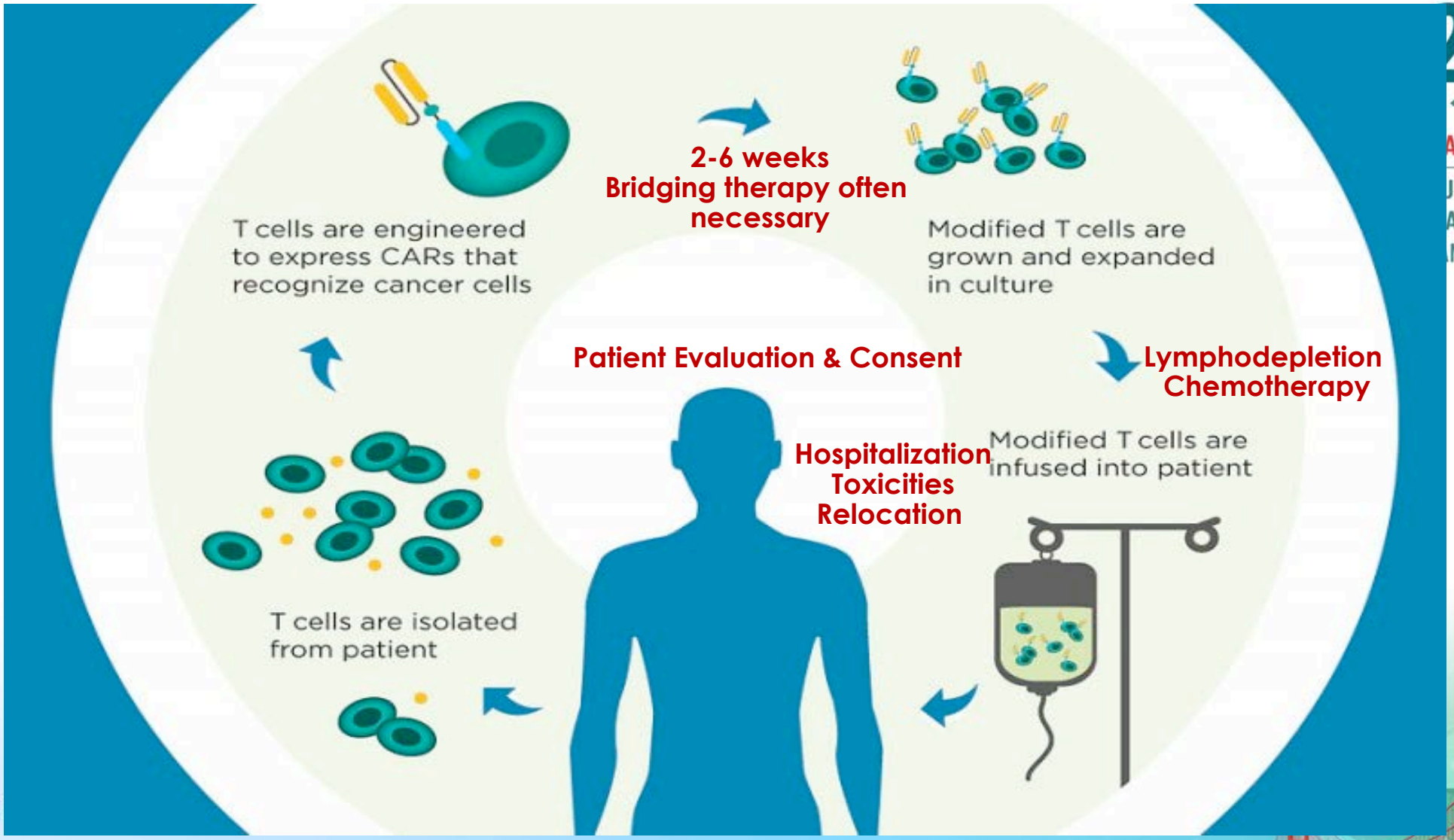
June C NEJM 2018

How CAR T Cells Work



CAR T Cells A re a Living Therapy!

CAR T Cell Therapy Delivery

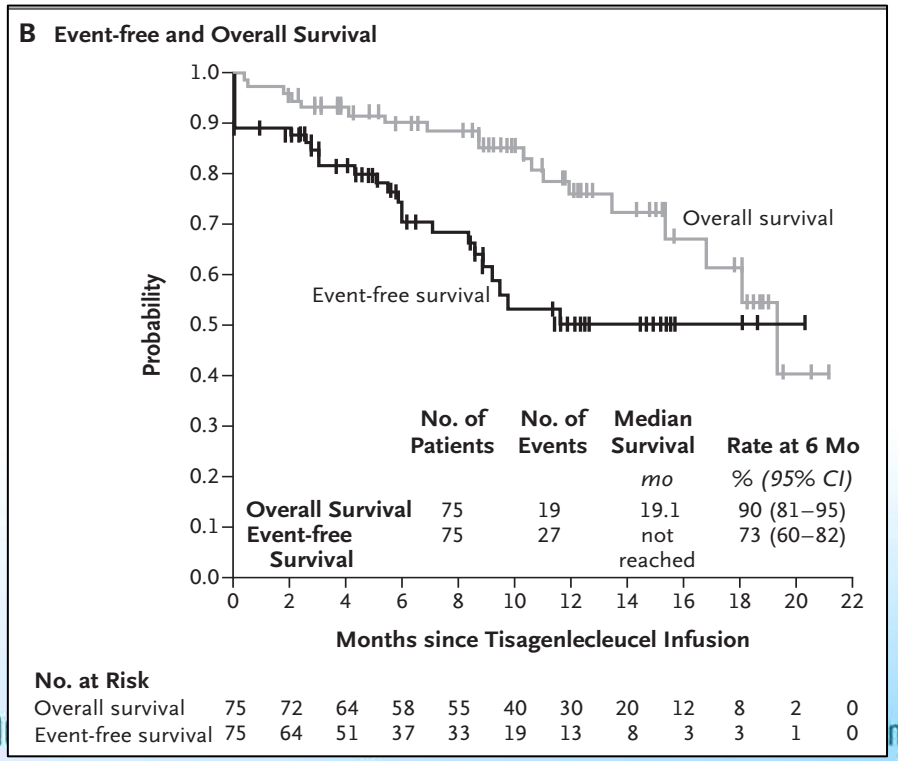


Pivotal Multicenter Trials in ALL & DLBCL

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

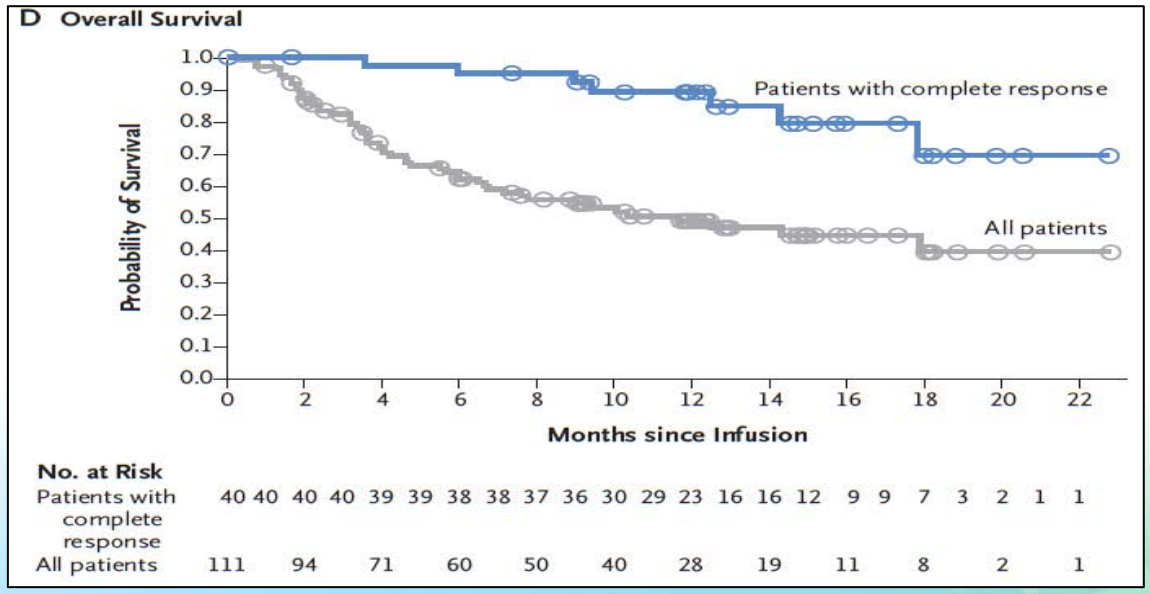
S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp



ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go



Maude et al. NEJM 2018; Neelapu SS et al. NEJM 2017

F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment

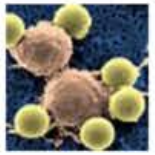
By DENISE GRADY JULY 12, 2017

343

F.D.A. Approves Second Gene-Altering Treatment for Cancer

By DENISE GRADY OCT. 18, 2017

RELATED COVERAGE



Immune System, Loaded With Remade T-cells, Vanquishes Cancer SEPT. 12, 2011

A Breakthrough Against Leukemia Using Altered T-Cells DEC. 9, 2012

Neil July 14, 2017

CAR Therapy: Past, Present, Future

Development of Chimeric T-cell receptor expressing CTL with antibody specificity[1]

Development and demonstration of in-vivo activity for scFv CAR[2,3]

Development of scFv CAR against a B-cell lymphoma idiotype[4]

Use of ligands to CD28 & 4-1bb to enhance CTL expansion[5]

First in-human data for the use of scFv CAR against Ovarian Cancer[6]

Development of CAR directed against CD19[7,8]

First in-human data for the use of CAR against CD19 expressing NHL[9]

Clinical Evaluation and Approval of Anti-CD19 CAR-T therapy in B-cell malignancies

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>300 CAR T Cell Clinical Trials Across Cancer Types

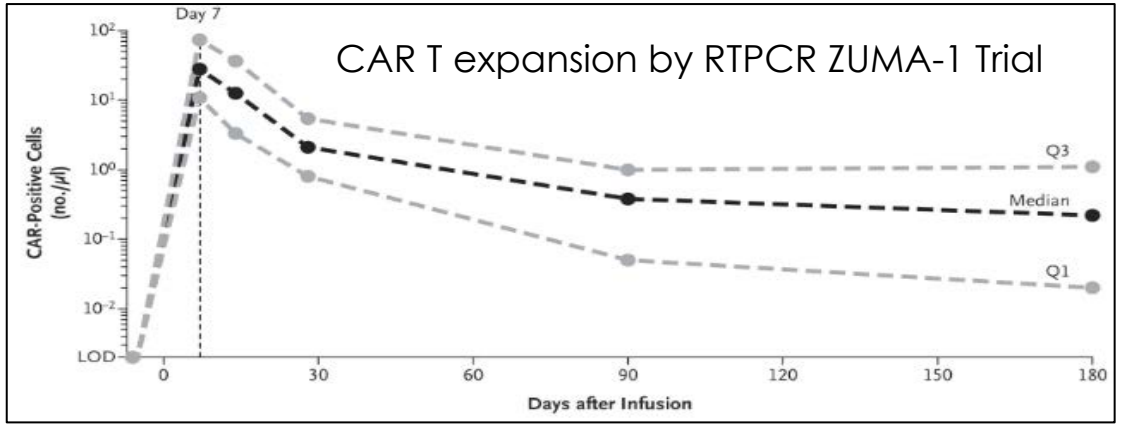
1. Gross G et al; Transplant Proc. 1989 Feb;21(1.1):127-30
2. Esshar Z et al; Proc Natl Acad Sci U S A. 1993 Jan 15;90(2):720-4
3. Hwu P et al; Cancer Res. 1995 Aug 1;55(15):3369-73
4. Gross G et al; Biochem Soc Trans. 1995 Nov;23(4):1079-82
5. 5. Maus MV et al; Nat Biotechnol. 2002 Feb;20(2):143-8
6. Kershaw MH et al; Clin Cancer Res. 2006 Oct 15;12(20.1):6106-15
7. Milone MC et al; Mol Ther. 2009 Aug;17(8):1453-64
8. Kochendorfer JN et al; J Immunother. 2009 Sep;32(7):689-702
9. Konchendorfer JN et al; Blood. 2010 Nov 18;116(20):4099-102

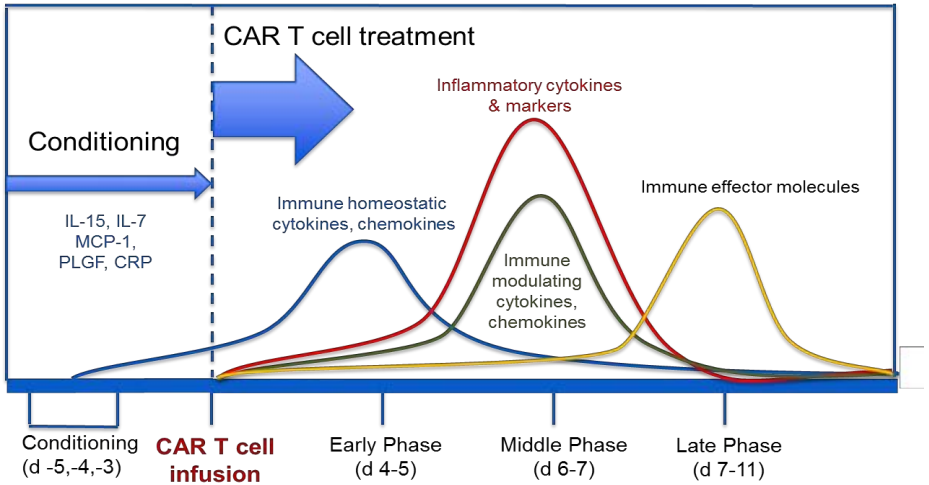
Case Presentation: Mr. W, cont.

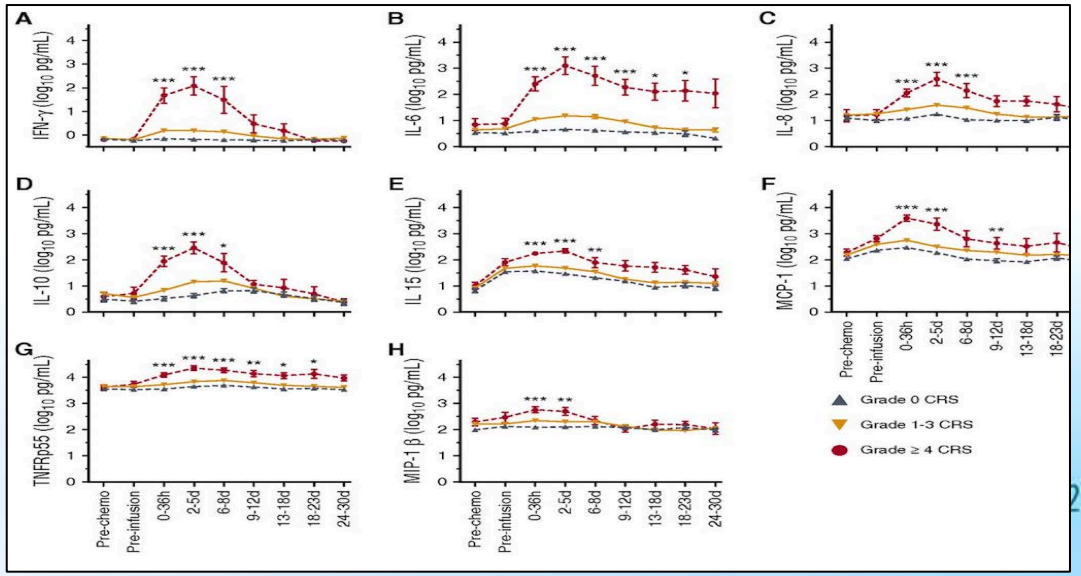
- 58 year old man with relapsed B-ALL, enrolled on clinical trial of CART 19-22
- Lymphodepletion followed by infusion of CART $3x10^6$/kg April 10, 2019 (Day 0)
- Day +4: febrile with hypoxemia requiring high flow oxygenation consistent with ***Grade 3 CRS***
- Received tocilizumab 8mg/kg IV x 1 and dexamethasone 10mg IV x 1

Cytokine Release Syndrome (CRS)

- **CRS:** Supraphysiologic response following immunotherapy- clinically presents as fever, hypotension, capillary leak







Associated with rise in IFN-, IL-6, IL-10, IL-2, others

Hay K et al Blood 2017

CRS Grading Scale

American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥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)

- CRS is common after CAR T cell therapy (50-95% incidence)
- Grade 3-4 CRS occurs in 5-30%

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CRS Management

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥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)

Supportive Care

Tocilizumab +/- Steroids

Tocilizumab + Steroids (Dex q6)

Alert ICU

Solumedrol 1 gm x 3

ICU Care

Tocilizumab: IL6 receptor antagonist, FDA approved for the treatment of CAR T associated CRS in Aug, 2017

Additional agents under investigation for CRS:

- Anakinra: IL1 receptor antagonist (FDA Indication: Rheumatoid arthritis)
- Siltuxumab: IL6 antibody (FDA Indication: Castleman's disease)

Case Presentation: Mr. W, cont.

- 58 year old man with relapsed B-ALL, enrolled on clinical trial of CART 19-22
- Lymphodepletion followed by infusion of CART $3x10^6$/kg April 10, 2019 (Day 0)
- Day +4: developed ***Grade 3 CRS***. Received Tocilizumab + dexamethasone
- Day +6: declining neurological status, ICE score 1/10 consistent with ***Grade 3 Neurotox***.
- Started on dexamethasone 10mg q6, increased Keppra to 1000mg BID, continuous EEG
- Day +7: somnolent, ICE score 0/10, Transferred to ICU and intubated for airway protection. Now consistent with ***Grade 4 Neurotox***.
- Solumedrol 1 gram x 3 days ordered. No seizure activity noted.

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Immune Effector-Cell Associated Neurotoxicity (ICANS)

Table 3
Neurologic and Psychiatric Adverse Reactions Reported with Approved CAR T Products

Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
Encephalopathy: includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism **Delirium:** includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness **Headache:** includes headache and migraine **Anxiety** **Sleep disorder:** includes sleep disorder, insomnia, nightmares	**Encephalopathy:** includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbed attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor **Delirium:** includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness **Headache** **Dizziness:** includes dizziness, presyncope, syncope **Aphasia:** includes aphasia, dysphasia **Motor dysfunction:** includes muscle spasms, muscular weakness **Tremor** **Ataxia** **Seizure** **Dyscalculia** **Myoclonus**

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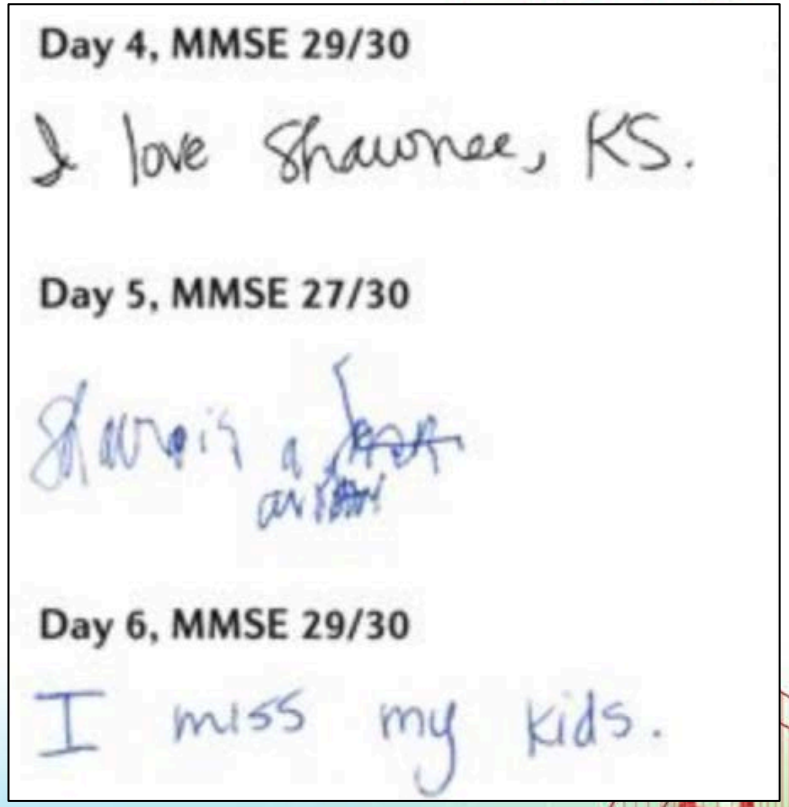
Immune Effector Cell-Associated Encephalopathy Score (ICE)

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point



Neelapu SS Nat Rev Clin Oncol 2018; Lee D et al BBMT 2019

ICANS Consensus Grading

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
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

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

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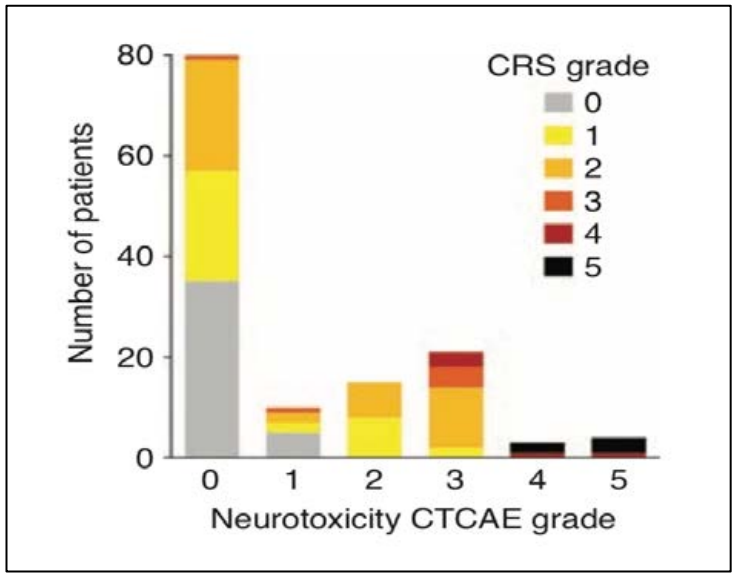
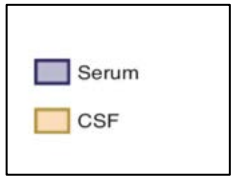
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

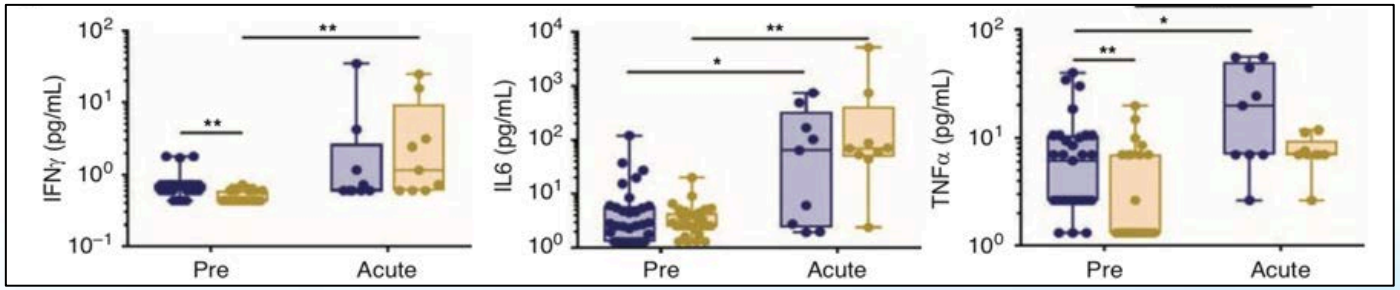
	Grade 1	Grade 2	Grade 3	Grade 4
	Some or all of the following: Spontaneous awakening Mild Confusion Word-finding difficulty Tremor No clinical seizures ICE 7-9	*Some or all of the following:* Awakening to voice Moderate Confusion Expressive aphasia Perseveration No clinical seizures ICE 3-6	*Some or all of the following:* Awakening to tactile stimulus Global aphasia Myoclonus Clinical seizure Brief electrographic seizures ICE 0-2	*Some or all of the following:* Coma/posturing Focal weakness Status epilepticus Pupillary/CN abnormalities Diffuse cerebral edema ICE 0
BMT Physician	• Monitor for progression • Evaluate/treat other causes of encephalopathy • Document neurologic exam • Consult psycho-oncology	• Consult Neurology • Consider neuro checks q2h	• Notify Neurology consultant • Discuss imaging with neurology • Order neuro checks q2h • **Discuss with MICU**	• ABC's; stabilize patient • **Page MICU and give handoff to MICU team** • Emergent CT head when stable to travel • Order neuro checks qhour pending ICU transfer
BMT Nurse	• Neuro checks q4h • Monitor for progression	• Neuro checks q4h • ICE score with neuro checks • Notify Crisis RN • Telemetry and continuous O2	• Neuro checks q2h • ICE score with neuro checks • Notify Crisis RN • Pupillometry with neuro checks if indicated • Telemetry and continuous O2	• Neuro checks qhour while awaiting ICU transfer • ICE score with neuro checks • Notify Crisis RN • Pupillometry with neuro checks • Telemetry and continuous O2 • Give handoff to E2 RN
Neurology Consult		• Consider CT head if focal symptoms • Consider EEG • Follow up EEG read in 1h • Consider empiric increase in AED regimen	• Consider urgent imaging • Consider EEG • Follow up EEG read in 1h if ordered • Consider empiric increase in AED regimen • Consider possibility of diffuse cerebral edema • **Discuss with Neurocritical Care**	• Emergent CT head when stable to travel • Continuous EEG after imaging • Discuss steroids/AED regimen with BMT • **Page Neurocritical Care and give neuro-specific handoff**
Interventions	• Continue Keppra 500 mg BID prophylactically • Reconcile medications to identify other potential contributors • Delirium precautions	• Consider increasing Keppra to 1000 mg BID empirically • Dexamethasone 10mg IV q6-12h depending on CAR-T product • Tocilizumab 8mg/kg if concurrent CRS • ~~Consider melatonin at bedtime~~	• Continue Keppra 1000 mg BID; may add Vimpat 100 mg BID • Dexamethasone 10mg IV q6h; reassess daily • Tocilizumab 8mg/kg if CRS, not to exceed 3 doses in 24 hours • ~~Consider atypical antipsychotic if hyperactive~~Consult psycho-oncology for delirium	• Adjust antiepileptic drugs based on EEG and discussion with NCC • Methylprednisolone 1g IV daily; reassess daily, taper when able • Tocilizumab 8mg/kg if CRS, not to exceed 3 doses in 24 hours • Consider Anikinra

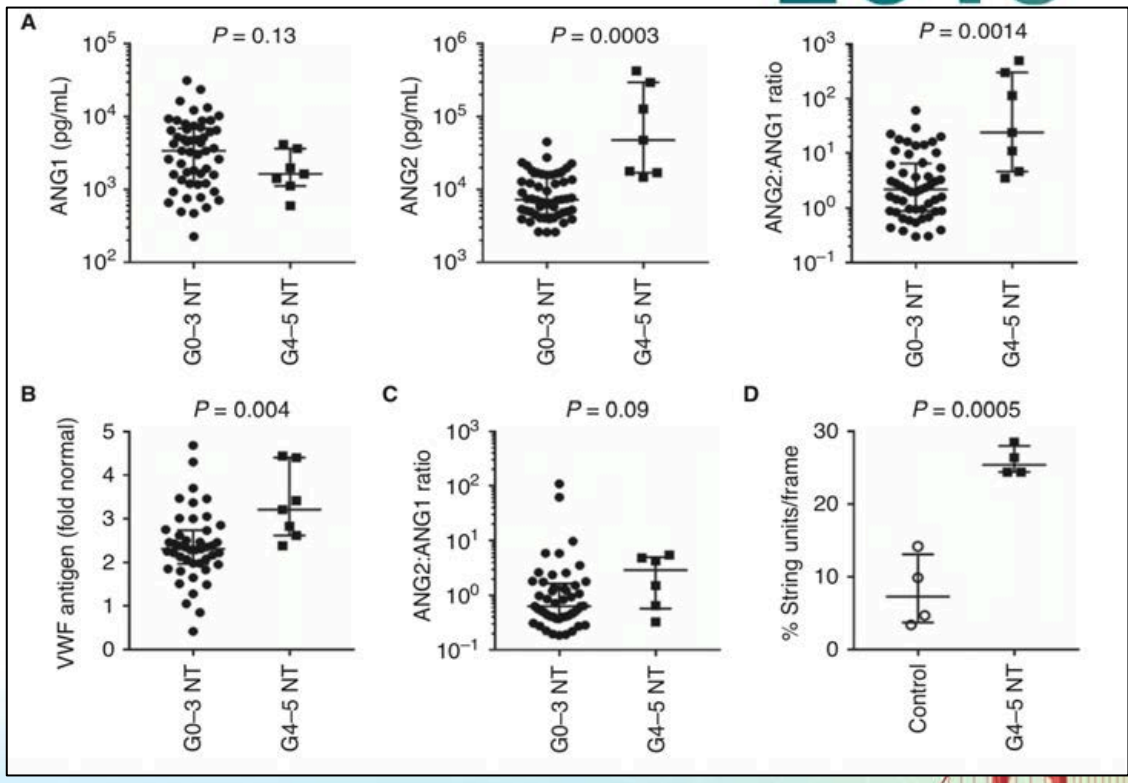
STEROIDS

CAR T Neurotoxicity: CRS, Cytokines, and Vascular Endothelial Activation



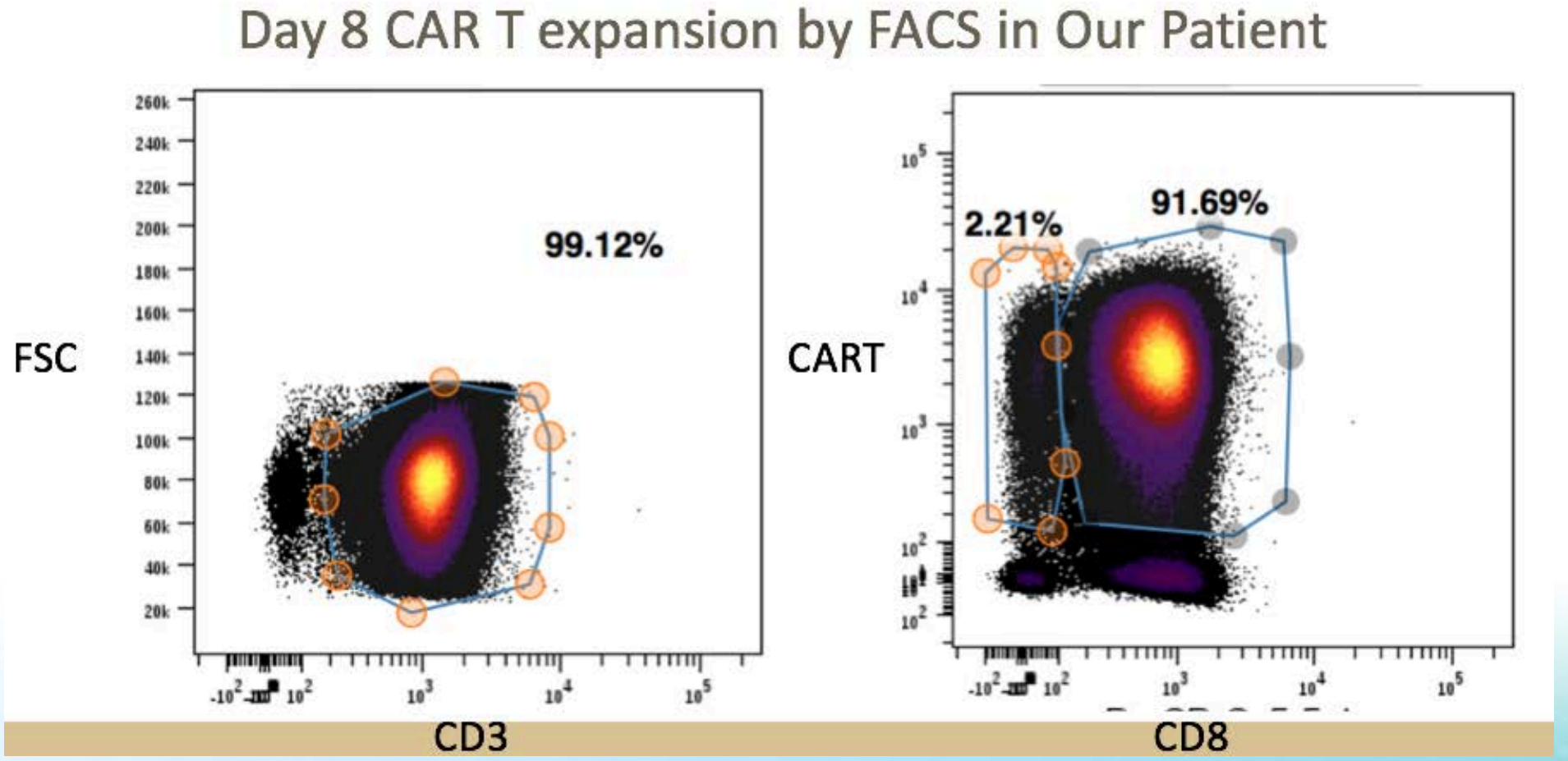






Gust J Cancer Discovery 2019

Why Did Mr. W Develop Grade 3-4 CRS/Neurotoxicity?



Case Presentation: Mr. W, cont.

- 58 year old man with relapsed B-ALL, enrolled on clinical trial of CART 19-22
- Lymphodepletion followed by infusion of CART $3x10^6$/kg April 10, 2019 (Day 0)
- Day +4: ***Grade 3 CRS***
- Day +7 to D+10: Intubated in ICU with ***Grade 4 Neurotoxicity***
- Day +11: neuro status improving, extubated transferred to floor
- Day +12 to D+25: Remained inpatient on BMT/CART floor. Steroids tapered. Very ***debilitated***- working with PT daily. Neurological status improved but with intermittent ***delirium.***
- Day +26: Discharged to local housing with ongoing transfusion needs due to ***prolonged severe pancytopenia.***

Other CAR T Related Side Effects

- Pancytopenia- often prolonged
- On target/off tumor effects
  - Example: hypogammaglobulinemia following CD19 CART
- Infections
- Delirium, cognitive decline, debilitation

CAR T Cell Therapy: The Patient Experience??

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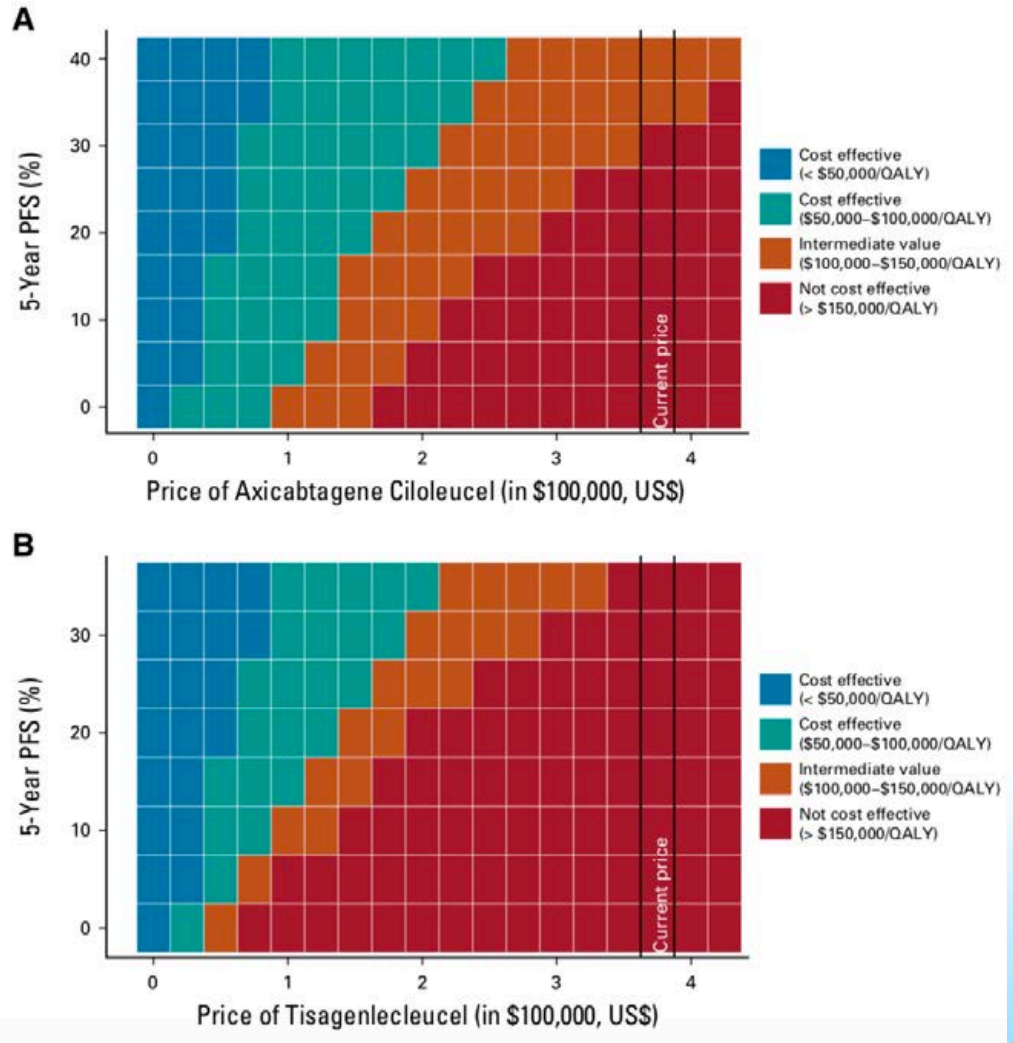
Patient-Reported Outcomes with Chimeric Antigen Receptor T Cell Therapy: Challenges and Opportunities

Rajshekhar Chakraborty[1], Surbhi Sidana[3], Gunjan L. Shah[2], Michael Scordo[2], Betty K. Hamilton[1]
Navneet S. Majhail[1,*]

[1] *Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio*
[2] *Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, New York*
[3] *Division of Hematology, Mayo Clinic, Rochester, Minnesota*

CAR T Cell Therapy: Patient and Societal Financial Toxicity?



Patient costs:

- Travel, co-pays
- Local housing (often extended)
- Mandatory caregiver
- Numerous follow-ups
- Outpatient Physical Therapy
- Skilled Nursing Facility

Lin J et al JCO 2019

The Reason to Continue On…

- 58 yo with refractory B-ALL, enrolled on clinical trial of CART 19-22
- No other treatment options at the time
- Received CAR T cells on April 10, 2019
- Day 28 evaluation showed a complete remission, MRD-negative
- Month 2 evaluation:

SAMPLE-LEVEL MRD RESULT

No Residual Sequence Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - 2) **

Sequence determining MRD result: IGH Sequence A

- Mr. W. is now at home with his family, mostly independent

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CAR T Cell Therapy Toxicity: Summary

- CAR T Cell therapy represents an exciting "living" cancer immunotherapy now available to patients commercially and through clinical trials
- CRS and neurological toxicity are common and can be severe; grading and management require multidisciplinary expertise
- Mainstay of therapy is currently tocilizumab (CRS) and steroids (CRS, neurotoxicity)
- Additional work is required to understand the impact of CAR T on patient-reported symptoms and functioning over time

Stanford CAR T Team

Crystal Mackall – Director

David Miklos - Clinical Ops

Lori Muffly, Kara Davis, Liora Schultz
Jay Spiegel, Matt Frank, Nash Hossain
Janet McDowell, Juliana Craig,
Jenny Yoon, Sharan Craig

Steve Feldman – Manufacturing

Matt Abramian, Shabnum Patel

Sharon Mavroukakis – Regulatory

Emily Egeler

Bita Sahaf - Correlative Science

Sean Bendall

Pathology: Jean Oaks
Eric Yang, Michael Ozawa
Katie Kong

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CIRM
CALIFORNIA'S STEM CELL AGENCY