Oncology Grand Rounds

New Agents and Strategies in Chimeric Antigen Receptor T-Cell Therapy

Tuesday, June 23, 2020

5:00 PM – 6:30 PM ET

Faculty

Krishna Komanduri, MD
Nikhil C Munshi, MD
Sattva S Neelapu, MD
Tiffany Richards, PhD, ANP-BC, AOCNP
Elizabeth Zerante, MS, AGACNP-BC

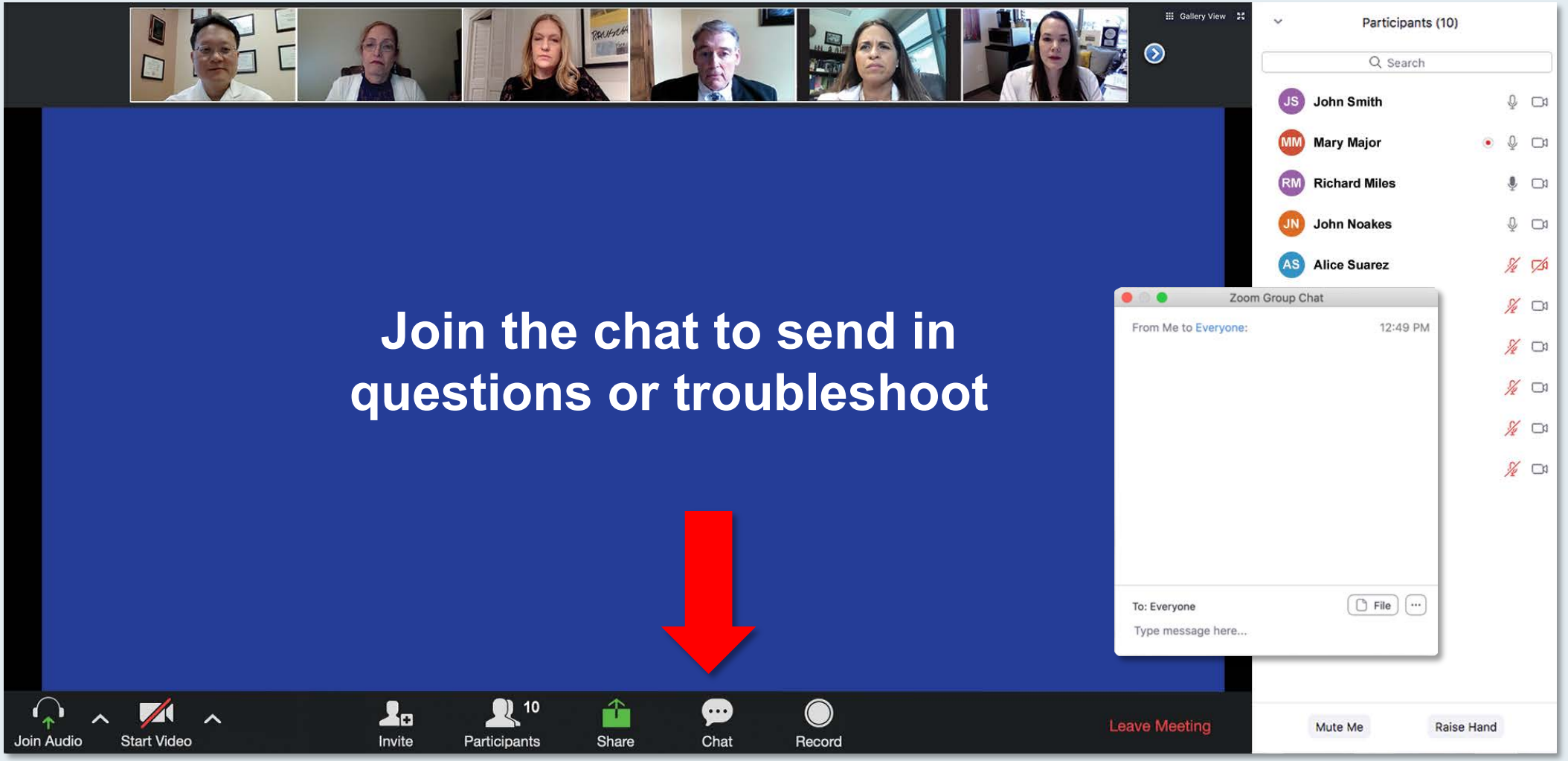
Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Familiarizing yourself with the Zoom interface

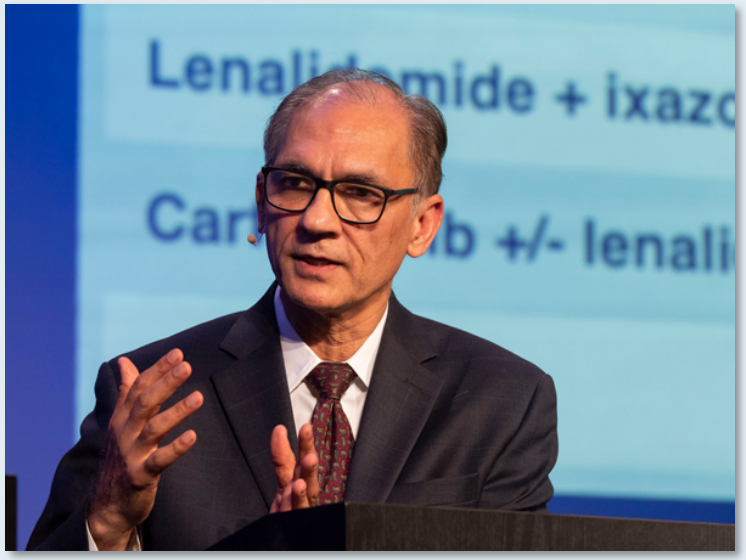
How to participate in the chat



RTP Live Webinar Nursing Series

Monday	Tuesday	Wednesday	Thursday	Friday
25	26 **Breast Ca** **5:00 PM**	27	28 **GI Ca** **5:00 PM**	29
Jun 1	2 **Lymphoma** **5:00 PM**	3	4 **CLL** **5:00 PM**	5
8	9 **GYN** **5:00 PM**	10	11 **Metastatic Lung Ca** **5:00 PM**	12
15	16 **Locally Advanced Lung Ca** **5:00 PM**	17	18 **Bladder Ca** **5:00 PM**	19
22	23 **CAR-T** **5:00 PM**	24	25 **PARP** **5:00 PM**	26
29	30 **Prostate Ca** **5:00 PM**	Jul 1 9 AM	2	3
6	7	8	9	10

About the Enduring Program



- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

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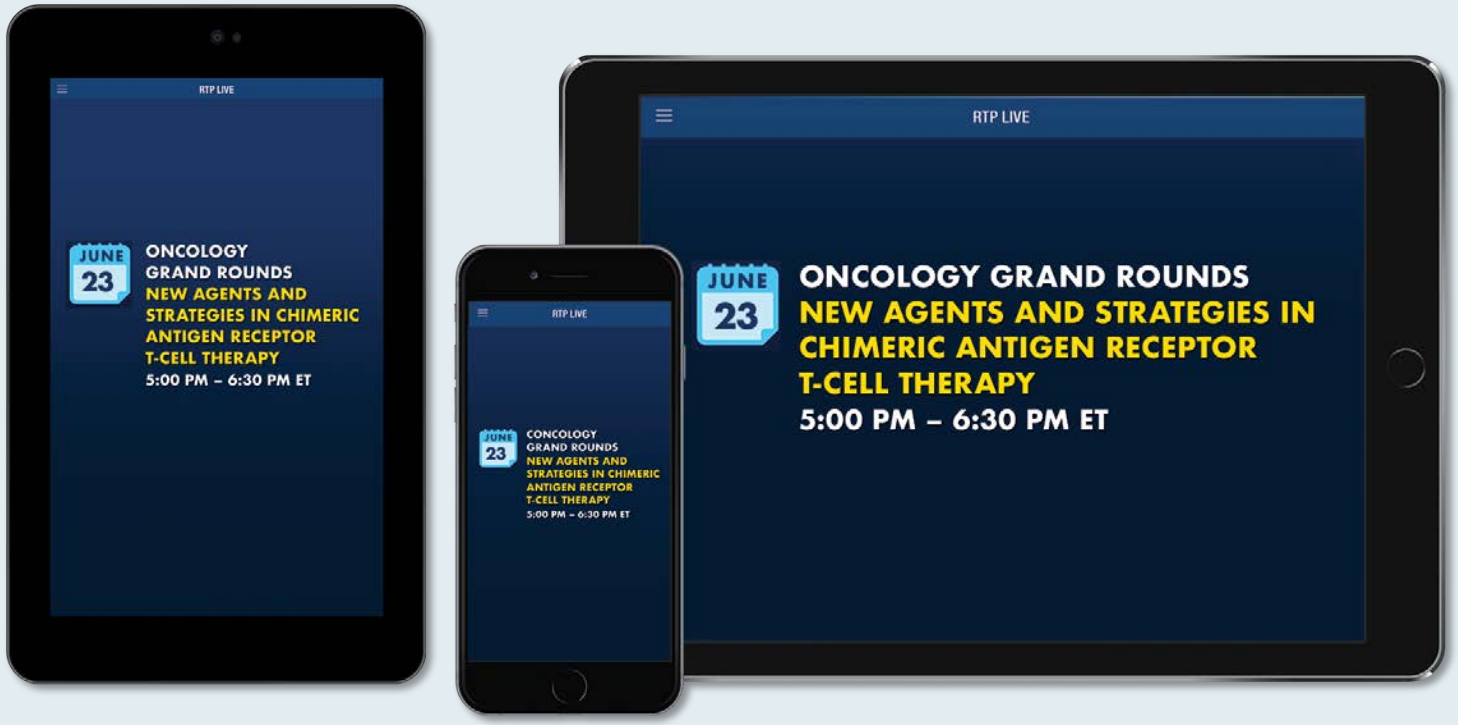

ONCOLOGY TODAY

WITH DR NEIL LOVE

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Chronic Lymphocytic Leukemia and Follicular Lymphoma

Wednesday, June 24, 2020
5:00 PM – 6:00 PM ET

Faculty

Jeff Sharman, MD

Julie M Vose, MD, MBA

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Acute Myeloid Leukemia and the General Medical Oncologist: New Agents and Treatment Strategies, Particularly for Older Patients

An Interactive Meet The Professor Series

Thursday, June 25, 2020
12:00 PM – 1:00 PM

Richard M Stone, MD
Chief of Staff
Director, Translational Research Leukemia Division
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

RTP
RESEARCH
TO PRACTICE

Oncology Grand Rounds

New Agents and Strategies in PARP Inhibition in the Management of Common Cancers

Thursday, June 25, 2020

5:00 PM – 6:30 PM ET

Faculty

Emmanuel S Antonarakis, MD
Gretchen Santos Fulgencio, MSN, FNP-BC
Erika Meneely, APRN, BC
Kathleen Moore, MD
Joyce O'Shaughnessy, MD
Michael J Pishvaian, MD, PhD
Deborah Wright, MSN, APRN, CNS

Moderator

Neil Love, MD

Research To Practice®

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

A Meet The Professor Series

Friday, June 26, 2020
12:00 PM – 1:00 PM

Nikhil C Munshi, MD
Professor of Medicine
Harvard Medical School
Director of Basic and Correlative Science
Associate Director, Jerome Lipper Multiple Myeloma Center
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Co-provided by USF Health RTP RESEARCH TO PRACTICE

DATA + PERSPECTIVES

Clinical Investigators Explore the Biology Underlying the Role of PARP Inhibition in the Management of Common Cancers

Tuesday, June 23, 2020

7:00 PM – 8:00 PM ET

Faculty

Maha Hussain, MD, FACP, FASCO
Ursula Matulonis, MD
Philip A Philip, MD, PhD, FRCP
Hope S Rugo, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Do you miss our music?

a. Very much
b. Not that much
c. I don’t know what you are talking about

Krishna Komanduri, MD
University of Miami Health System
Miami, Florida

Nikhil C Munshi, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

Sattva S Neelapu, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas

Tiffany Richards, PhD, ANP-BC, AOCNP
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Elizabeth Zerante, MS, AGACNP-BC
University of Chicago Medicine
Chicago, Illinois

Agenda

Module 1: Overview of Chimeric Antigen Receptor (CAR) T-Cell Therapy

- Case Presentation: Ms Zerante — 73-year-old woman with DLBCL

Module 2: Side Effects Associated with CAR T-Cell Therapy

- Case Presentation: Ms Zerante — 23-year-old woman with ALL

Module 3: Anti-BCMA CAR T-Cell Therapy in Multiple Myeloma (MM)

- Case Presentation: Dr Richards — 58-year-old woman with MM
- Case Presentation: Dr Richards — 62-year-old man with MM

Module 4: CD19-Directed CAR T-Cell Therapy for Aggressive Lymphomas

- Case Presentation: Ms Zerante — 79-year-old man with DLBCL

Module 5: CAR T-Cell Therapy in Acute Lymphoblastic Leukemia (ALL)

- Case Presentation: Ms Zerante — 41-year-old woman with ALL

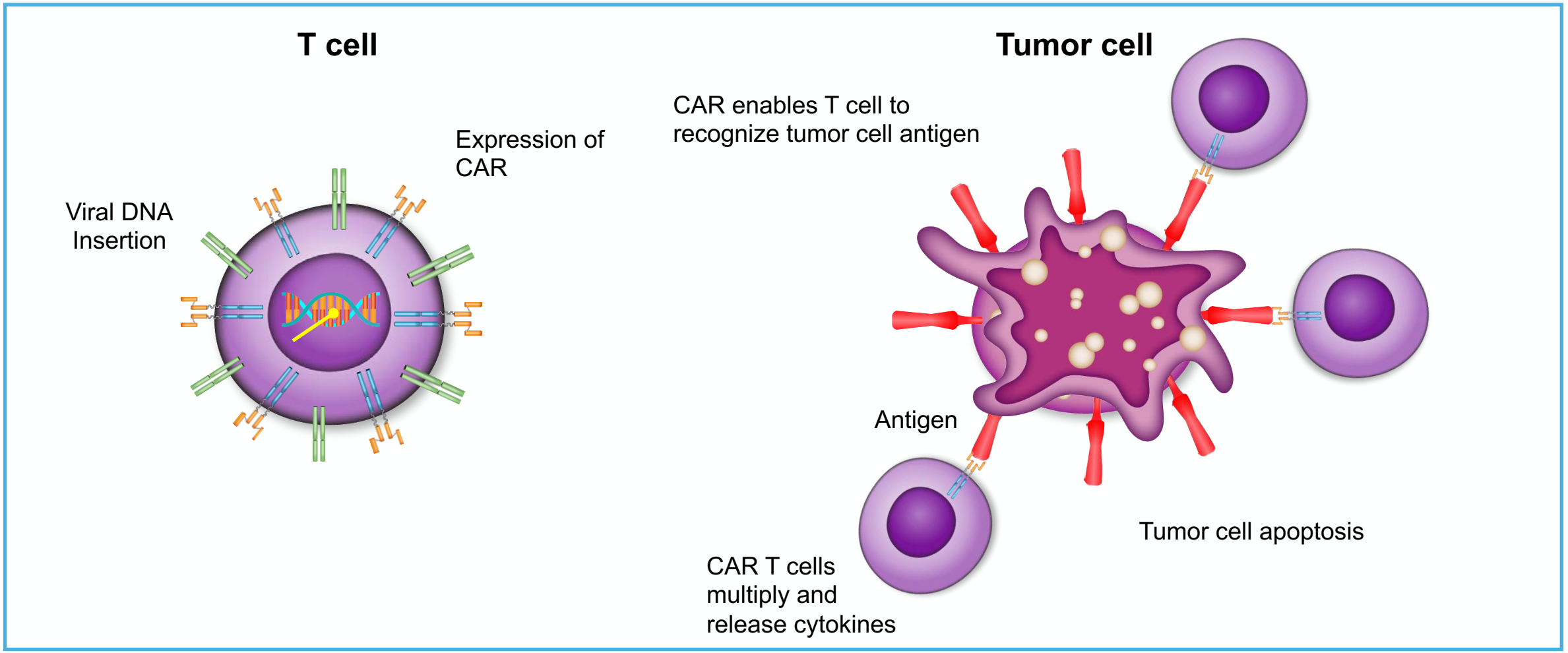
Module 1: Overview of Chimeric Antigen Receptor (CAR) T-Cell Therapy

- Immune mechanisms and therapies in oncology
  - Allogeneic transplant
  - Checkpoint inhibitors
  - Vaccines (eg, sipuleucel-T)
- Biology of CAR-modified T cells
- Production and administration of CAR T cells
- Available CAR-T products
- Overview of efficacy of CAR-T therapy

When is the last time a patient in your practice or care died of large cell lymphoma, multiple myeloma or acute lymphoblastic lymphoma?

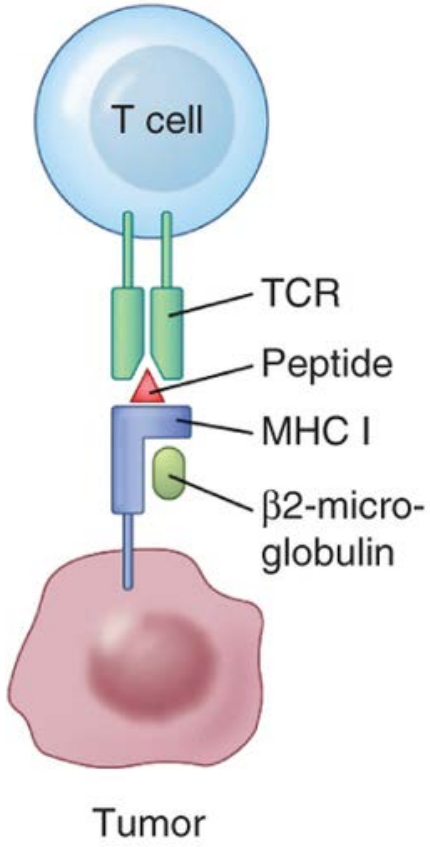
a. Within the past week
b. Between 1 week and 1 month ago
c. Between 1 month and 6 months ago
d. Between 6 months and 1 year ago
e. More than 1 year ago
f. I have not encountered a patient death by these causes

CAR T Cells: Mechanism of Action

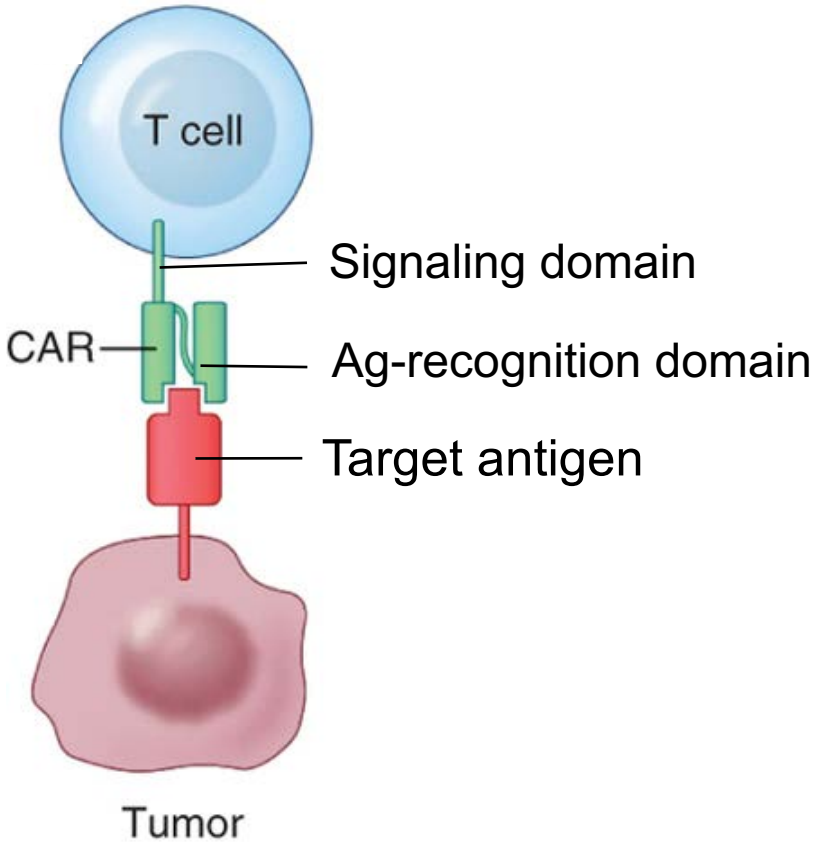


Chimeric Antigen Receptor (CAR) Modified T cells

Normal T cell



CAR T cell

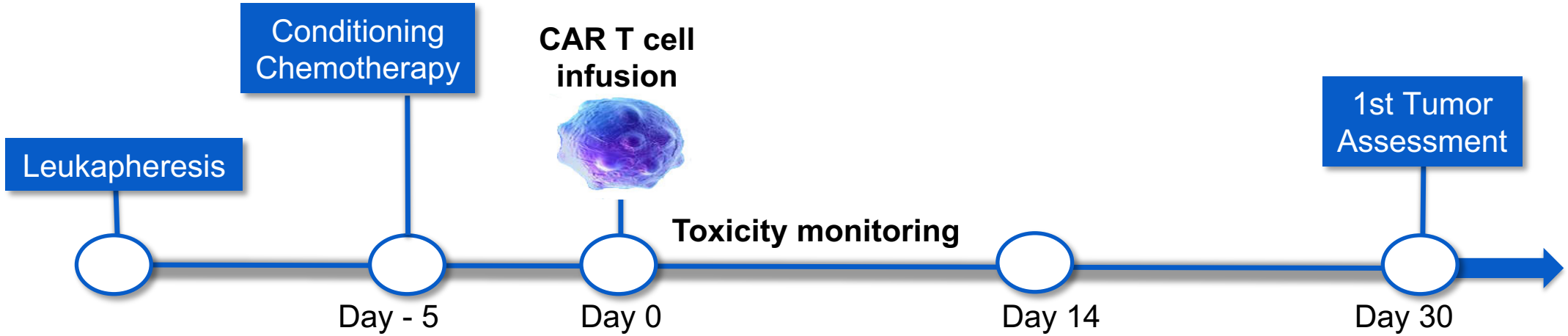


- **Genetically engineered T cells altered to express an artificial receptor, CAR**

Courtesy of Sattva S Neelapu, MD

Adapted from Hinrichs & Restifo. Nat Biotech 2013

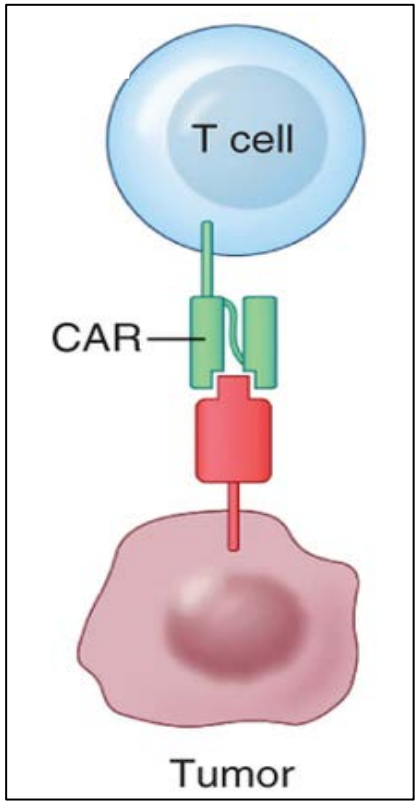
Treatment schema for CAR T-cell therapy



Courtesy of Sattva S Neelapu, MD

CAR T cell response to antigen

CAR T cell



- Proliferate
- Make cytokines
- Kill the target cells

Courtesy of Sattva S Neelapu, MD

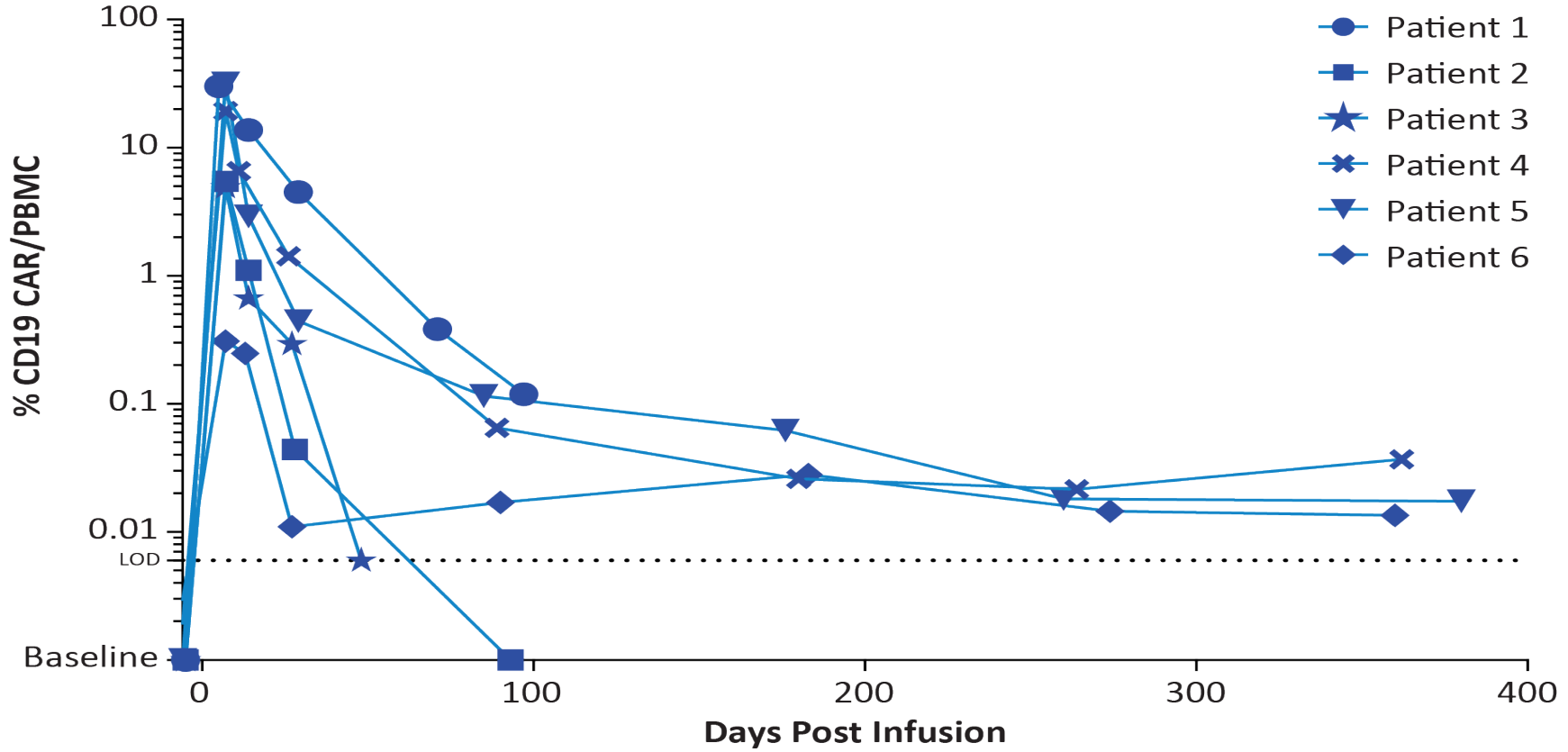
CD19 CAR T products in pivotal trials in NHL

	NCI	U Penn	FHCRC / SCH
CD19 Ab	FMC63	FMC63	FMC63
Hinge	CD28	CD8a	CD28
Transmembrane			
Signal 2	CD28	4-1BB	4-1BB
Signal 1	CD3ζ	CD3ζ	CD3ζ
Gene transfer	Retrovirus	Lentivirus	Lentivirus
	KTE-C19 **Axicabtagene ciloleucel** **Axi-cel**	**CTL-019** **Tisagenlecleucel**	**JCAR017 (CD4:CD8 = 1:1)** **Lisocabtagene maraleucel** **Liso-cel**

Courtesy of Sattva S Neelapu, MD

Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

CAR T-cell expansion and persistence after axi-cel infusion

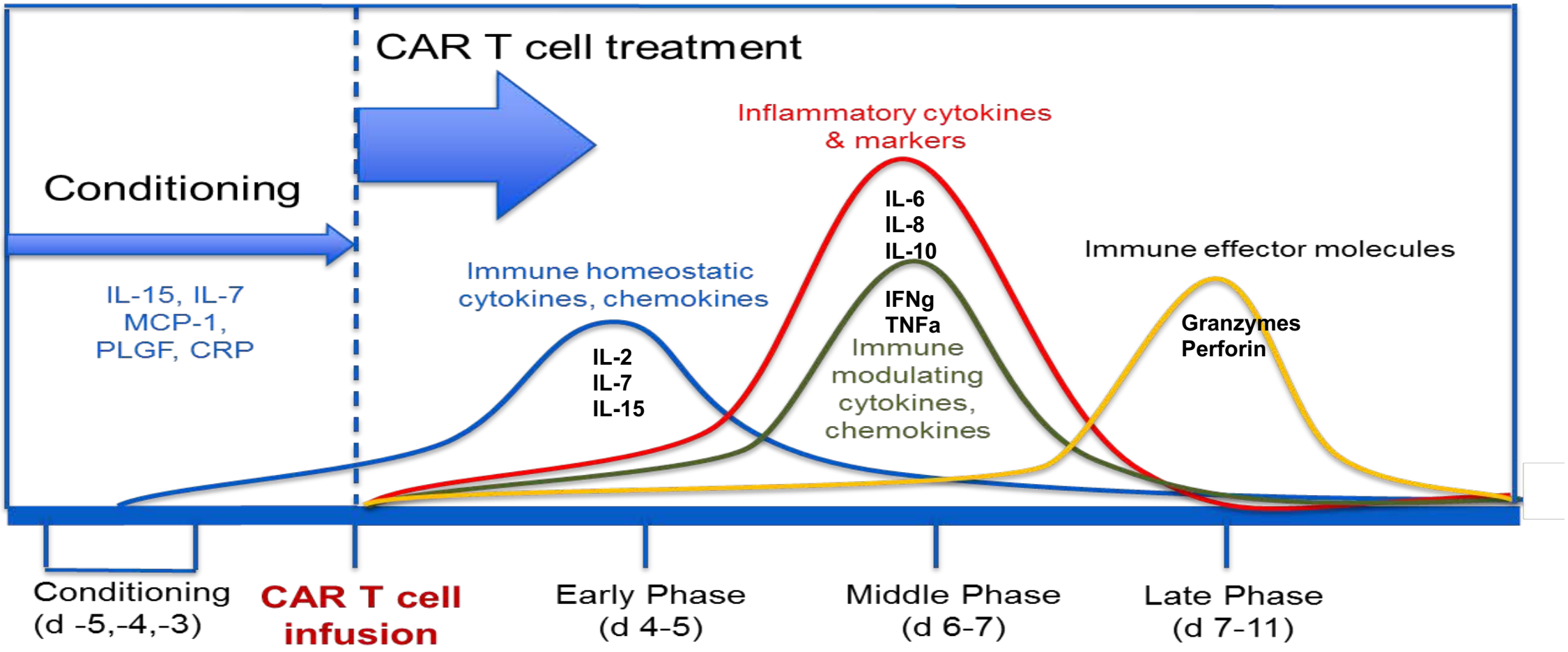


- Peak expansion observed within 2 weeks
- CAR T cells detectable beyond two years after infusion
- Each infused CAR T cell can proliferate to >10,000 cells in the body

Courtesy of Sattva S Neelapu, MD

Locke, Neelapu et al, Mol Ther, 2017

Cytokine pattern after axi-cel CAR T infusion



Courtesy of Sattva S Neelapu, MD

Perez, et al, ASH, 2015

Chimeric Antigen Receptor T cells (CAR T Cells)

- Exploit native antibody or T cell recognition and signaling pathways
- Introduction of unique genes through viral vectors to allow recognition of tumor cells
- Dramatic expansion after infusion, and effective tumor cell killing
- After initial trials proving the efficacy in B cell malignancies, other targets, cancers and molecular constructs are being explored

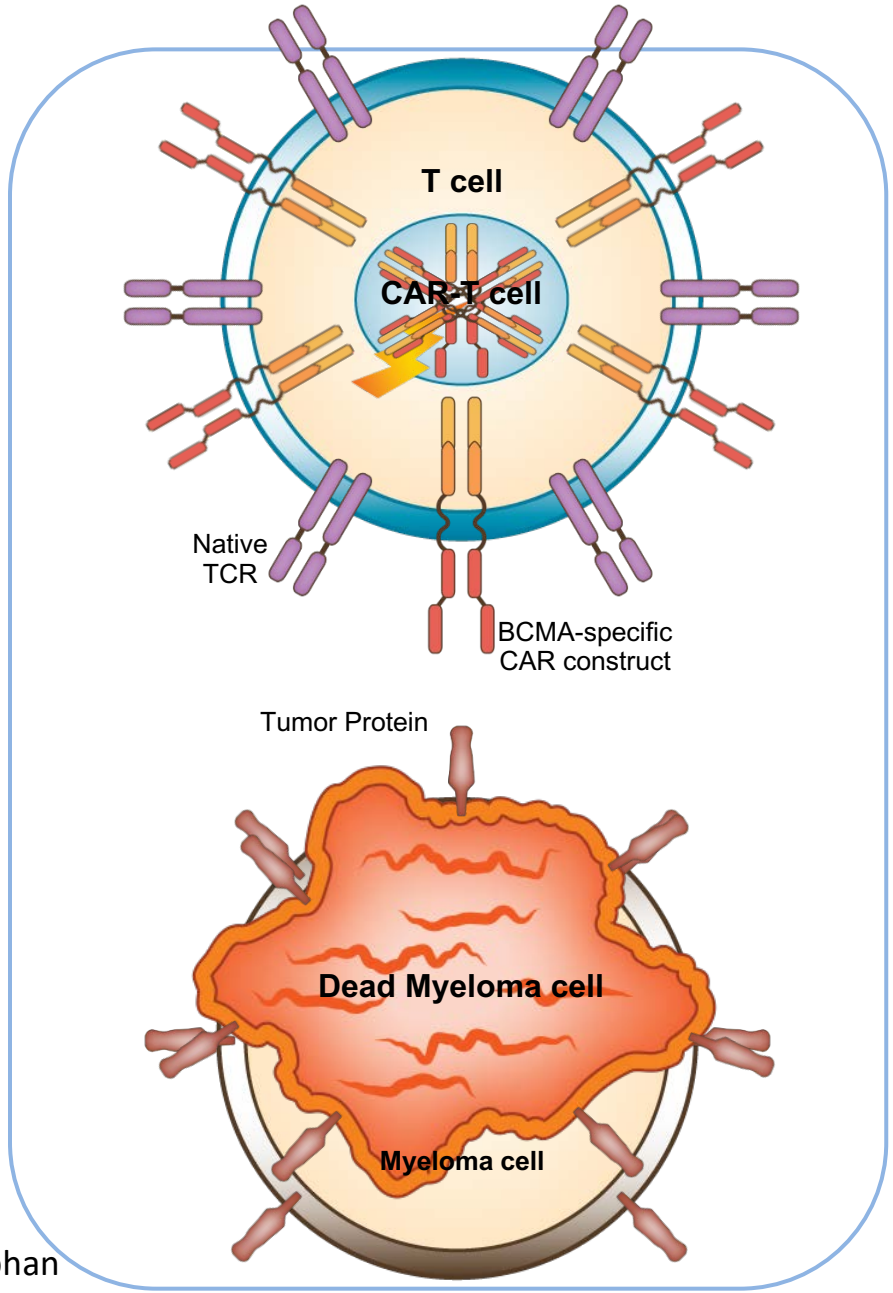


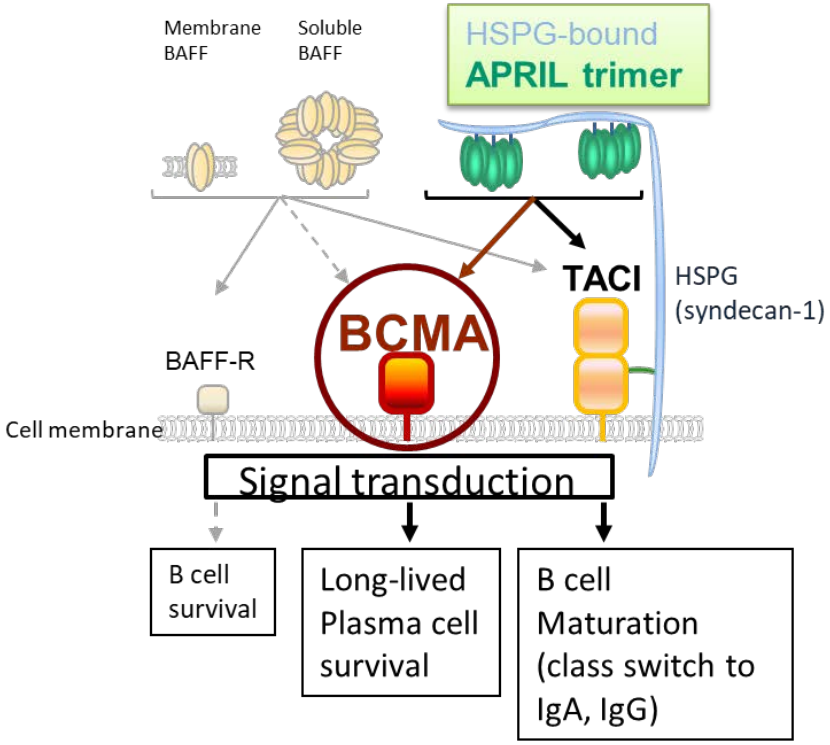
Image courtesy of Stephan Grupp, UPenn

Courtesy of Nikhil C Munshi, MD

BCMA – A Promising Target in Multiple Myeloma

- **BCMA is member of the TNF receptor superfamily**
  - Expressed nearly universally on MM cells
  - Expression largely restricted to plasma cells and some mature B cells

BCMA Is A Selective Plasma Cell Antigen



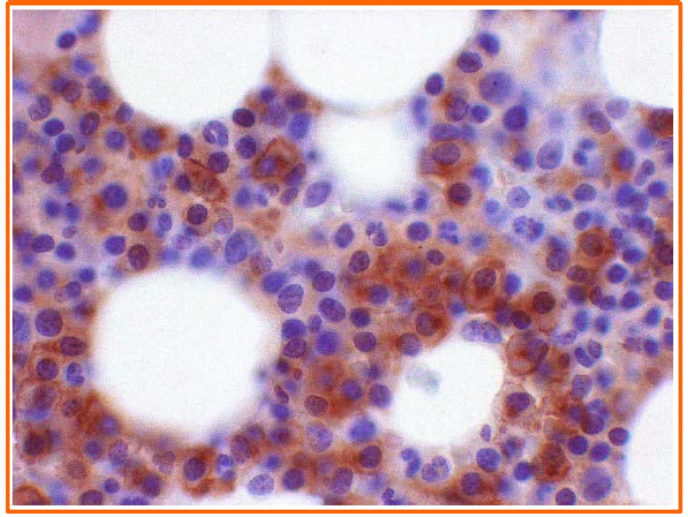
Ligands
by neutrophil, myeloid cell, DC, osteoclasts, tumor cell

Affinity to BCMA:
APRIL (nM) >> BAFF (μM)
Elevated in sera of MM patients

Receptors
on B cells

BCMA >> TACI
by ~2-100-fold in MM
(loss of BAFF-R in MM)

Multiple myeloma cells expressing BCMA



(brown color = BCMA protein)

Courtesy of Nikhil C Munshi, MD

Tai & Anderson Immunotherapy 2015; 7: 1187-99.

73-year-old woman with DLBCL (from the practice of Ms Zerante)

- 2015: Diagnosed with follicular lymphoma → multiple treatments (outside oncologist)
- Presents with refractory, transformed DLBCL, with a significant disease burden
- During COVID-19 pandemic: Fludarabine/cyclophosphamide lymphodepleting chemotherapy
  - Robust fever – no identifiable cause, including COVID-19, after extensive infectious work up → resolves
- CAR T cell infusion
  - D+2-3 persistent fever → tocilizumab + dexamethasone
  - D+10 double vision
  - Recurrent diarrhea, significant elevation of inflammatory markers
  - D+13 discharged
  - D+30 PET: CR
- Currently, discharged and at home, with recurrent infections
  - CMV viremia, with pancytopenia, bacteremia, recurrent clostridioides difficile

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Module 2: Side Effects Associated with CAR T-Cell Therapy

- Overall performance criteria to receive CAR-T therapy
- Cytokine release syndrome (CRS)
  - Clinical manifestations and management
- Neurotoxicity: Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Apps and guidelines (eg, MD Anderson Cancer Center CARTOX app)

The “cytokine storm” observed with CAR T-cell therapy shares some characteristics with a similar syndrome in patients with COVID-19.

a. Agree
b. Disagree
c. I don’t know

ICANS is a formalized hierarchy of neurologic sequelae of CAR T-cell therapy.

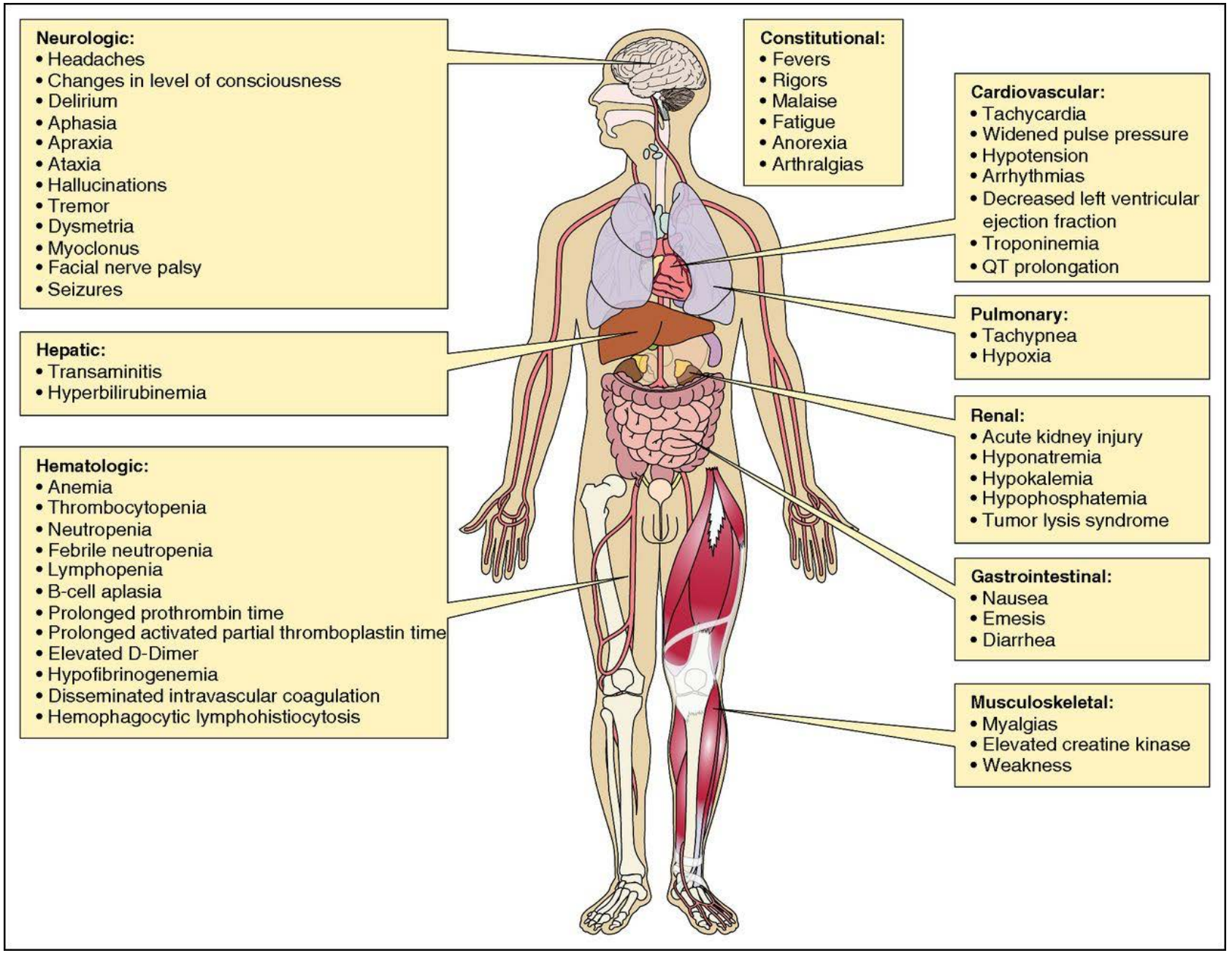
a. Agree
b. Disagree
c. I don’t know

CD-19-directed CAR T-cell therapy can deplete normal B cells but seems to have minimal adverse consequences.

a. Agree
b. Disagree
c. I don’t know

Cytokine release syndrome (CRS)

- Systemic inflammatory response caused by cytokines released by CAR T cells and other immune cells and results in reversible organ dysfunction

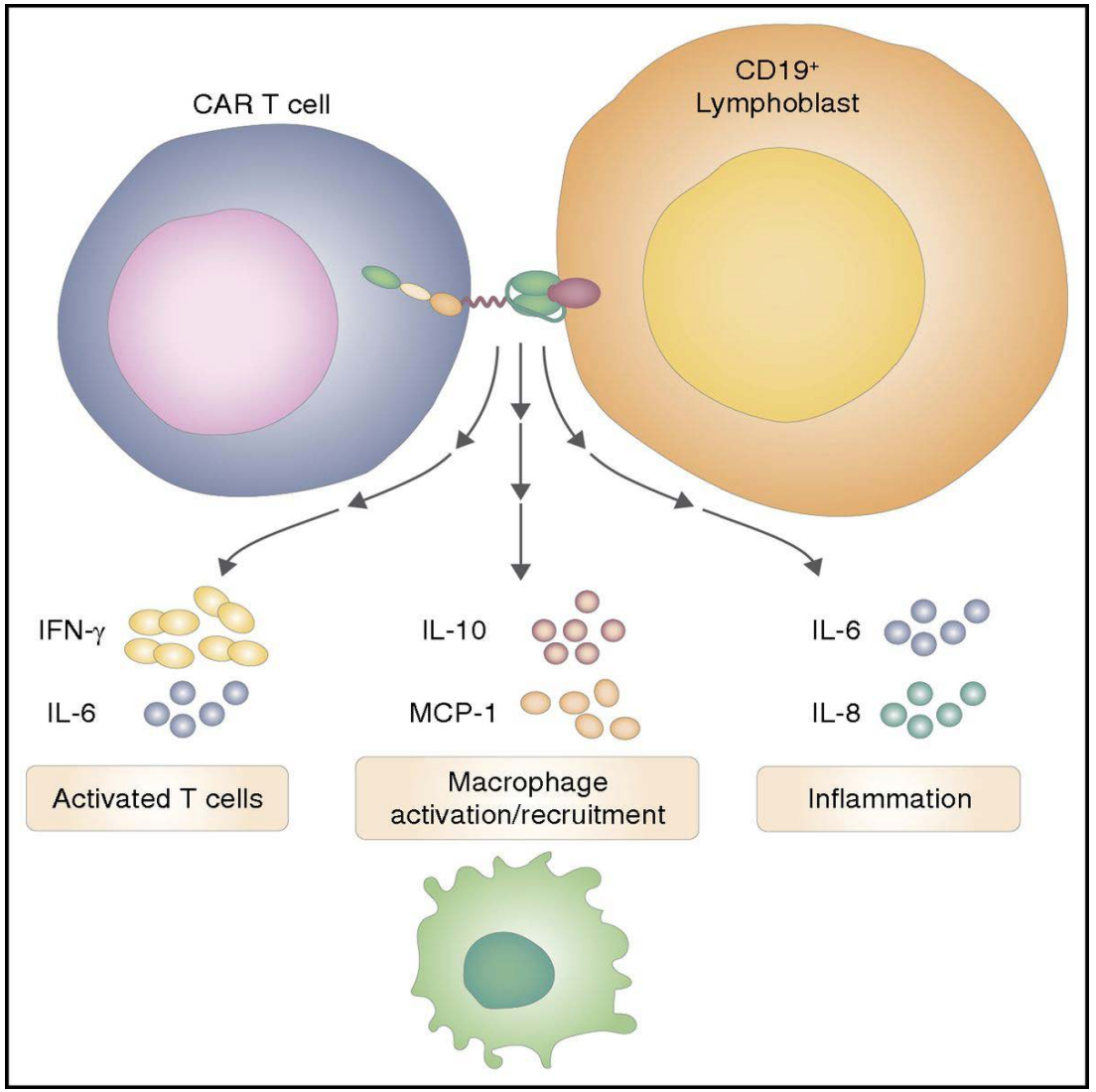


Courtesy of Sattva S Neelapu, MD

Brudno and Kochenderfer, Blood 2016; 127:3321-3330

Cytokines are produced by T cells and bystander immune cells and may be inhibited by corticosteroids

Corticosteroids



Tocilizumab

Block IL-6 receptor

Courtesy of Sattva S Neelapu, MD

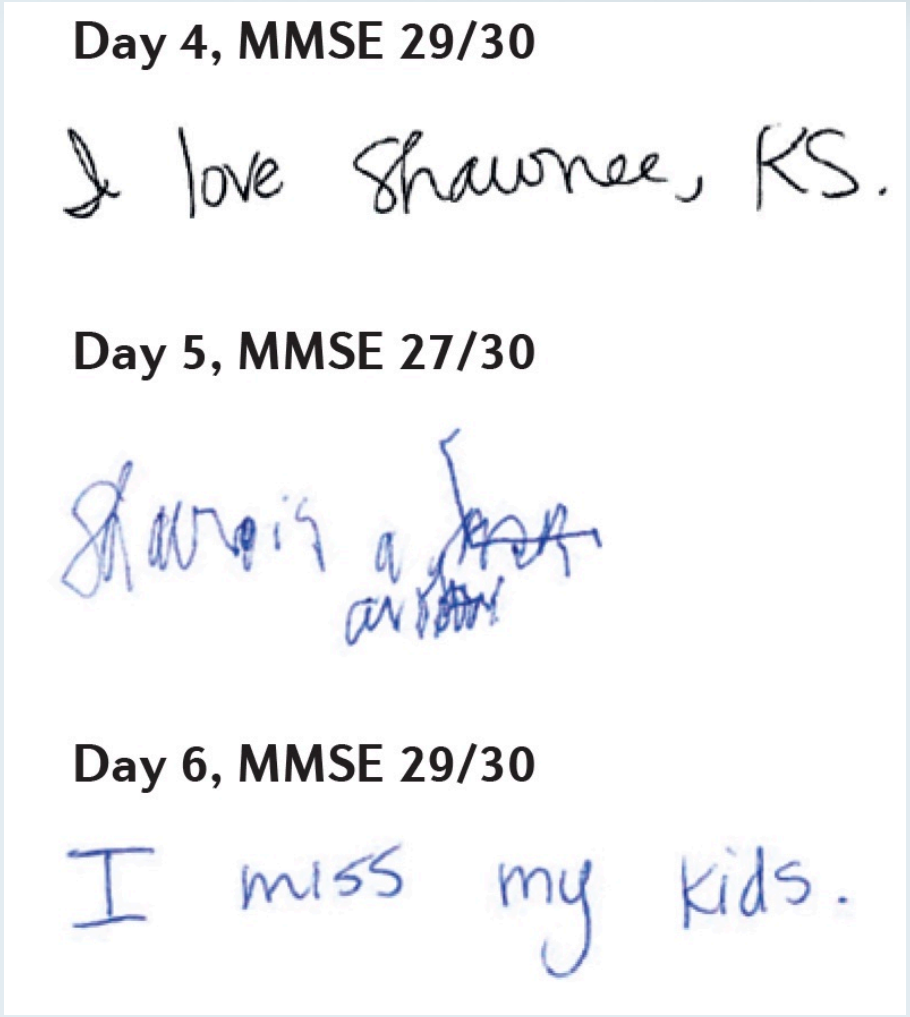
Hay et al. Blood 2017; 130:2295-2306
Maude SL. *Blood* 2017;130:2238-2240

Neurotoxicity or ICANS
(Immune effector Cell-Associated Neurotoxicity Syndrome)

- Typically manifests as a toxic encephalopathy
  - CRES – CAR-Related Encephalopathy Syndrome
  - Word finding difficulty, confusion, disorientation, agitation, dysphasia, aphasia, somnolence, tremors, and impaired handwriting
  - In more severe cases, seizures, motor weakness, incontinence, increased intracranial pressure, papilledema, and cerebral edema may also occur
- Onset may be during CRS or after CRS symptoms have subsided
- May last few hours to several days
- Generally reversible with no permanent neurological deficits

Courtesy of Sattva S Neelapu, MD

Handwriting Samples and MMSE After CAR T-Cell Therapy

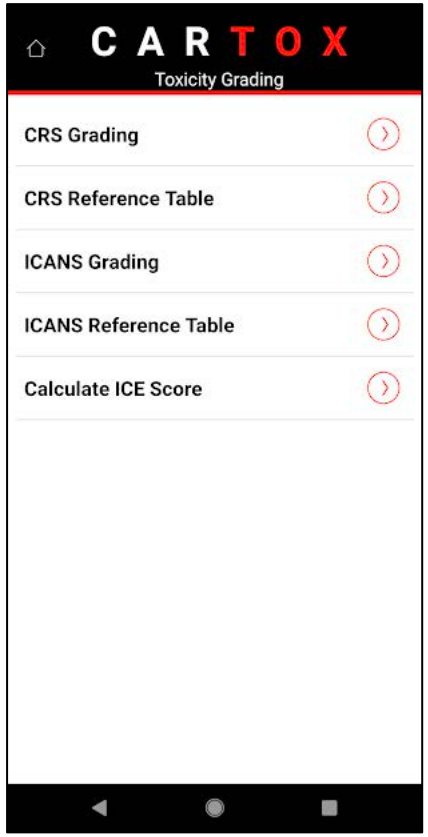


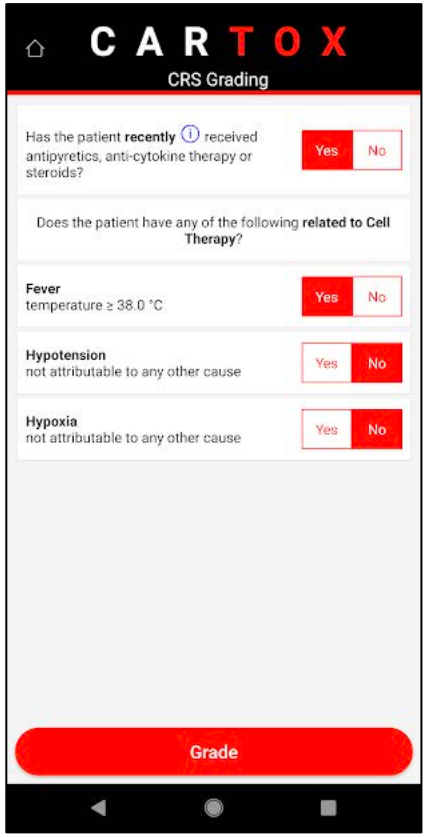
- Handwriting samples and mini mental status exam (MMSE) scores obtained on days 4, 5, and 6 after CAR T-cell therapy
- Note how the patient's handwriting was markedly impaired on day 5, despite only a small decrease in their MMSE score.

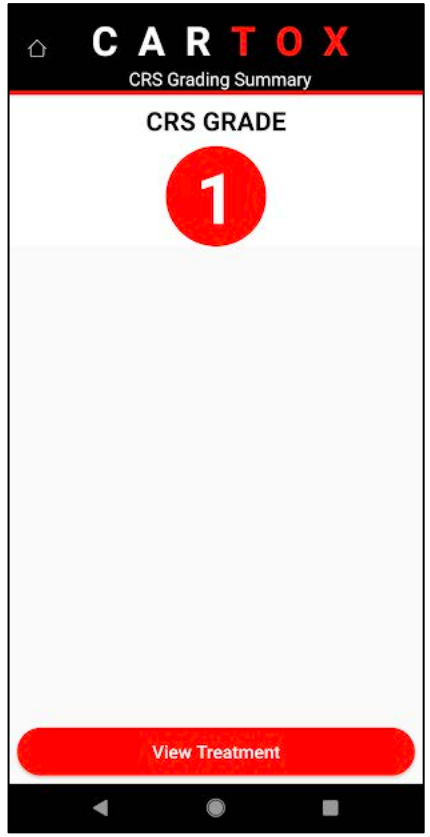
Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.

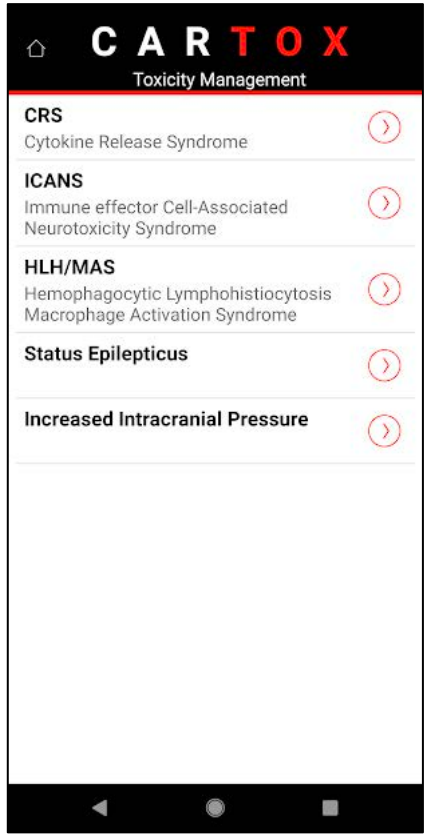
CARTOX App for Grading and Management of CRS and ICANS

Smart phone app available free on both App Store (iPhone) and Google Play (Android)









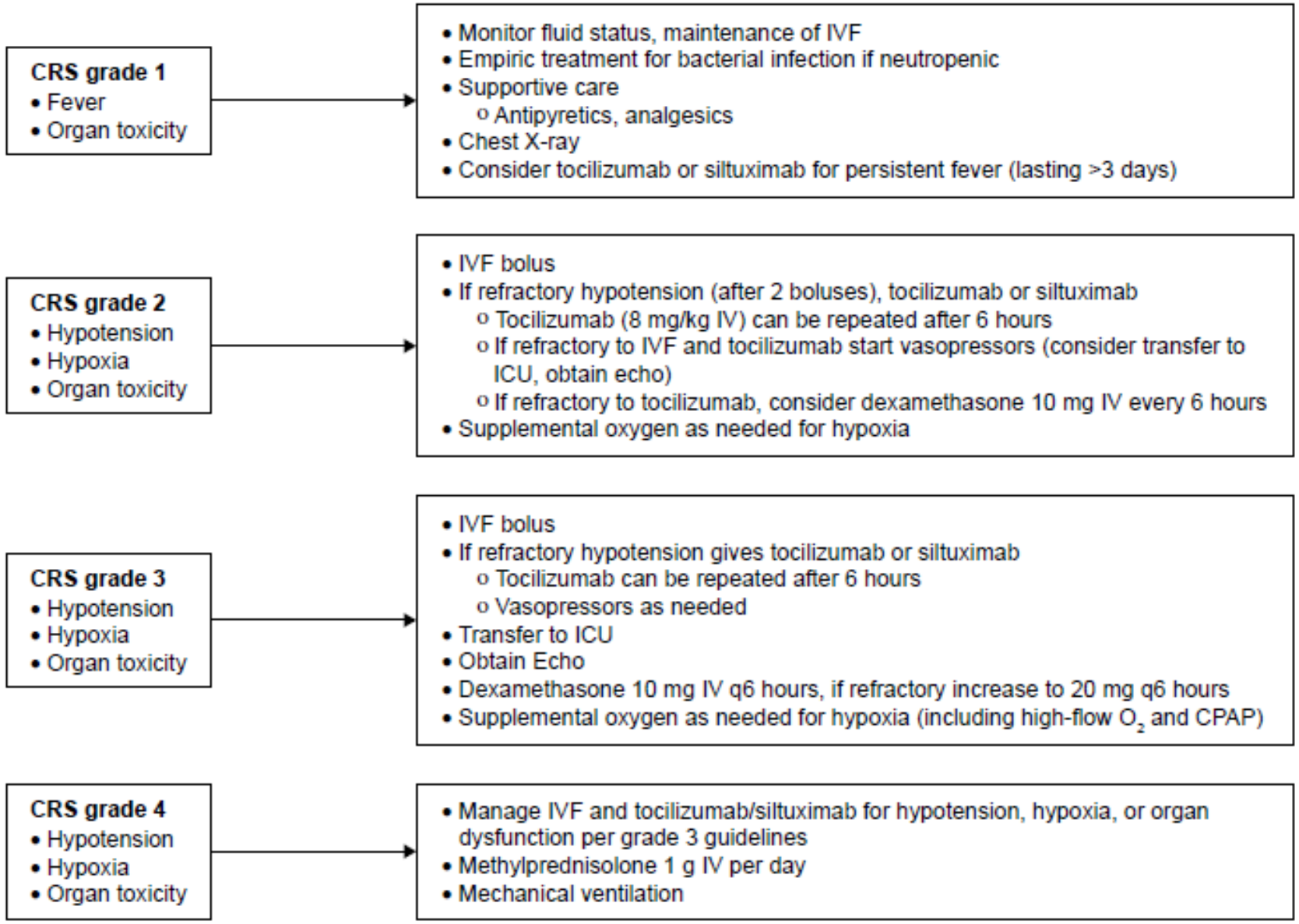
Sherry Adkins

Courtesy of Sattva S Neelapu, MD

Neelapu et al. *Nat Rev Clin Oncol,* Jan 2018

Lee et al. *Biol Blood Marrow Transplant,* 2019 Apr;25 (4):625-638

CARTOX Working Group



Riegler et al, Ther Clin Risk Manage 2019 (adapted from Neelapu et al, Nat Rev Clin Onc 2017)

Courtesy of Nikhil C Munshi, MD

Patient Education Regarding Car T Cell Therapy

CRS	Neurotoxicity	Management of Toxicities
• Fever • Hypotension • Tachycardia • Hypoxia • Chills	• Tremors • Dizziness • Delirium • Confusion • Agitation • Cerebral Edema	• Tocilizumab • Steroids

Adkins, S. (2019). Car T cell therapy: adverse events and management. J. Adv Pract Onco Supple3. 21-28..

Patient Education Regarding Car T Cell Therapy

Logistics	Pancytopenia	Other
• Stay locally for 30 days • Inpatient vs outpatient • Frequent visits to hospital • Local Oncologist to coordinate care • Caregiver 24 hours a day	• Decreased blood counts • Blood and Platelet Transfusions • Growth Factor Support • Infections • Prophylactic Antibiotics	• When to come to ER • When to call the clinic • Ensure caregivers are present • Contact local oncologist

Adkins, S. (2019). Car T cell therapy: adverse events and management. J. Adv Pract Onco Supple3. 21-28..

23-year-old woman whose treatment is complicated by psychiatric issues (from the practice of Ms Zerante)

- 2017: Ph-negative ALL (normal cytogenetics) → Treated per CALGB protocol → Relapsed → Blinatumomab
- Mental status change due to dissociative amnesia, conversion disorder → resolved
- AlloSCT → POMP maintenance
- Inotuzumab x 2 + steroids as bridging treatment
- 11/2019: tisagenlecleucel (tisa-cel) CAR T
  - Renal, cardiac and hepatic dysfunction; Fungemia
  - CRS D+1, ICANS D+13, HLH, DIC requiring transfusion support
  - Adjustment disorder, with depressed mood, anxiety, PTSD
  - D+28 bone marrow biopsy: NED
  - Discharged ~D+55-60
  - 2/2020: D+84 BMBx: NED
- 3-4/2020: Relapsed disease → Inotuzumab + dexamethasone → BMBx: Residual disease
- 4/2020: Dexamethasone/venetoclax/vincristine pulses
- 5/2020: S/p lymphodepleting chemo → CD22 CAR product → no response → PD → Home hospice

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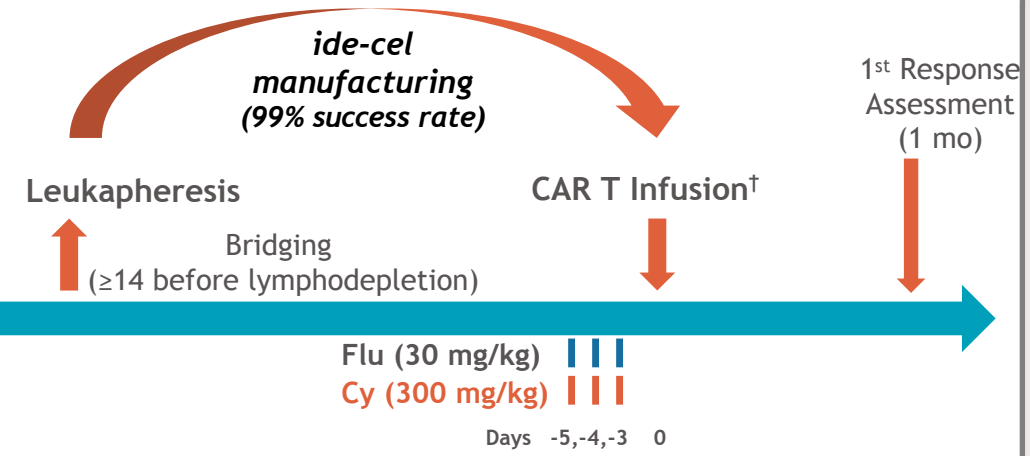
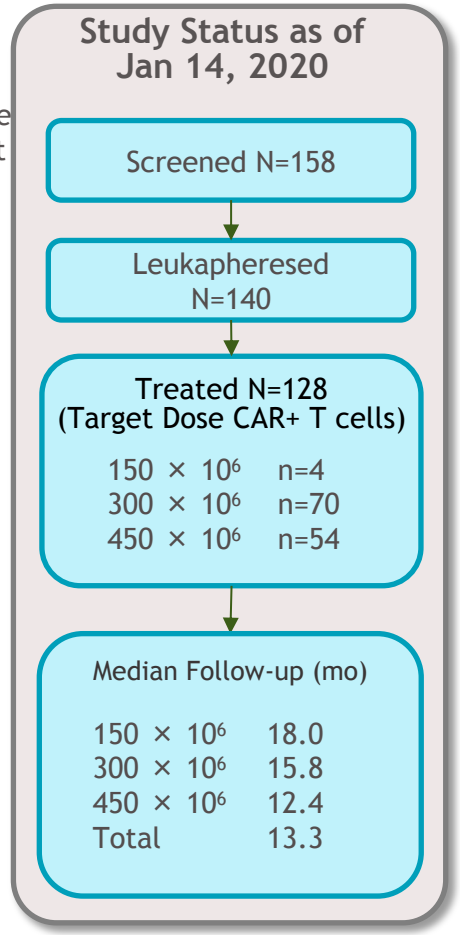
Module 3: Anti-BCMA CAR T-Cell Therapy in Multiple Myeloma (MM)

- Overview of current management of MM
  - Key current issues
    - Up-front management of MM (daratumumab)
    - Minimal residual disease (MRD)/role of transplant
    - Sequencing of therapies in relapsed disease
- BCMA and related therapies
- Key data sets: KarMMa, EVOLVE, CARTITUDE-1
- Current role for CAR-T trials and other trials of BCMA-related therapies

Phase II Pivotal KarMMa Study

- RRMM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG*





Endpoints

- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary**: CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory**: Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

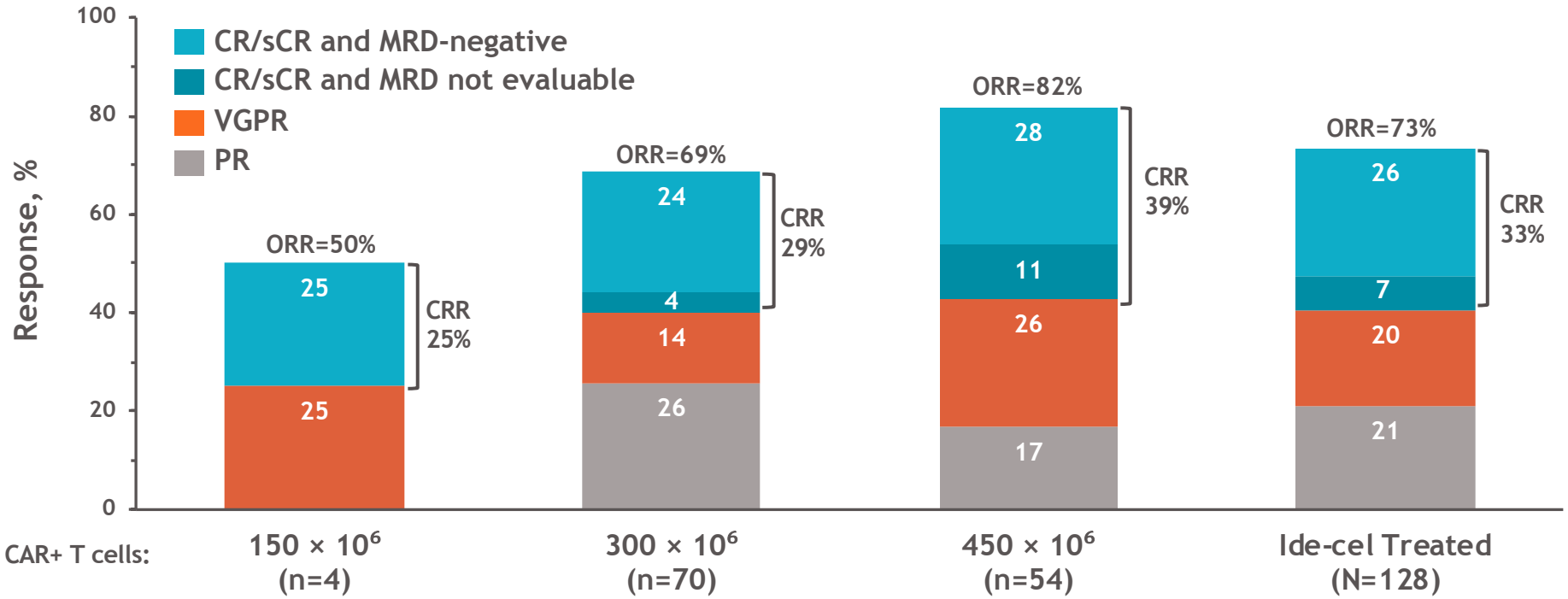
Time since initial diagnosis, median (range)		**6 (1–18)**
No. of prior anti-myeloma regimens, median (range)		6 (3–16)
Prior autologous SCT, %	1	94
	>1	34
Any bridging therapies for MM, %		88
Refractory status, %	Anti-CD38 Ab-refractory	94
	Triple-refractory	84

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

Courtesy of Nikhil C Munshi, MD

Munshi et al ASCO 2020

Best Overall Response



- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

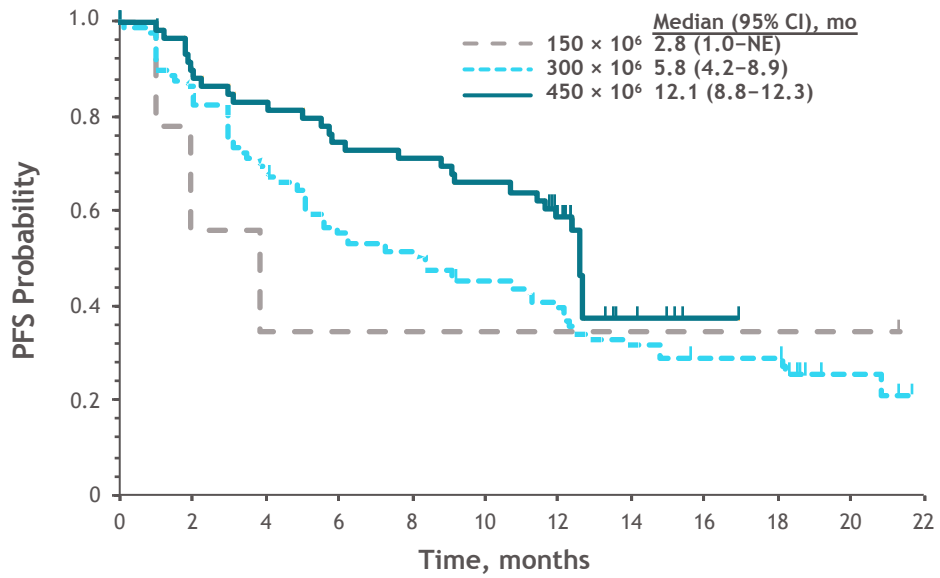
Data cutoff: 14 Jan 2020. MRD-negative defined as $<10^{-5}$ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered.
Values may not add up due to rounding.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR. **P* value at the primary data cutoff with same ORR and 95% CI.

Courtesy of Nikhil C Munshi, MD

Munshi et al ASCO 2020

Progression-Free Survival

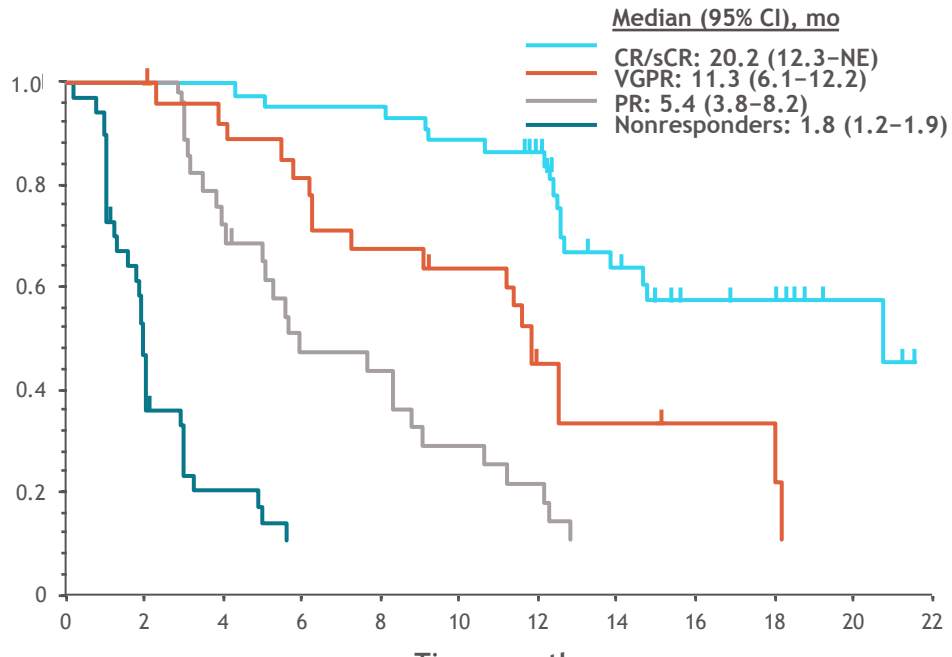
PFS by Target Dose



At risk, N												
150 × 10⁶	4	2	1	1	1	1	1	1	1	1	1	0
300 × 10⁶	70	56	42	33	29	24	17	14	11	7	2	0
450 × 10⁶	54	44	40	36	34	31	17	4	1	0	0	

- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10⁶ CAR+ T cells

PFS by Best Response



CR/sCR	42	42	42	40	39	37	26	16	11	8	4	0
VGPR	25	25	22	20	16	14	8	3	2	0	0	
PR	27	16	10	9	5	1	0	0	0	0	0	
Nonresponders	34	8	83	70	64	56	35	19	13	8	4	0

- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Data cutoff: 14 Jan 2020. NE, not estimable; PFS, progression-free survival.

Courtesy of Nikhil C Munshi, MD

Munshi et al ASCO 2020

Recent CAR-T Studies - Characteristics

	KarMMa: idecabtagene vicleucel (n=128)	EVOLVE: orvacabtagene autoleucel (n=62)	CARTITUDE-1: JNJ-4528 (n = 29)
Age	61 (33-78)	61 (33-77)	60 (50-75)
High Risk Cytogenetics, %	35	41*	27
Tumor Burden in BM, %	>50% PC = 51	—	≥60% PC = 24
Extramedullary PCs, %	39	23	10
Median prior lines of therapy	6 (3-16)	6 (3-18)	5 (3-18)
Triple refractory, %	84	94	86
Bridging therapy, %	88	63	79
Unique properties	Human BCMA, 4-1BB, CD3z	Modified spacer, CD4:CD8 enriched for CM	Median cell dose **$0.72x10^6$** cells/kg 2 BCMA single chain antibodies

Courtesy of Nikhil C Munshi, MD

Patel et al ASCO 2020

Recent CAR-T Studies – Safety and Efficacy

Safety

	KarMMa	EVOLVE	CARTITUDE-1
↓ANC ≥G3, %	89	90	100
↓plts ≥G3, %	52	47	69
CRS: all, ≥G3,%	84, 6	89, 3	93, 7
Med. time to CRS, duration, days	1 (1-12) 5 (1-63)	2 (1-4) 4 (1-10)	7 (2-12) 4 (2-64)
ICANS: all, ≥G3,%	17, 3	13, 3	10, 3
HLH/MAS, %	--	5	? 7 (lfts)
Infections: all, ≥G3 %	69, --	40, 13	--, 19
Toci/steroid/ anakinra use, %	52/15/0	76/52/23	79/21/21

? This was not listed at MAS/HLH, I am just speculating → could this have been early MAS

Efficacy

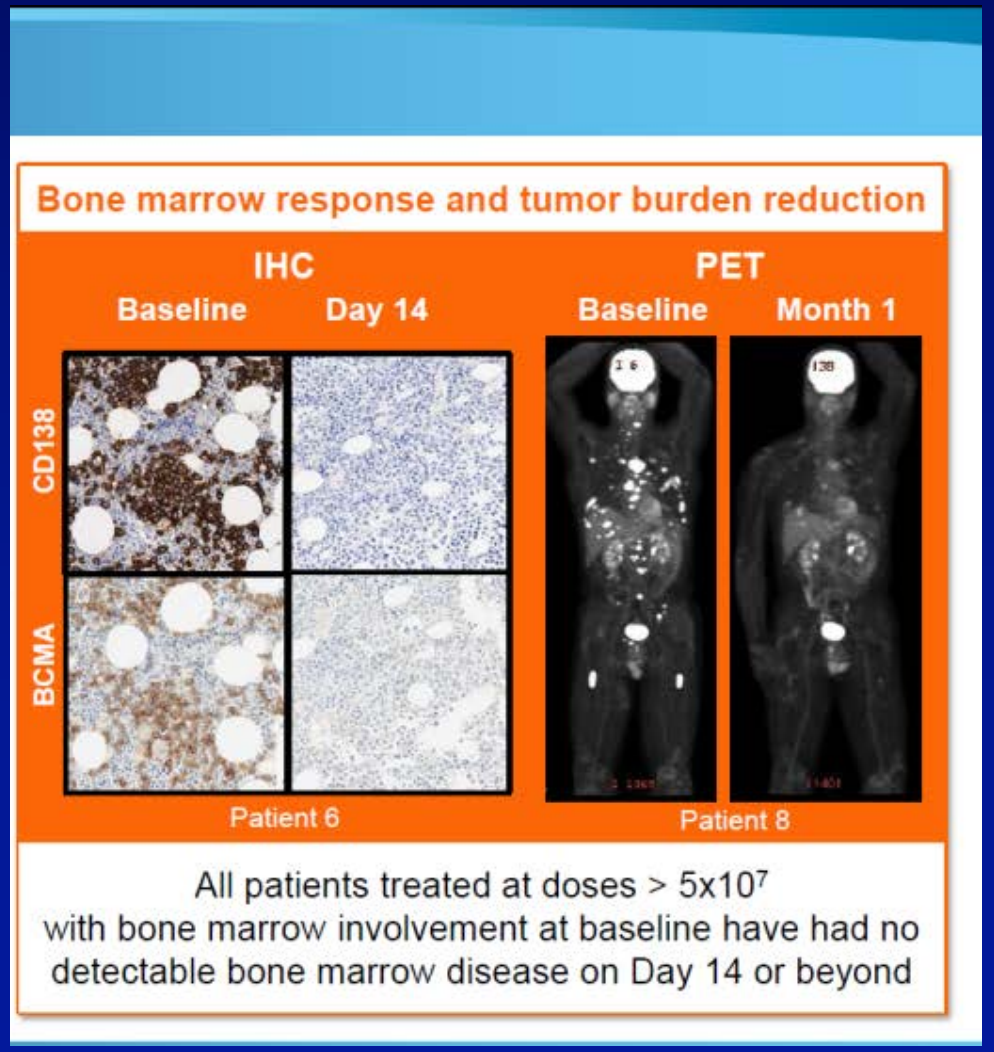
	KarMMa (n = 128)	EVOLVE (n = 62)	CARTITUDE-1 (n = 29)
ORR, %	73 (66-81)	92	100
sCR/CR, %	33	36	86
MRD neg ≥10^{-5}, % (of evaluable)	94	84	81
PFS/DoR, months	8.8/10.7	NR*	NR**
Screened Apheresed Treated	150 140 128	--	35 35 29

* 300 x10^6 cell dose cohort (lowest) = PFS 9.3 months, other med F/U = 8.8 and 2.3 month
** 9 mo PFS = 86%

Courtesy of Nikhil C Munshi, MD

Patel et al ASCO 2020

bb2121: Anti-BCMA Chimeric Antigen Receptor T-Cell in Multiple Myeloma



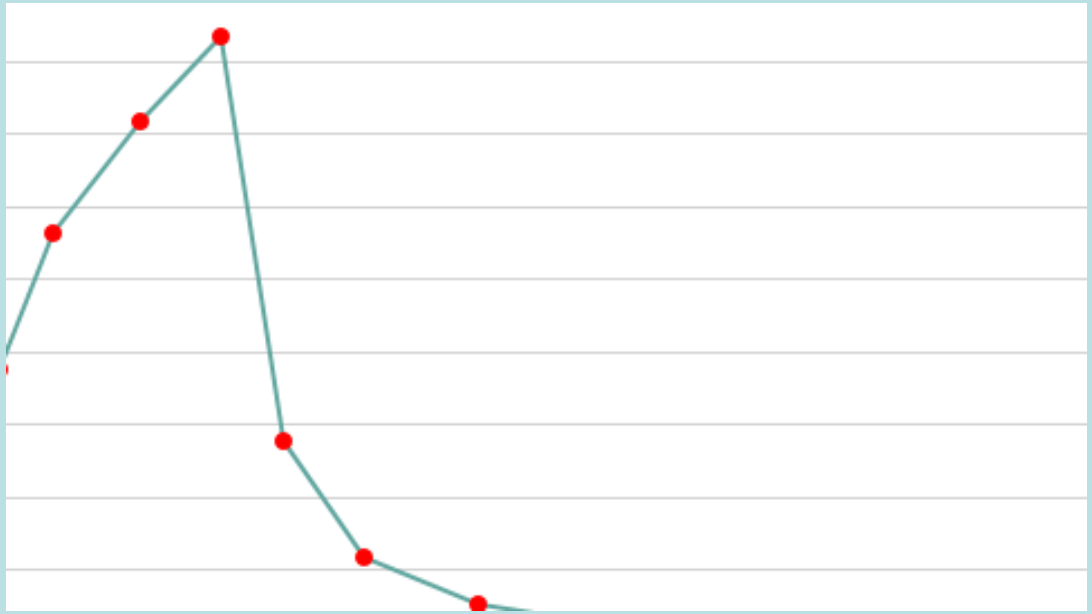
Courtesy of Nikhil C Munshi, MD

58-year-old woman with MM (from the practice of Ms Richards)

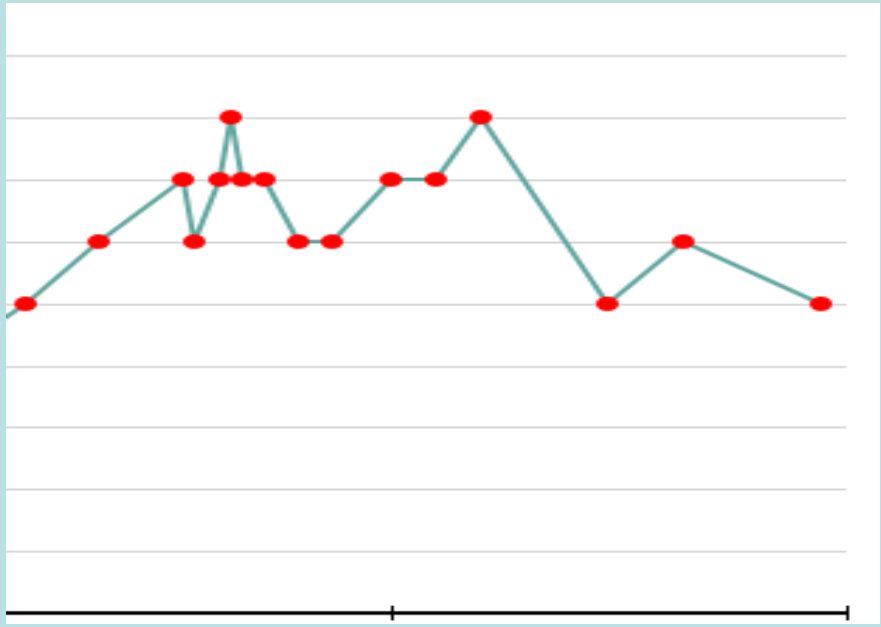
- 2012: Diagnosed with IgG lambda light chain multiple myeloma, with CKS1B amplification
- VRd x 5 with minimal response → changed to CyBorD with PR
- Autologous cell stem cell transplant → relapsed 1 month post ASCT
- Multiple lines of therapy with initial response with quick subsequent relapse
  - Daratumumab/lenalidomide/dexamethasone
  - Daratumumab/pomalidomide/dexamethasone
  - Pomalidomide/cyclophosphamide/dexamethasone
- Clinical trial of BCMA CAR T therapy
  - Minimal Response (off therapy for 6 months)
  - Diffuse arthralgias 6 weeks post-CAR T cell infusion
- Restart daratumumab/pomalidomide/dexamethasone → PD
- Currently, receiving cyclophosphamide/pomalidomide/dexamethasone

58-year-old woman (from the practice of Ms Richards)

Response to ASCT



Response after CAR T

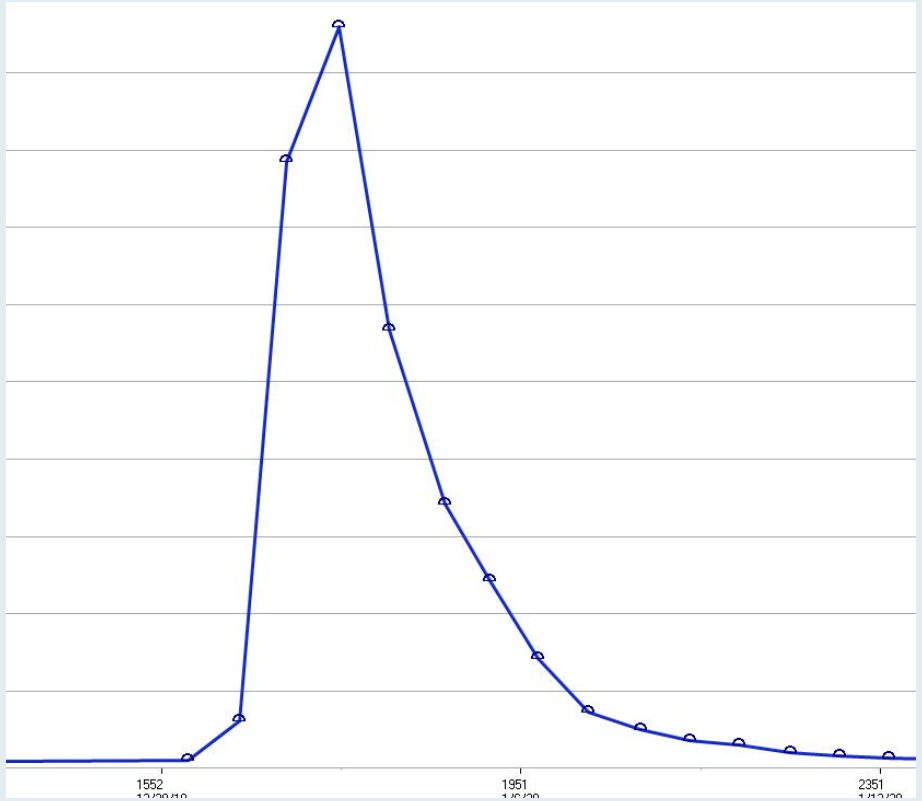


62-year-old man with MM (from the practice of Ms Richards)

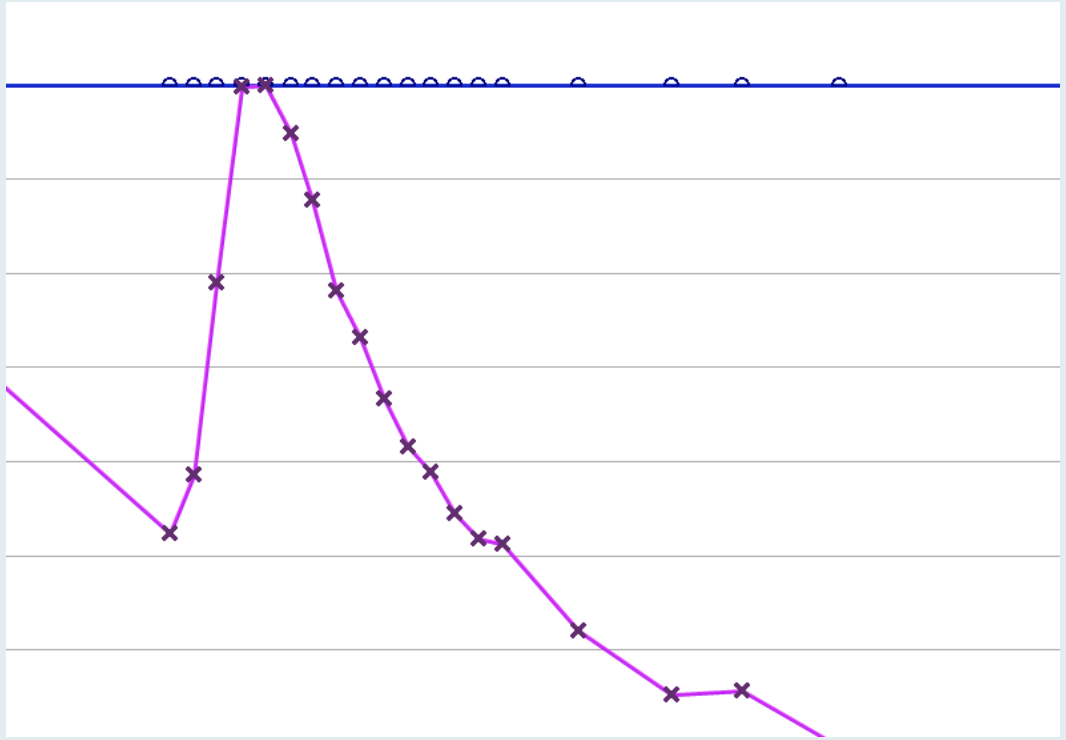
- 2017: Diagnosed with multiple myeloma, t(14;16)
- VRd → 2018 ASCT → maintenance lenalidomide x 4 months → PD
- Daratumumab/lenalidomide/dexamethasone
- Daratumumab/bortezomib/dexamethasone with PD after 2 months
- 12/2019: Clinical trial with bb2121 → Complete remission
  - Fever, rigors, wheezing; Required oxygen
  - Grade 2 CRS (Tylenol, Duoneb inhaler -- albuterol and ipratropium) → resolved after 2 days
- 6/17/2020: Currently, still in CR

62-year-old man with MM (from the practice of Ms Richards)

C-reactive protein (CRP)

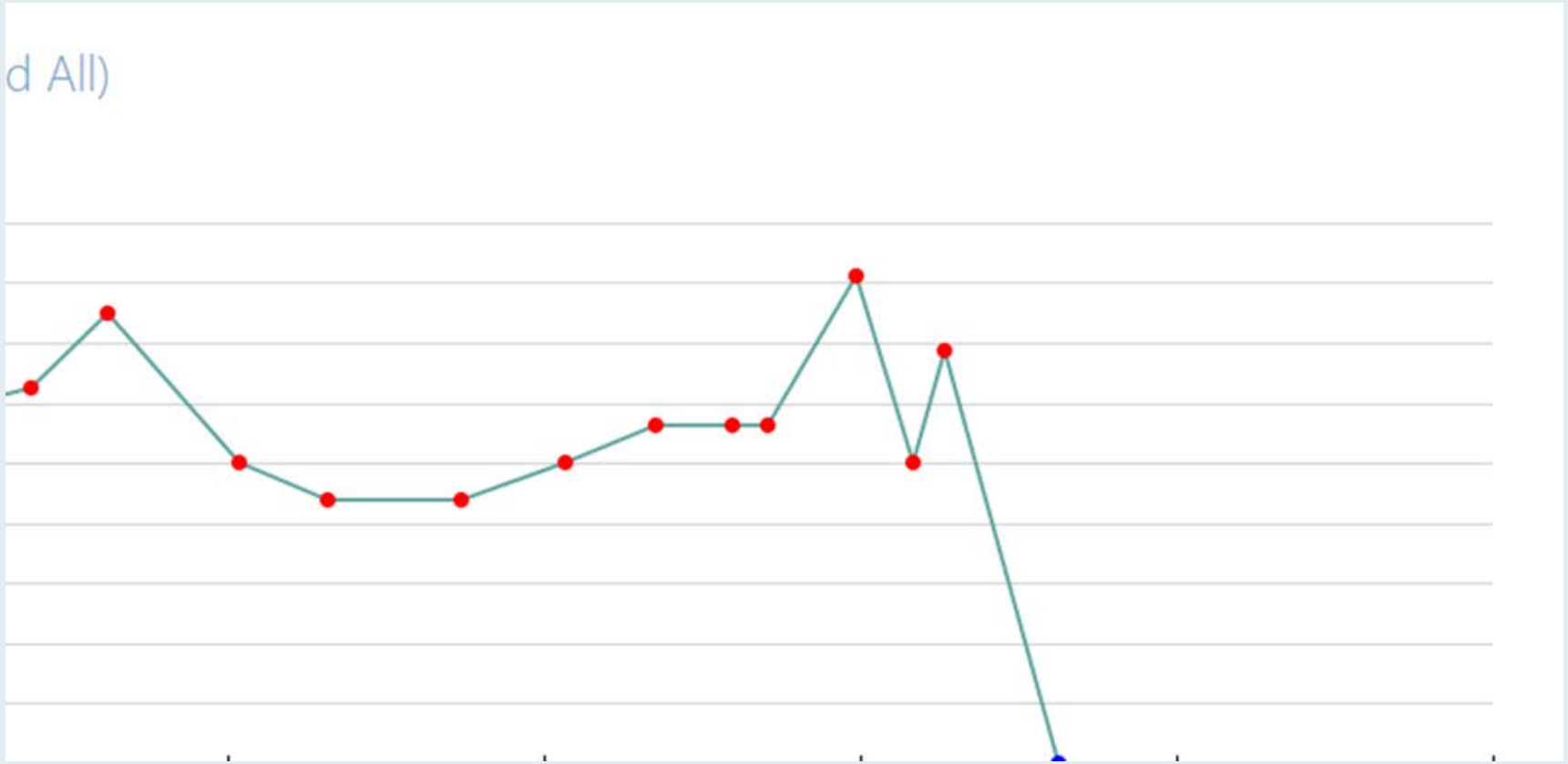


Ferritin



62-year-old man with MM (from the practice of Ms Richards)

Excellent response to CAR T-cell
Remains in remission 6 months post CAR T-cell therapy



Agenda

Module 1: Overview of Chimeric Antigen Receptor (CAR) T-Cell Therapy

- Case Presentation: Ms Zerante — 73-year-old woman with DLBCL

Module 2: Side Effects Associated with CAR T-Cell Therapy

- Case Presentation: Ms Zerante — 23-year-old woman with ALL

Module 3: Anti-BCMA CAR T-Cell Therapy in Multiple Myeloma (MM)

- Case Presentation: Dr Richards — 58-year-old woman with MM
- Case Presentation: Dr Richards — 62-year-old man with MM

Module 4: CD19-Directed CAR T-Cell Therapy for Aggressive Lymphomas

- Case Presentation: Ms Zerante — 79-year-old man with DLBCL

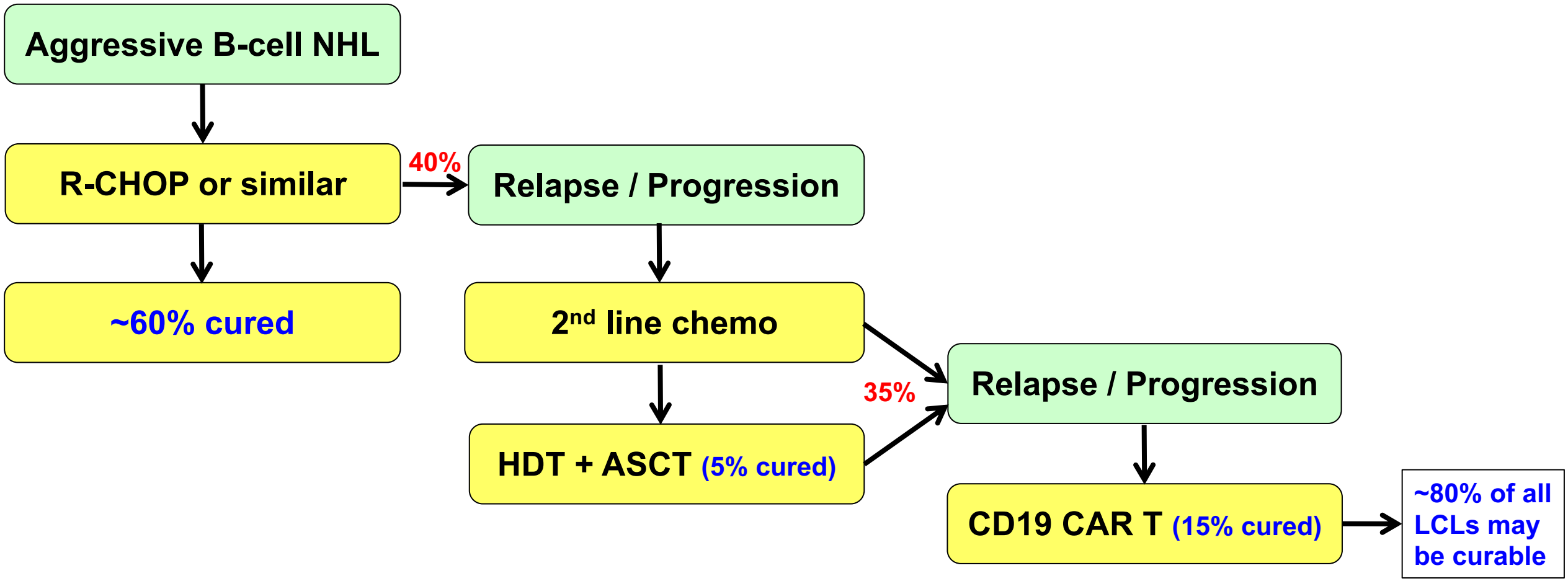
Module 5: CAR T-Cell Therapy in Acute Lymphoblastic Leukemia (ALL)

- Case Presentation: Ms Zerante — 41-year-old woman with ALL

Module 4: CD19-Directed CAR T-Cell Therapy for Aggressive Lymphomas

- Overview of current management of diffuse large B-cell lymphoma (DLBCL)
  - Key current issues
    - Autologous stem cell transplant for recurrent disease
    - Antibody-drug conjugates (polatuzamab vedotin)
    - Other novel agents
  - CD-19 as a target for treatment
  - Key data sets: ZUMA-1, JULIET, TRANSCEND NHL 001
- Overview of current management of mantle cell lymphoma (MCL)
  - Key data sets: ZUMA-2, ZUMA-5
- Current clinical role for CAR-T therapy

CD19 CAR T in NHL: Beginning of a paradigm shift



Courtesy of Sattva S Neelapu, MD

Multicenter CD19 CAR T-cell trials in aggressive NHL

Study	ZUMA-1	JULIET	TRANSCEND
Reference	Neelapu et al. NEJM 2017 Locke et al. Lancet Oncol 2019	Schuster et al. NEJM 2019	Abramson et al. ASH 2019
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	Up to 0.6-6 x 10^8	0.5-1.5 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes Percentage	DLBCL / PMBCL / TFL 78 / 7 / 15	DLBCL / TFL / Other 79 / 19 / 2	DLBCL / PMBCL / TFL / Other 64 / 6 / 22 / 8
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	23%	49%	35%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	99%
Treated/Enrolled	108/120 (90%)	111/165 (67%)	269/344 (78%)*

*Additional 7% received nonconforming product

Courtesy of Sattva S Neelapu, MD

Efficacy in multicenter CD19 CAR T trials in adult LBCL

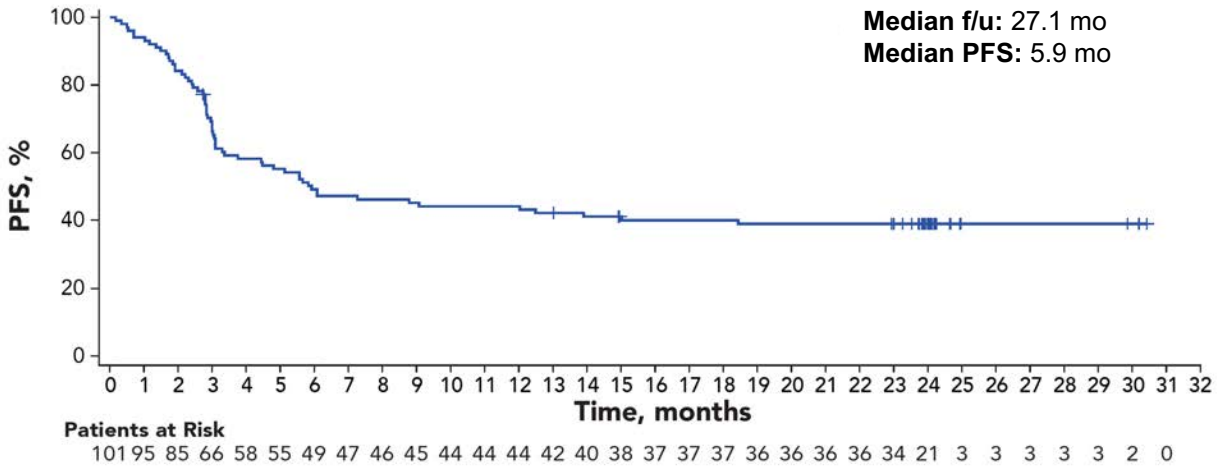
			Best response		PFS/OS		
Study	**Product**	**N**	**Best ORR**	**Best CR rate**	**Median PFS**	**Median OS**	**Ref**
ZUMA-1	CD19/CD3ζ/ CD28	108	83%	58%	5.9 mo	25.8 mo	Neelapu et al, NEJM 2017; ASH 2019 Locke et al, Lancet Oncol 2019
JULIET	CD19/CD3ζ/ 4-1BB	93	52%	40%	2.9 mo	12 mo	Schuster et al, NEJM 2019
TRANSCEND	CD19/CD3ζ/ 4-1BB	256	73%	53%	6.8 mo	21.1 mo	Abramson et al, ASH 2019

Courtesy of Sattva S Neelapu, MD

Durable responses with CAR T-cell therapy in r/r large B-cell lymphoma

ZUMA-1: PFS with axi-cel

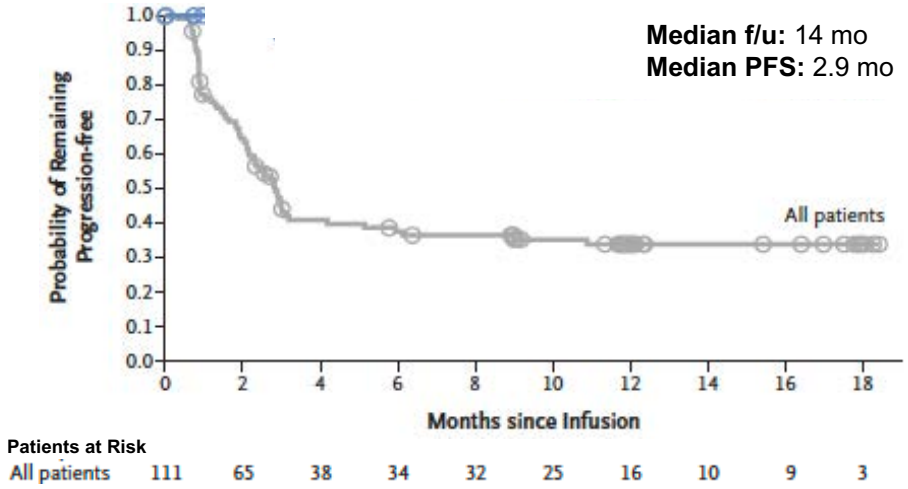
39% progression-free at 27.1 mo



Neelapu et al. *N Eng J Med* 2017
Locke et al. *Lancet Oncol* 2019

JULIET: PFS with tisagenlecleucel

34% progression-free at 14 mo#



#Calculated value from publication

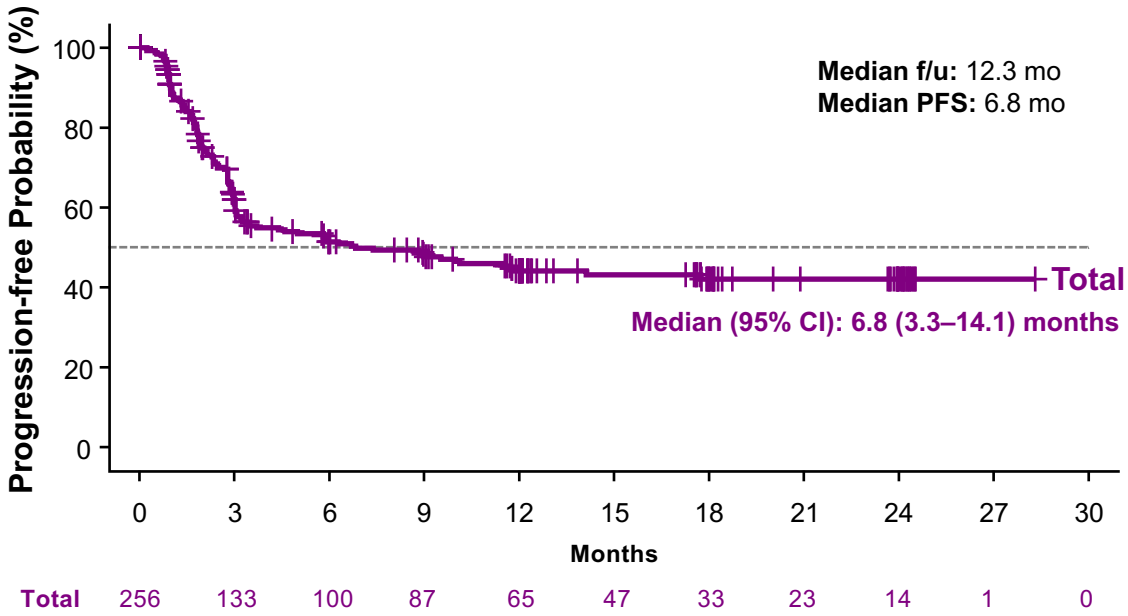
Schuster et al. *N Eng J Med* 2019

Courtesy of Sattva S Neelapu, MD

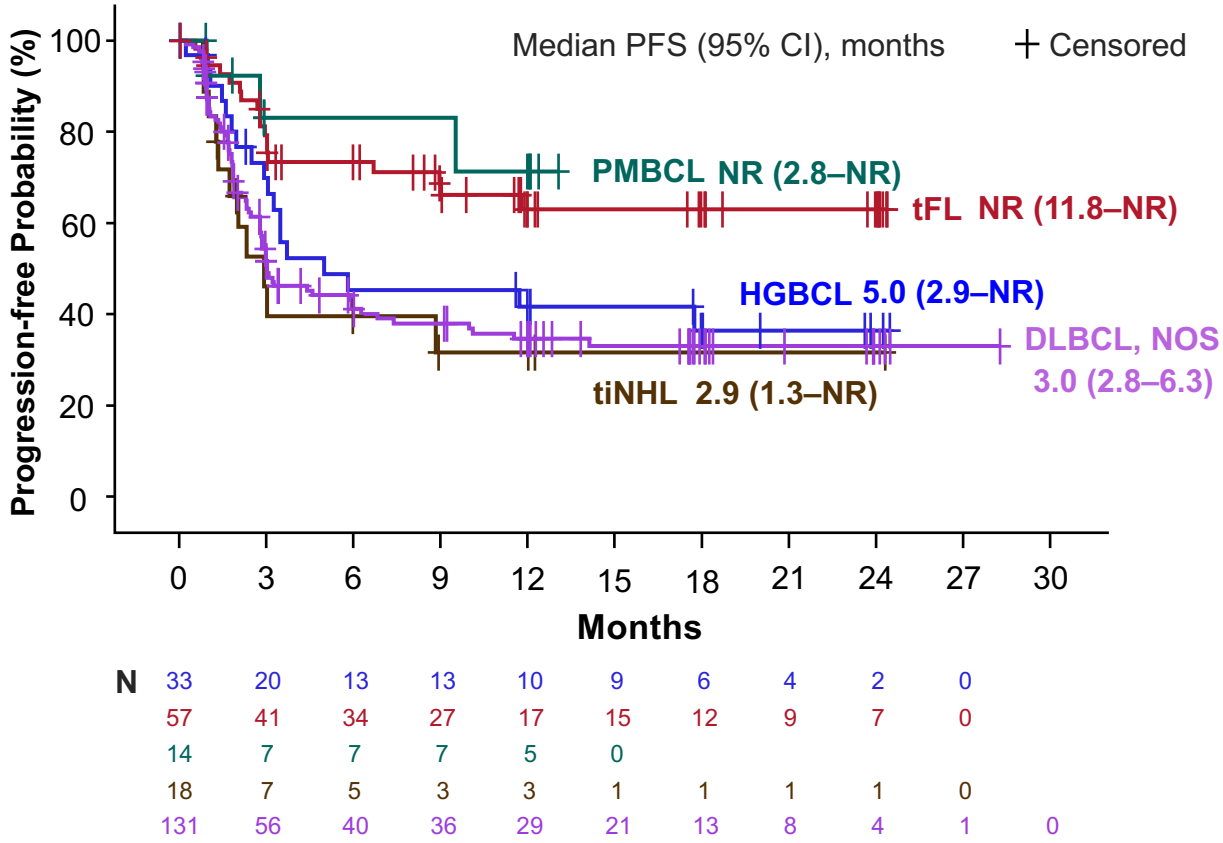
Durable responses with liso-cel in r/r large B-cell lymphoma

TRANSCEND: PFS for all patients

12-month PFS = 44%



TRANSCEND: PFS by lymphoma subtype



Courtesy of Sattva S Neelapu, MD

- **Patients with co-morbidities have inferior PFS**

Abramson et al. ASH 2019, Abstract 241

Axicabtagene ciloleucel and tisagenlecleucel: Current indications in NHL

- Axicabtagene ciloleucel (CD19/CD3ζ/CD28)
  - ✓ Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including DLBCL, high-grade B cell lymphoma, PMBCL, and transformed follicular lymphoma
- Tisagenlecleucel (CD19/CD3ζ/4-1BB)
  - ✓ Adult patients with relapsed/refractory large B cell lymphoma after two or more lines of systemic therapy including DLBCL, high-grade B cell lymphoma and transformed follicular lymphoma

Courtesy of Sattva S Neelapu, MD

ZUMA-2: Ph 2 study of KTE-X19 in r/r mantle cell lymphoma

Eligibility

- R/R MCL not responding or progressing after last therapy
- 1-5 prior therapies that must have included anthracycline/bendamustine, anti-CD20 and BTKi
- ECOG 0-1
- ALC ≥100/μL
- Adequate organ function

- Enrolled = 74
- Manufactured = 71 (96%)
- CAR-T infused = 68 (92%)
- No chemo bridging

- Cy/Flu conditioning
- CAR-T dose = 2 x 10^6/kg

Efficacy

- ORR = 93%
- CR rate = 67%

- Median f/u = 12.3 mo
- 57% of all patients and 78% of CR patients remain in remission
- Median PFS and OS were not reached

Safety

- CRS = 91% all grades; 15% grade ≥3
- NEs = 63% all grades; 31% grade ≥3

Courtesy of Sattva S Neelapu, MD

Wang et al. ASH 2019; Abstract 754
Wang et al, N Eng J Med, 2020

ZUMA-5: Ph 2 study of axi-cel in r/r indolent NHL

Eligibility

- R/R follicular lymphoma (FL) or marginal zone lymphoma (MZL)
- ≥ 2 prior lines of therapy - must have included anti-CD20 and alkylating agent

- Enrolled = 148
- CAR-T infused = 140 (95%)
- 4 pending infusion

- Cy/Flu conditioning
- CAR-T dose = 2 x 10^6/kg

- Data cut-off: Dec 16, 2019
- 140 evaluable for safety
- 96 evaluable for safety (80 FL+16 MZL)

Efficacy

- ORR = 93%
- CR rate = 80%

- Median f/u = 15.3 mo
- 68% of all FL patients and 80% of CR patients remain in remission
- Median PFS was 23. 5 mo and median OS were not reached

Safety

- CRS = 79% all grades; 8% grade ≥3
- NEs = 58% all grades; 17% grade ≥3

Courtesy of Sattva S Neelapu, MD

Jacobson et al. ASCO 2020; Abstract 8008

79-year-old man with DLBCL (from the practice of Ms Zerante)

- 2005: Diagnosed with CLL and high-grade B-cell lymphoma, with MYC and BCL2 rearrangements
  - Active surveillance
- 2017: B-cell lymphoma
- Multiple prior treatments for DLBCL
- Presents with a significant disease burden
- CAR T-cell therapy with axi-cell
  - Peak grade 2 CRS (hypotension and fever) day 4-5. Received Toci x1
  - Peak 0 ICANS (though noted slowed speech)
  - Developed C. Diff diarrhea during admission
- Currently, 2 years later and patient remains in CR

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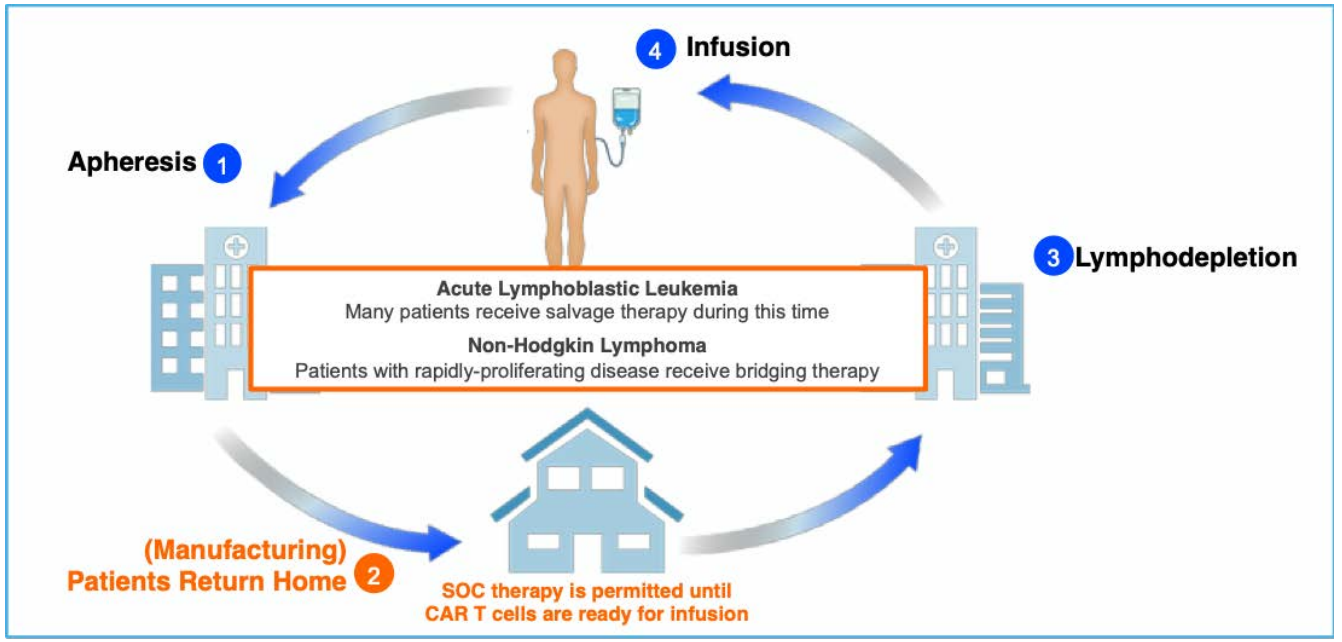
Module 5: CAR T-Cell Therapy in Acute Lymphoblastic Leukemia (ALL)

- Overview of current management of ALL
  - Blinatumumab
    - Administration/toxicity compared to CAR-T therapy
- Key data set: ELIANA
- Current clinical role for CAR-T therapy

The CAR-T journey: phases of care for patient, developer, clinician



Pre-treatment period
(therapies to achieve disease control, assessment, apheresis, cell manufacturing)

CAR-T

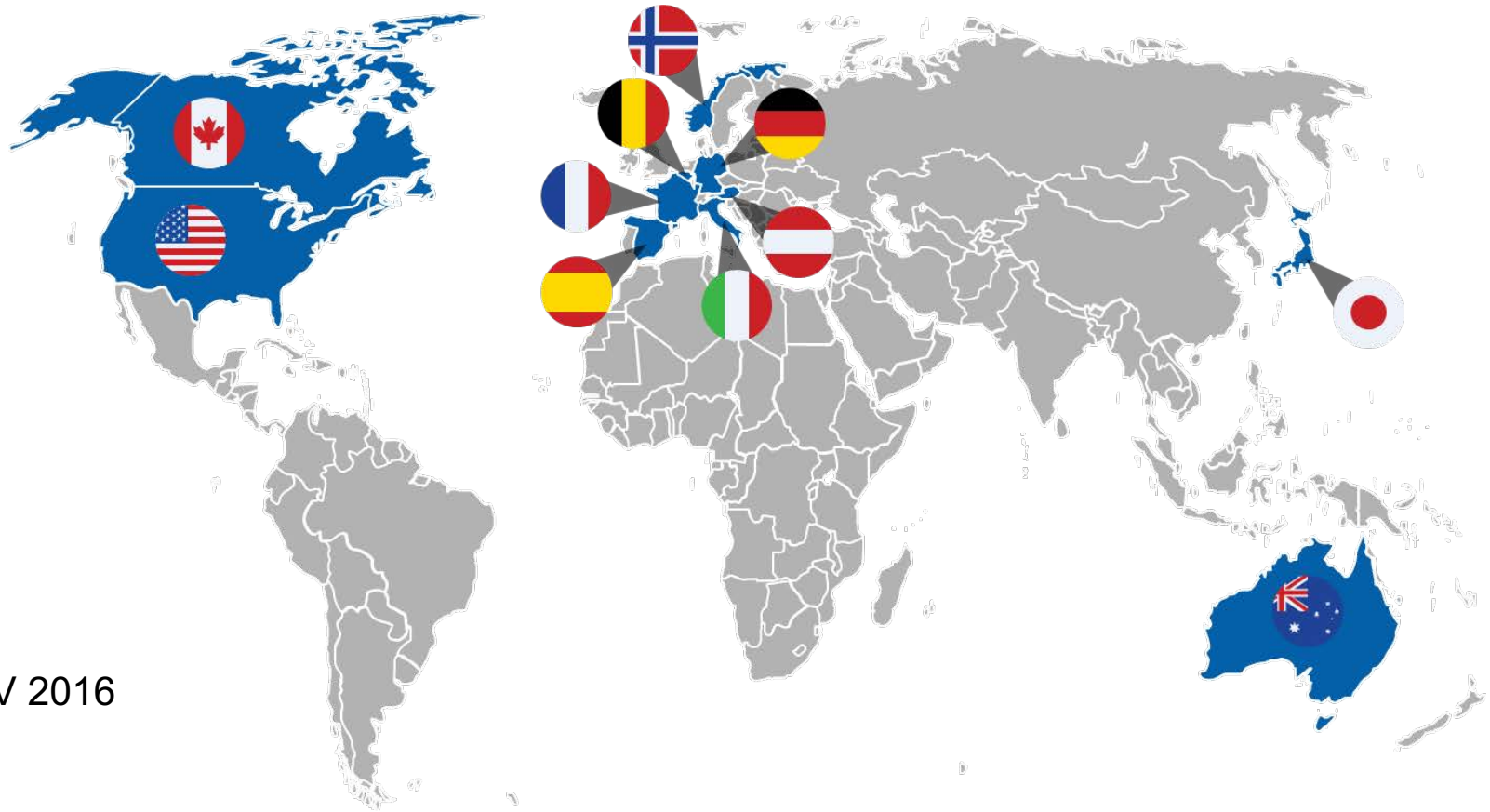
Inpatient
typical 0-2w stay; major toxicities before one month

Follow-up
Care primarily with referring oncologist
Relapse greatest cause of mortality

Few late complications but ongoing relapses (typically plateau by 2 years)

Global, Multicenter ELIANA Trial: ALL Registration Study

- ELIANA is a single arm global study with centralized manufacturing of tisagenlecleucel
- 25 sites in 11 countries across North America, Europe, Australia, and Asia



FPFV=8 APR 2015
Data cutoff: 23 NOV 2016

ELIANA: Primary Efficacy Analysis[1]

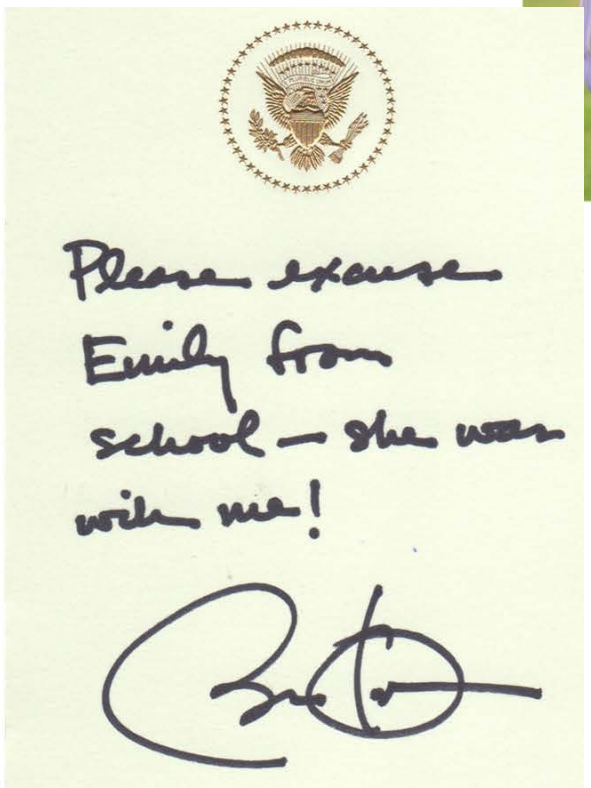
Parameter	Efficacy Analysis Set[a] (n = 63)		
Primary endpoint	% (n/N)	95% CI	*P*
Overall remission rate (CR + CRi) within 3 months	83 (52/63)	(71-91)	< .001[d]
Best overall response, %[b]			
CR	63		
CRi	19		
Secondary endpoint			
Best overall response of CR or CRi within 3 months with MRD-negative[c] BM	83	(71-91)	< .001[d]

- Primary efficacy analysis consistent with interim analysis where primary endpoint was met

[a] Patients infused with CTL019 ≥3 months prior to data cutoff. [b] The response was unknown in 6 patients. [c] MRD negative = MRD <0.01%.
[d] Nominal *P* value presented to test null hypothesis of overall remission rate <20% for comparison with historical control.
1. Buechner J at al. 23rd Annual Congress of the European Hematology Association 2017 (EHA 2017). Abstract S476.


1 Year
Cancer
Free!

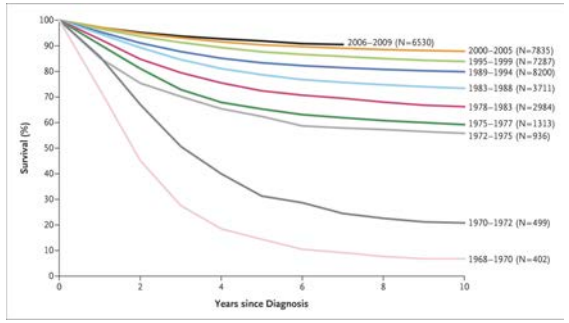

8
years
cancer
free!

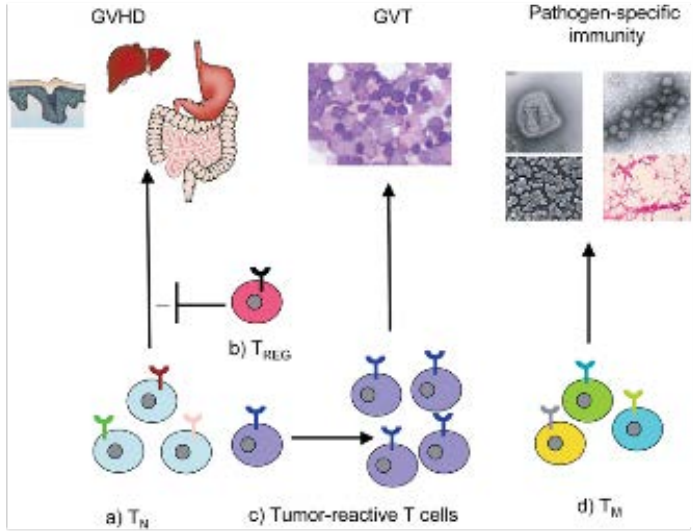

Please excuse
Emily from
school – she was
with me!

No effective therapies → *Chemotherapy era* → *Stem Cell Transplant era (Combinations of chemotherapy, immunotherapy)* → *Our future: Increasingly effective immunotherapies*

1825
First description of acute leukemia

1960s
Combination chemotherapy + stem cell transplants





1990s
T cells critical for transplant cures—dramatic increase in success

2017
Approval of engineered T cell therapies

41-year-old woman with ALL (from the practice of Ms Zerante)

- 4/2013: Pre-B-cell ALL (normal cytogenetics) → CALGB-10403 pediatric regimen, with CR → NED
- 11/2016: Relapse t(4;16)
- 2/2017: Hyper-CVAD course B with rituximab followed by course A → Transplant
- 2/2018: Relapse
- 5/2018: Completes inotuzumab x 4 with remission
- Early 2019: Relapse, with CD22-negative B-ALL
- DOMP, intrathecal methotrexate bridging therapy to CAR-T
- CAR-T cell infusion → D+7 fever, hypotension, tachycardia (tocilizumab)
  - Discharged home D+16
- 4/10/2020: Relapse → Inotuzumab
- 5/5/2020 Bone marrow biopsy: Hypocellular marrow with residual CD19, CD22+ disease
- 5/14/2020: Admitted for blinatumomab, escalated to full dose 5/17 and discharged
- Plan: Continue blinatumomab: If MRD-negative CR, then second TMI marrow transplant from unrelated donor

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.